The London School of Economics and Political Science

Cancer medicines: clinical impact, economics, and value

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Declaration

I certify that's the thesis I have presented for examination fully MPhil/PhD degree at the London School of Economics and Political Science is solely my own work other than where I have clearly indicated that the work of others (in which case the extent of any work carried out jointly by me and any other persons clearly identified in it – see 'Statement of Conjoint Work').

I warrant that this authorization does not, to the best of my belief, infringe the rights of any third party.

I declare that my thesis consists of 63,084 words (excluding bibliography and appendix).

Statement of Conjoint Work

The work that is presented in Chapter 2, and part of the work that is presented in Chapter 4, has been published.[1] My co-authors on these publications include: Dr Elias Mossialos of the London School of Economics and Political Science (London, UK) and Dr Othon Iliopoulos of the Harvard Medical School and Massachusetts General Hospital (Boston, MA, US), who provided guidance on research methodologies and clinical input. Mr Rayden Llano of the London School of Economics and Political Science (London, UK) could not be named as co-author in one of these publications due to policies on publishing by federal employees. His contributions are nevertheless acknowledged: he assisted with data collection by serving as a second, independent reviewer of cancer drug appraisals in Chapter 2. For the same chapter, Dr Mossialos was asked to serve as a third reviewer if consensus with Mr Llano could not be reached. This consensus-based approach was used to minimize the introduction of investigator bias during the review of HTA appraisals. All major work related to Chapter 2, including analysis and interpretation of data, was conducted by me. Copyeditor Sarah Moncrieff assisted with designing Figure 5. For the published aspects of this thesis (Chapters 2, 4), I conceived and designed studies, acquired, analyzed, and interpreted data, and drafted manuscripts. Dr Mossialos offered feedback on the published aspects of this thesis, as well as all remaining chapters. Journal reviewers provided feedback, and suggested secondary analyses, that have been incorporated into this thesis. Additional publications are being

[1] Salas-Vega S, Mossialos E. Cancer Drugs Provide Positive Value In Nine Countries, But The United States Lags In Health Gains Per Dollar Spent. Health Aff (Millwood). 2016;35(5):813–23. Salas-Vega S, Iliopoulos O, Mossialos E. Assessment of Overall Survival, Quality of Life, and Safety Benefits Associated With New Cancer Medicines. JAMA Oncol. 2016;116(14):3493–504.

prepared from the work that is presented in the remaining chapters of this thesis. Other than where I have cited the relevant contributions of others, I confirm that I am responsible for the entirety of the work presented in this doctoral thesis.

Abstract

Background and Importance: There has been much debate recently over rapidly growing drug expenditures. Cancer medicines, in particular, have driven new brand spending over recent years, and US oncological expenditures have risen faster than for many other disease areas, in part because of rapidly growing drug prices, as well as increased rates of use.

Objective: In the face of ongoing debates on how to reasonably control growth in pharmaceutical spending, while also providing patients with the best possible care, this thesis sets out to help address the question of whether growing pharmaceutical expenditures are providing value-for-money to patients and society.

Novelty and Empirical Contributions: This thesis is based in part on a systematic review with narrative synthesis of English-language HTA appraisals of the comparative clinical risks and benefits of new cancer medicines, as well as on the novel use of (b) (4) methods to generate comparative evidence on their use and cost. Adapting established methods, these data are then used to examine existing questions over whether growing expenditures are worth the cost to patients and society. This thesis makes five major contributions to the literature on value-based spending on cancer medicines: 1) approximately one in three newly licensed cancer medicines provide no known overall survival benefit, while one in five provide no known overall survival, quality of life, or safety benefit; 2) novel use of methodologies to model treatment course and duration reveals that cancer drug use and costs vary greatly between individual medicines, and across Australia, France, the UK, and the US; 3) the monetized value of survival gains attributable to cancer drug innovation, net of growth in cancer drug

spending, varies across individual medicines, and, at a country-level, remains unambiguously positive in Australia, France, and the UK, but negative in the US; 4) spending on new cancer medicines is often only weakly associated with their clinical benefits; and 5) the strength of this association nevertheless varies across countries, with the UK demonstrating the strongest evidence of value-based spending on new cancer medicines.

Clinical and Policy Implications: Findings from this thesis provide a resource for value-based clinical decision-making by patients and physicians. Moreover, growing expenditures on cancer medicines may only weakly be associated with meaningful clinical benefits, though the extent to which this is true differs across countries. These findings highlight the important role that health policy can have in encouraging value-based cancer drug spending. In particular, it is argued that managed access schemes promoting access and evidence development, as well as the use of value-based spending policies, can help expedite access to new treatments, incentivize the development of clinically meaningful medicines, and rationalize growing cancer drug expenditures.

Future Research Directions: The comparative clinical risks and benefits from new cancer medicines using real-world data, and how they compare with trial-based results; how evidence on the comparative impact from new treatments is measured, weighted, and rewarded in decision-making by regulators and payers; and how it is effectively linked through policy and regulation to cancer drug spending.

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List of Abbreviations

(b)	
ACoS:	American College of Surgeons
ACS:	American Cancer Society
AE:	Adverse events
AHRQ:	Agency for Healthcare Research and Quality
AMA:	American Medical Association
ARTG:	Australian Register of Therapeutic Goods
ASCO:	American Society for Clinical Oncology
ASMR:	Amelioration du Service Medical Rendu
ATC:	Anatomical therapeutic chemical
ATV:	Added therapeutic value
AU:	Australia
AusPAR:	Australian Public Assessment Report
BSA:	Body surface area
CDC:	Centers for Disease Control and Prevention
CDF:	Cancer Drugs Fund
CEPS:	*Comité Economique des Produits de Santé*

CER:	Comparative effectiveness research
CML:	Chronic myeloid leukemia
CMS:	Centers for Medicare & Medicaid Services
CoC:	Commission on Cancer
CP3R:	Cancer Program Practice Profile Reports
CQIP:	Cancer Quality Improvement Program
DAC:	Drug acquisition cost
DALY:	Disability adjusted life years
DDD:	Defined daily doses
DoT:	Duration of treatment
DUSC:	Drug Utilization Sub Committee
EMA:	European Medicines Agency
EPAR:	European Public Assessment Reports
ESC:	Economics Sub Committee
ETP:	Episode treatment price
EU:	European Union
FDA:	Food and Drug Administration
FR:	France
GBD:	Global Burden of Disease
HAS:	Haute Autorité de Santé
HCBR:	Hospital Comparison Benchmark Reports
HCUP:	Healthcare Cost and Utilization Project
HSCIC:	Health & Social Care Information Centre
HTA:	Health technology assessment
IHME:	Institute for Health Metrics and Evaluation
IMM:	Irreversible morbidity or mortality

IPAC:	Interventional Procedures Advisory Committee
IRA:	Interrater agreement
IRR:	Interrater reliability
MEPS:	Medical Expenditure Panel Survey
MIDAS:	Multinational Integrated Analysis System
MIPPA:	Medicare Improvements for Patients and Providers Act
MMA:	Medicare Modernization Act
NCCN:	National Comprehensive Cancer Network
NCDB:	American College of Surgeons National Cancer Database
NCDR:	National Cancer Data Repository
NME:	New molecular entities
NSRC:	National Schedule of Reference Costs
NCI:	National Cancer Institute
NHB:	Net health benefit
NHS:	National Health System
NICE:	National Institute for Health and Care Excellence
NIH:	National Institutes for Health
NOS:	Not otherwise specified
OECD:	Organisation for Economic Cooperation and Development
ORR:	Objective response rates
OS:	Overall survival
p25:	25th percentile
p50:	50th percentile
p75:	75th percentile
PAS:	Patient access scheme
PBAC:	Pharmaceutical Benefits Advisory Committee

PBPA:	Pharmaceutical Benefits Pricing Authority
PBS:	Pharmaceutical Benefits Scheme
PCORI:	Patient-Centered Outcomes Research Institute
PDP:	Prescription drug plan
PFS:	Progression-free survival
PI:	Product information
PLICS:	Patient Level Information and Costing Systems
PPACA:	Patient Protection and Affordable Care Act
PPRS:	Pharmaceutical Price Regulation Scheme
QoL:	Quality of life
R&D:	Research & development
RQRS:	Rapid Quality Reporting System
RR:	Response rates
RWD:	Real-world data
SACT:	Systemic anti-cancer therapy
SAE:	Serious adverse events
SD:	Standard deviation
SEER:	The Surveillance, Epidemiology, and End Results
SEM:	Standard error of the mean
SMR:	Service Medical Rendu
TA:	Technology appraisal
TAC:	Technology Appraisal Committee
TAG:	Technology assessment group
TEAE:	Treatment-emergent adverse events
TGA:	Therapeutic Goods Administration
TSD:	Technical support document

UK:	United Kingdom
UNCAM:	*Union Nationale des Caisses d'Assurance Maladie*
US:	United States
USCS:	United States Cancer Statistics
VHA:	Veterans Health Administration
VBP:	Value-based pricing
VSL:	Value of a statistical life
VSLY:	Value of a statistical life year
WHO:	World Health Organization
WTP:	Willingness to pay
YLD:	Years lost to disability
YPLL:	Years of potential life lost

1

Introduction

There has been much debate recently over spending on medicines, with discussions over their clinical toxicity often giving way to discussions over their "financial toxicity".(1) On a net price basis, total spending on medicines in the US reached $315 billion in 2015, an increase of 8.5% from 2014.(2) Of this, $121 billion was spent on high-cost, specialty medicines, a figure that was 15% higher than that spent one year prior.(2) Growing expenditures on medicines may be explained by growing prescription drug volumes, but also by rapid increases in prescription drug prices.(2)

Western governments have launched new efforts aimed at bending the cost curve for prescription medicines downwards.(3) These developments come alongside recent controversies related to pharmaceutical pricing,(4,5) as well as growing budgetary pressures. For their part, pharmaceutical companies have expressed concern over what they perceive to be "growing political pressure on drug prices,"(6) with the suggestion being that cost-containment measures may be insensitive to the clinical benefits from pharmaceutical innovation. Caught in the middle are providers and patients, who may prefer and indeed benefit from new treatments, but who may also be burdened by growing drug costs and levels of cost-sharing.(7)

In the face of ongoing debates on how to reasonably control growth in healthcare spending, while also providing patients with the best possible care, some have turned to the question of whether growing expenditures are worth it to both patients and society.(8,9)

This question may help frame the positions that are taken on the issue of pharmaceutical spending. Regulatory concerns over drug price escalation may be based in part on the belief that drug-related expenditures exceed their worth to patients and payers. Indeed, as recent discussions show,(10) it may be difficult for governments or payers to decide against paying for new medicines that have a large budgetary impact if they are also associated with demonstrable improvements to health. Industry may defend pharmaceutical price increases by pointing to the argument that they incentivize pharmaceutical R&D and clinical breakthroughs.(11) During clinical decision-making, physicians and patients may also consider drug costs, clinical impact, and tradeoffs between the two.(12)

Empirical evidence on the worth of added pharmaceutical spending—its value—may therefore provide an opportunity to move away from interest-driven debates and towards evidence-based policy and practice that promotes cost-efficient care. With this as a backdrop, this thesis focuses on the issue of value-based spending on medicines, and cancer pharmaceuticals, in particular.

Value-Based Healthcare

Before going any further, it is necessary to provide a few definitions. Michael Porter in 2010 defined value in healthcare as the outcomes relative to costs from treatment.(13) This definition takes the value of healthcare interventions as a function of their cost and impact on clinical outcomes:

$$Value = f(cost, clinical\ outcomes) \quad (1)$$

According to Porter's definition, higher value can be achieved if new treatments improve outcomes at lower cost; improve outcomes with no increase in cost; worsen outcomes, though with proportionally larger decreases in cost; lower costs, while having no effect on outcomes; or indeed raise costs, though with proportionally larger improvements in outcomes. The relationship between costs, clinical outcomes, and value from treatments can therefore be represented through the following formula:

$$Value = \frac{desired\ clinical\ outcome}{cost} \quad (2)$$

To provide some context to the use of this concept in healthcare, a brief overview of governmental, payer, industry, and clinical perspectives is now given on how to define, measure, and respond to the value of medical treatments.

Governmental Perspective

Regulatory authorities focus on the clinical dimension to value in healthcare spending when considering whether to authorize new treatments. That is, licensing decisions in the US, EU, and Australia, by the FDA, EMA, and TGA, respectively, focus on ensuring that safety, efficacy, and quality criteria are met. Regulatory authorities are generally not expected to assess the economic impact from new treatments. Discrepancies may therefore exist between regulatory assessment and any respective HTA process that may occur in these countries.

At the same time, legislative and regulatory action has often focused on the economic dimension to value in healthcare spending. Recent examples of this include congressional investigations into drug pricing, regulatory backlogs, the generics industry, and price competition.(3) Indeed, of the healthcare-related bills that were introduced during the 114th US Congress, a majority focused on mechanisms for cost mitigation (Appendix 1.1).

There nevertheless appears to be interest in the development of value-based policy that cuts across the issues of treatment costs and clinical impact. The Medicare Access and CHIP Reauthorization Act of 2015, for instance, amended the Social Security Act by replacing Medicare's Sustainable Growth Rate Formula with a merit-based payment system that links spending on physician services with performance.(14) Elsewhere, the Patient Protection and Affordable Care Act of 2010 added Sec. 1115A to the Social Security Act to establish a Center for Medicare and Medicaid Innovation, whose purpose is to develop and test innovative payment and service delivery models that reduce healthcare spending while preserving or improving the quality of care.(15) While both pieces of

legislation directly or indirectly attempt to control costs, they also take into consideration the impact to patients from the therapies that are provided.

Industry/Payer Perspective

Value-based spending initiatives have also been adopted by industry in recent years. Aetna and Cigna, two private insurers in the US, recently negotiated an innovative, value-based payment mechanism with Novartis for its new heart failure medicine, Entresto.(16) Under this payment model, Cigna has agreed to scale its payments to Novartis based on how well treatment with Entresto improves the relative health of Cigna enrollees.(16) While the long-term cost and clinical implications of this innovative payment model remain unclear, it establishes a framework in which growth in spending is linked to clinically meaningful drug innovation.

Clinical Perspective

Clinicians have also pointed to the need to consider both the cost and clinical impact from treatments, and the AMA has recently expressed its support for value-based pricing of medicines. At an Interim Meeting of the AMA in November 2016, physicians adopted a policy outlining principles to change the "fundamentals of prescription drug pricing without compromising patient outcomes and access."(17) As AMA President Gurman explains, this policy represents the belief that the "carte blanche approach to drug pricing" needs to change so that high-quality care is also based on value. He explains that this change should "support drug prices based on overall benefits to patients,"(17) so that growth in pharmaceutical spending is slowed and costs balance with clinical benefits.

Disease Area of Focus: Cancer

Value-based initiatives that target healthcare spending may be particularly helpful in the case of cancer.

Spending

Cancer treatment is often associated with significant expense. The US alone spent close to $125 billion in 2010 on cancer care; this is expected to rise by more than one quarter to a real total value of $158 billion by 2020 (2010 dollars).(18) It is in fact the most expensive disease area to treat on a per capita basis,(19,20) and has been one of the leading drivers of growth in healthcare expenditure.(21,22) New anticancer medicines, in particular, have driven recent increases in spending,(23) and projections estimate that they will contribute the most to global pharmaceutical spending growth through 2021, particularly in developed countries.(24) One-third of US cancer patients go into debt as a result of cancer treatment, and approximately 3 percent file for bankruptcy.(25) The economic impact from cancer treatment is also higher than that of other disease areas, with US cancer patients being 2.65 times more likely than age-matched controls to declare personal bankruptcy.(26)

There is evidence to suggest that the high-cost of cancer care may also influence patient care and outcomes: most cancer patients apply for copayment assistance, and a large proportion of those patients take less than the prescribed amount of medicine, partially fill prescriptions, or avoid filling prescriptions altogether.(27) From a clinical perspective,

therefore, it is particularly important to consider potential tradeoffs between the cost and NHB of new therapies in the field of cancer.

Cancer research is also the largest recipient of R&D spending. Moses and colleagues (2015) report that in 2010 the US NIH allocated $5.621 billion to cancer research, which, at 32.7% of its total research funding, was the highest figure among 27 conditions evaluated by the study.(28) Proportional to cancer-related DALYs, a measure of disease burden, cancer is in fact the most well-funded disease area for research in the US.(29) Public expenditure on cancer R&D has also trended upwards over recent years, both in the US and around the world.(30) Likely as a result of these investments, there has been a significant amount of innovation in cancer medicines over the last decade: as a few examples, this has included the first anti-angiogenic medicine for cancer (bevacizumab licensed in 2004), the first new kidney cancer drug in over a decade (sorafenib, 2005), the first treatment for peripheral T-cell lymphoma (pralatrexate, 2009), and two new medicines for melanoma in which treatment is personalized to the genetic profile of the patient (dabrafenib, trametinib, 2013).(31) Despite comparatively high rates of spending, and the emergence of many new anticancer medicines, little attention has been paid to the costs and patient outcomes from new cancer treatments.(22,32–35)

In the face of scarce resources, high levels of spending on cancer may in part reflect the notion that societies deem it 'fair' to prioritize the development and use of cancer treatments. As Nord and colleagues explain,(36) ethical theory and public opinion in industrialized nations suggest that people often attribute greater utility to interventions that treat more severe disease. Indeed, regulators and HTA agencies, including England's NICE, may give additional weight to the survival benefits associated with medicines that

are indicated for patients with terminal disease and short life expectancies.(37) To the extent that societies prioritize cancer drug development and use, this may therefore suggest that spending relative to the clinical impact of new therapies differs across countries and exceeds that observed in other disease areas.

Burden of Disease

Cancer is also associated with a high, and growing, burden of disease. In the US, cancer accounted for 12,363,000 DALYs lost in 2010.(29) At 21.6% of total DALYs lost from 27 conditions provided with NIH research funding, cancer was associated with the largest burden of disease. Proportional to total DALYs lost, there are reasons to believe that the burden of disease from cancer will continue to increase due to several factors: a rise in the incidence and prevalence of cancer due to population growth and the aging of the population, and better control of competing sources of mortality.(12) With the escalation in treatment costs for cancer, as well as greater cost-sharing, health systems owe it to their patients to assess the value from spending on new cancer medicines.

Value-Based Healthcare: The Case of Cancer Medicines

As cancer-related treatment costs and disease burdens grow, regulators and clinicians have proposed value-based initiatives to link expenditures on cancer treatments with their clinical benefit.

The US Department of Health and Human Services, for instance, recently proposed a plan to introduce a two-stage Part B Payment Model that would help reduce expenditure

on medicines that are administered in outpatient settings—typically high-cost, and encompassing cancer medicines—while maintaining or improving health outcomes.(38)

The UK government established a dedicated cancer drugs funding program, the CDF, in 2011. As is explained in the government's White Paper on the matter,(39) this effort was driven by concerns regarding access to new cancer medicines in the UK, where there was often a lower likelihood of survival from cancer than in other Western European states. However, with expenditures on the CDF rising from £38 million in 2010/2011 to £416 million in 2015/2016,(40) and with little evidence demonstrating improved clinical outcomes from prescription drug use,(41) lawmakers in the UK recently reformed the CDF into a managed access fund with the aim of ensuring sustainability, "genuine [therapeutic] promise," and stronger value-for-money in drug spending.(42,43)

For their part, oncologists may be uncertain of how economics should influence clinical care.(12) Clinical experts in the treatment of CML have argued that current rates of growth in cancer drug prices are unsustainable and may be clinically counterproductive,(44) particularly if growing costs hinder patient access.(45) However, reflecting the AMA's position on the need to develop VBP mechanisms, these same medical oncologists acknowledge that "if drug price reflects value, then it should be proportional to the benefit to patients in objective measures."(44) This perspective is widely shared. Lin and colleagues (2016), for instance, argue that the value of cancer care should ideally be measured not in terms of only price, but rather in terms of the outcomes achieved per unit of cost incurred.(22) Mailankody makes a similar argument, contending that high costs for medicines may be justified if they bring equally large clinical benefits to patients.(46) To date, however, there have been few systematic

attempts at comparing cancer drug spending and its clinical impact, and examining the degree to which this is the case.

Approaches to Measuring Value

Health care systems may employ HTA to perform, and respond to, pharmaceutical value assessments. The following section provides an overview of how value is appraised in Australia, France, the UK, and the US, and used to reward clinical innovation.

Australia

In Australia, once a new medicine has received market licensure, sponsors may apply to request that their product be made available for public subsidy through the nation's PBS. Australia's Pharmaceutical Benefits Advisory Committee (PBAC) is an independent expert body that is appointed by the Australian Government and tasked with determining whether it is in the social interest for medicines to be publicly reimbursed. To inform its decisions, PBAC considers the medicine's indication for use, its clinical effectiveness, safety and cost-effectiveness ('value-for-money') compared with other treatments.(47,48) PBAC recommendations also consider the clinical need underlying drug use; estimates of the annual cost that would be incurred from public subsidization; and concerns over drug prescribing that could create challenges for subsidy limits.(48)

The PBAC is composed of two sub-committees that advise on economic matters related to new medicines, the PBAC DUSC and the PBAC ESC. The DUSC is responsible for generating estimates of the expected use of new medicines, as well as the financial

impact to public purchasers from their subsidization. The ESC is responsible for advising the PBAC on the clinical and health economic data submitted to the agency through drug dossiers.

Prior to 2014, a non-statutory body, the PBPA, was then tasked with advising Australia's Department of Health and Ageing on appropriate drug pricing. The organization utilized a variety of methods to suggest pricing for new treatments, including: 1) the cost-plus method (used predominately since 2007 PBS reforms); 2) reference pricing (used predominantly before 2007 PBS reforms); 3) weighted Average Monthly Treatment Cost; and 4) statutory price arrangements. As of 2014, price negotiations are undertaken by the Pricing Section on behalf of the Minister following a positive PBAC recommendation, and relies on cost-plus, reference pricing, and weighted pricing methods.(49) To negotiate the price of new treatments, the Pricing Section considers: PBAC advice on their clinical and cost-effectiveness; prices of alternative brands; comparative prices of items containing drugs in the same Anatomical Therapeutic Chemical (ATC) groups; cost information; prescription volumes, economies of scale, special storage requirements, product stability, special arrangements; prices of items containing the drug in reasonably comparable overseas countries; other factors the applicant may wish the Pricing Section to consider; and directions from the Minister.(49)

France

The main HTA body in France is the *Haute Autorité de Santé* (HAS). A scientific group of experts within HAS called the *Commission de la Transparence* is responsible for evaluating submissions for reimbursement for drugs that have been issued market

authorization, and using the clinical evidence to assess the absolute (SMR) and relative therapeutic benefit (ASMR) provided by new treatments. This information is then fed into drug reimbursement and pricing decisions.

SMR is assessed on the basis of five criteria: 1) efficacy and safety; 2) position of the medicine in the therapeutic strategy, and the existence or absence of therapeutic alternatives; 3) severity of the disease; 4) type of treatment, i.e., preventive, curative or symptomatic; and 5) public health impact.(50) In a process that is coordinated by UNCAM, SMR assessments are then used to set pharmaceutical reimbursement levels across the nation's three major health insurance schemes. "Irreplaceable" drugs, as well as those that are indicated for 30 severe chronic diseases (e.g., HIV/AIDS, diabetes), are reimbursed at 100% of their price. Those that are indicated for severe conditions, but not deemed "irreplaceable", are reimbursed at 65%; those indicated for acute, less serious conditions are reimbursed at 35%; and those that are being transitioned to non-reimbursable status are reimbursed at 15%.(51) Therefore, medicines that do not provide any clinical benefit to patients may not be reimbursed, while those that provide substantial clinical benefit to patients may be reimbursed at higher levels.(50)

When classifying a drug's relative medical benefit, the *Commission de la Transparence* evaluates comparative clinical data that is available for applicant drugs and assigns each an ASMR ("improvement in actual benefit") score, which represents the drug's supposed therapeutic improvement over existing, comparable treatments. ASMR scores fall within one of five levels, listed in order of decreasing therapeutic improvement: ASMR I ("significant"), ASMR II ("important"), ASMR III ("moderate"), ASMR IV ("minor"), and ASMR V ("nonexistent"). ASMR ratings are then used by CEPS to internally assess the

value of new treatments, and help set pharmaceutical pricing. Drug pricing decisions are based on: ASMR scores; the price of the local comparators; prices of the product in other European markets (mainly UK, Germany, Italy, Spain); sales forecasts for the next three years; predictable or real conditions for use; and size of the target population.(50)

United Kingdom

In the UK, HTA falls within the remit of the National Institute for Health and Care Excellence (NICE), a non-departmental public body that operates independently of the government. Among other responsibilities, NICE is tasked with developing evidence-based guidance and advice for health, public health, and social care practitioners. This guidance consists of: NICE guidelines, providing recommendations on the use of treatments and clinical services; and technology appraisal guidance, which assess the clinical and cost-effectiveness of health technologies, such as new pharmaceutical products. Several units within NICE carry out the function of guidance development, including IPAC, TAC, and academic centers ('technology assessment groups').(52)

NICE technology assessment groups generate new drug assessment reports; these are then used by TAC to develop recommendations on whether the English NHS should cover those treatments. TAC recommendations are based on both clinical and economic evidence, and consider patient perspectives of risks and benefits, estimates of cost-effectiveness, and the quality of the evidence. TAC uses cost-effectiveness analyses—which may include incremental cost-effectiveness ratios—as the main tool to assess the value of new treatments. NICE typically adheres to a value cap of £20,000-£30,000/QALY gained when deciding whether to recommend the adoption of new technologies.

However, the agency can recommend reimbursement of treatments that exceed this cost-effectiveness threshold, and the agency may be particularly inclined to do so when drug therapeutic benefits coincide with social preferences (e.g. cancer treatment).(53) Since 2002, the NHS has been required to fund treatments that are recommended by NICE's technology appraisal guidance.(54) Local commissioners may however adopt technologies that have not been appraised, not yet been issued a recommendation for coverage, or which may not have been deemed cost-effective by NICE.(54)

Managed entry agreements, otherwise known as PAS, are an important part of the technology appraisal process for medicines. PAS are an arrangement between the manufacturer and the Department of Health that are designed to improve the cost-effectiveness of a drug. There are two types of PAS: financially-based PAS involve the pharmaceutical company providing a discount on a new drug, depending on the number of patients who are expected to use the medication or other factors, such as patient group characteristics, clinical response, or dosing regimens.(55) The second type of PAS is outcome-based. Under this scheme, future discounts or rebates may be linked to the results from ongoing clinical trials, helping to ensure an association between long-term costing trends and clinical impact.(55)

In the UK, pricing of all licensed, branded drugs is not directly regulated, but is often managed through the voluntary PPRS, which institutes mechanisms for price cuts, as well as profit controls—typically defined via return on capital—that weigh price and volume. Reserve statutory powers to control pharmaceutical prices also exist for medicines that are not regulated through the PPRS.(56) The PPRS is a voluntary arrangement between the Department of Health and the Association of British

Pharmaceutical Industry that is designed to give both industry and regulators additional certainty over pharmaceutical pricing and market entry in the UK. The latest version of the PPRS (2014) failed to incorporate VBP mechanisms linking national health technology assessments to price setting due to "technical problems and uncertainty,"(57) it may offer a platform to directly negotiate VBP of medicines in the future. However, in response to calls for value-based pricing, PPRS 2009 nevertheless implemented a flexible pricing arrangement that, among other stipulations, allowed companies to increase or decrease their original list price once by up to 30% in light of new evidence.(56)

United States

The US is a major producer of HTA evidence. CMS and private insurers commission HTA reports on new medical technologies to inform coverage decisions at national and local levels; AHRQ provides significant support for HTA research; the VHA performs pharmaceutical HTA through its Pharmacy Benefits Management Strategic Healthcare Group; and the NIH also develops evidence reviews to inform clinical practice. More recently, the PPACA of 2010 created PCORI, an agency whose mission is to fund and encourage the development of CER.

Yet, public use of HTA in the US is modest compared with Australia, France, and the UK. In accordance with its enabling legislation, the US FDA only requires that new treatments be safe and efficacious for the agency to grant them licensing authorization. The agency does not mandate that efficacy be demonstrated against active comparators: comparative efficacy data is optional, except when ethical considerations would bar the use of non-active comparators in patient trials. Cost-effectiveness is not considered

during pre-authorization reviews. CMS's Medicare Coverage Division may commission HTAs to support national decision-making on treatment coverage, and the agency uses public fora to weigh the evidence from HTA.(58) By law, however, the Coverage Division is barred from considering the cost or cost-effectiveness of new treatments when making coverage determinations.(58)

High-level policies or regulations to control pharmaceutical spending are not used in the US. The social insurance programs Medicare and Medicaid are not allowed to directly negotiate pharmaceutical pricing once new medicines have entered the market,(59) may not consider costs within the drug reimbursement decision-making process, and yet may be required to cover new medicines.(60) Medicare PDPs are required to cover "all or substantially all" medications within six protected classes of medicines, including antineoplastics and immunosuppressants, under various regulations, including the MIPPA of 2008 and PPACA of 2010.(61) Bach and Pearson (2015) argue that Medicare's ability to apply a VBP system is hindered by policies that require Part D private drug plans to cover all drugs of certain protected classes, while a flat co-insurance rate without an upper limit has put highly effective but expensive medicines out of reach for Medicare beneficiaries without supplemental health insurance.(59) For their part, private insurers are required to provide coverage for most new medicines, and may be unable to obtain significant price concessions from manufacturers, especially for drugs offering clinical advantages or using novel mechanisms of action.(59) While insurers may in theory negotiate lower prices for drugs that have therapeutic substitutes or questionable benefits by excluding them from formularies,(62) the extent to which this occurs in the US nevertheless remains unclear.

Empirical Challenges in Measuring Value

Although value-based healthcare is not a new concept,(63) there is relatively little empirical evidence examining the extent to which spending on new cancer medicines is 'worth it.'(22,32–35) As Lee and colleagues (2016) state (34):

> "Few large health care organizations have accurately measured total care costs at the individual patient level and have related costs to quality."

This may be explained by several factors, including: the historical lack of a framework to define and measure the value generated from use of cancer medicines; and a dearth of comparative evidence on their use or cost.

Conceptual Framework on Value of Cancer Medicines

Patient perception of value is highly individualized in the case of cancer.(12) Although overall survival is generally taken as the gold standard for clinical efficacy, several surrogate markers of efficacy have emerged over recent decades to minimize delays in marketing of new cancer medicines. When making treatment decisions, however, patients often consider efficacy alongside other clinically-relevant parameters, including quality of life and toxicity.(12) In part owing to a multiplicity of clinical outcome measures,(64) there has historically been no evidence-based framework that could be used to weight across clinically-pertinent endpoints, measure the clinical impact from new cancer treatments, and therefore be used to rigorously assess the value from spending on cancer medicines.

There has been progress in this regard, with the recent publication of frameworks to assess the value of tools and treatments in healthcare.(65–68) Neumann & Cohen (2015) offered an early review of five of them,(65) of which four were developed in 2015 and could be applied to oncology. Just as "value" may be interpreted differently by different people, all value frameworks vary in their goals and methods.(65–68) Of the four frameworks that could be used in oncology, ASCO's Value Framework is specific to cancer; was designed through a deliberative consensus process; is rules-based; weights clinical measures according to their perceived value to patients; explicitly synthesizes clinical benefits; and incorporates direct costs from treatment (Table 1). It is therefore used in this thesis as a conceptual framework to assess the value from spending on cancer medicines.

Table 1. Overview of Therapy Value Frameworks

Organization	Disease Area	Value Definition	Year	Factors Considered	Cancer Specific	Deliberative Consensus Process	Rules-Based	Weighted Clinical Measures	Explicit Clincial Synthesis	Treatment Costs
Institute for Clinical and Economic Review (ICER)	General	Cost / Outcomes	2015	ICER + care value components Comparative clinical effectiveness Budget impact		✓	✓	✓	✓	✓
Memorial Sloan Kettering Cancer Center	Oncology	Outcomes	2015	Efficacy (survival) Toxicity Novelty R&D cost Rarity Population health burden	✓			✓	✓	
National Comprehensive Cancer Network (NCCN)	Oncology	Cost / Outcomes	2015	Efficacy Safety Evidence quality Evidence consistency Affordability	✓	✓				✓
American Society for Clinical Oncology (ASCO)	Oncology	Cost / Outcomes	2015	Clinical benefit OS PFS (if OS unavailable) RR (if PFS unavailable) Toxicity Bonus Factors (QoL) Cost per month	✓	✓	✓	✓	✓	✓

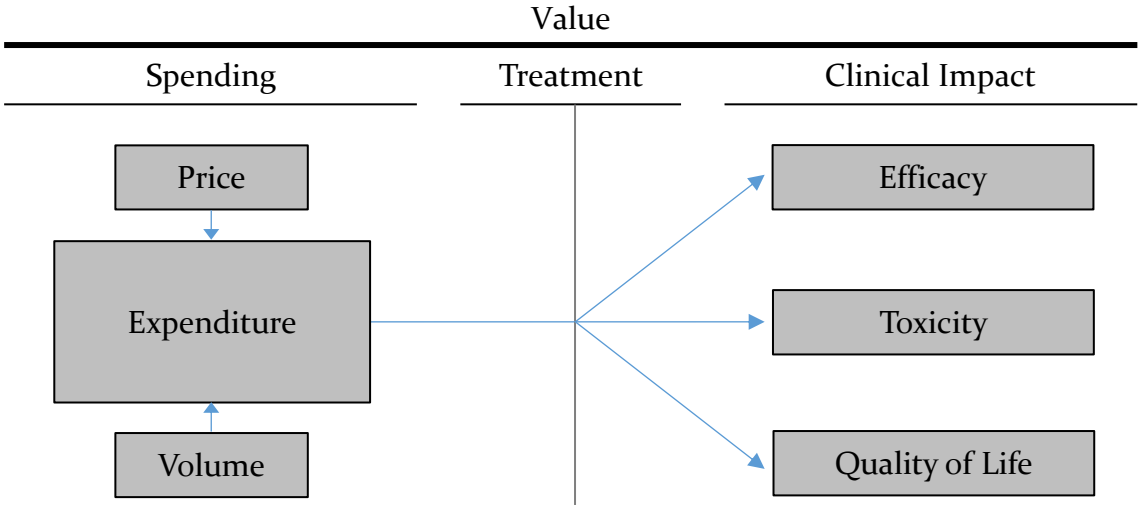
Source:

Adapted from Frakt (2016); Neumann & Cohen (2015); Maervoet et al. (2016); and Chandra et al. (2016).(65–68)

ASCO published its draft framework for assessing the value from cancer treatments in 2015 ("ASCO Value Framework")(Figure 1).(12) Based on consensus among oncologists, patients, payers, and manufacturers, the ASCO Value Framework identifies key clinical outcome measures that represent tangible harms and benefits to cancer patients, including efficacy, quality of life, and toxicity (Figure 1), while also proposing a set of weights for clinical endpoints. Clinical benefits and toxicity are combined to generate an NHB score, which is then juxtaposed against the direct cost of the treatment, to inform shared clinical decision-making. As the authors of this framework explain, this effort is based on the assumption that (12):

> "the cost of a given intervention should bear a relationship to the beneficial impact it has for patients who receive that treatment."

Figure 1. Conceptual Framework to Assess the Value from Cancer Drug Expenditures



Source:

Adapted from Schnipper et al.,(12) ASCO Value Framework.

Without a conceptual framework in place to identify the key clinical outcome measures that represent tangible harms and benefits to cancer patients, it would otherwise be difficult to: assess the value associated with cancer drug spending by comparing the costs and clinical impact from new cancer medicines, and test whether the hypothesis that drug spending is indeed associated with their clinical benefits.

Comparative Data on Cancer Drug Use and Cost

There is as well a dearth of publicly available and comparable evidence on the use and cost associated with new cancer medicines. Even if evidence on the clinical risks and benefits from cancer medicines were available, this lack of data makes it difficult to examine whether spending is associated with the beneficial impact that new treatments provide to patients.

First, there is often a significant amount of uncertainty in the total cost that will be incurred from treatment with cancer medicines. This owes in part to an often-unpredictable length of treatment, which may be defined by progression-free survival, incidence of unacceptable toxicities, or death.[e.g. (69–71)] Unlike in other disease areas, response to cancer treatment is often highly variable, and associated with a wide distribution in length of treatment. To overcome this issue, cancer drug costs may be annualized,(72) or evaluated as monthly DAC or the ETP, both of which refer to the monthly cost for acquisition of cancer medicines based on list prices.(12,73) This approach however does not adjust for potential differences in treatment duration across cancer medicines, and thus may reflect biased estimates of total treatment-related costs.

The lack of globally comparable costing data also makes it difficult to examine the value from cancer drug spending in any one context.

Spending on cancer medicines however is defined by price, as well as use. From a societal perspective, the economic impact, and indeed relevance, of high cancer drug prices may be mitigated by value-based mechanisms that shift demand towards cheaper alternatives, *ceteris paribus*. On this however, comparative studies into cancer drug utilization are complicated by a lack of comparative information on cancer drug usage.(74–76) To add to this issue, methodological challenges, such as the lack of DDDs from the WHO for cancer medicines, makes it difficult to reliably compare usage purely in terms of drug volumes.(74,75) This adds another obstacle to studies that wish to examine the association between spending and drug-related clinical benefits.

Thesis Overview

Theory, Empirical Gaps, and Thesis Outline

This thesis collects data on the clinical impact, use, and cost associated with new cancer medicines, before then examining whether cancer drug spending is providing patients and society with value-for-money. As is shown in Figure 3, these efforts are framed around ASCO's Value Framework, and are designed to reflect its approach for assessing the value of new cancer treatments.

Chapter 2: Clinical Risks and Benefits of New Cancer Medicines

Developed through consensus among oncologists, patients, payers, and manufacturers, ASCO's recently published Value Framework identifies the clinical outcome measures that represent tangible harms and benefits to patients from cancer treatments.(12) **Chapter 2** of this thesis uses it within the context of a systematic review with narrative synthesis of English-language HTA appraisals from Australia, France, and the UK to assess the clinical impact from treatment with new cancer medicines. These countries were selected because they publish English-language HTA appraisals, and also have comparable economic conditions and pharmaceutical systems.(77) Public bodies within each of these countries may utilize their own frameworks to inform value assessments, but may ultimately be held to the same standard with regards to ensuring that cancer drug expenditures reflect value-for-money.

Chapter 3: Spending on New Cancer Medicines

Moreover, there is a dearth of reliable and comparable evidence on the use and cost of cancer medicines, creating a second obstacle in assessing their value to health.(12) This owes in part to a lack of standardized units for comparing cancer drug use, as well as a dearth of publicly available, patient-level data on the factors that influence total prescribable drug dosage, including anthropometrics and DoT, cancer drug use, and cost. To address this challenge, **Chapter 3** uses (b) (4) , and incorporates recent methodological advances,(78,79) to generate comparative evidence on the expected use and cost of new cancer medicines in Australia, France, the UK and the US.

Given data on the clinical impact from new treatments, and their use and cost, the literature has generally taken two approaches to examine whether healthcare spending provides value-for-money. The first approach assesses whether spending on new treatments results in net positive economic returns to patients and society.(22,33,35,80–82) The second assesses whether and to what extent spending is associated with measures of clinical benefit from use of those treatments.(73,83–87)

Chapters 4 & 5: Assessing the Value of New Cancer Medicines

Using data on the clinical impact from new cancer medicines (**Chapter 2**), and their use and cost (**Chapter 3**), **Chapters 4** and **5** adopt both empirical approaches to examine whether cancer drug spending is providing patients and society with value-for-money. **Chapter 4** adapts the methods from previous studies within the context of a cost-benefit analysis to analyze whether the monetized value of survival gains attributable to cancer drug innovation exceeds growth in drug spending, both at a societal- and drug-level. **Chapter 5** then incorporates evidence from prior chapters within a regression-based framework to test the value-based hypothesis that spending on new cancer medicines is associated with their beneficial impact to patients. An overview of the conceptual framework and empirical gaps that underlie these efforts, as well as thesis research questions and outline is provided in Figure 3.

Chapter 6: Synthesis & Conclusion

This thesis ends with **Chapter 6**, which synthesizes research findings, and provides a conclusion on the issue of value-based spending on cancer medicines.

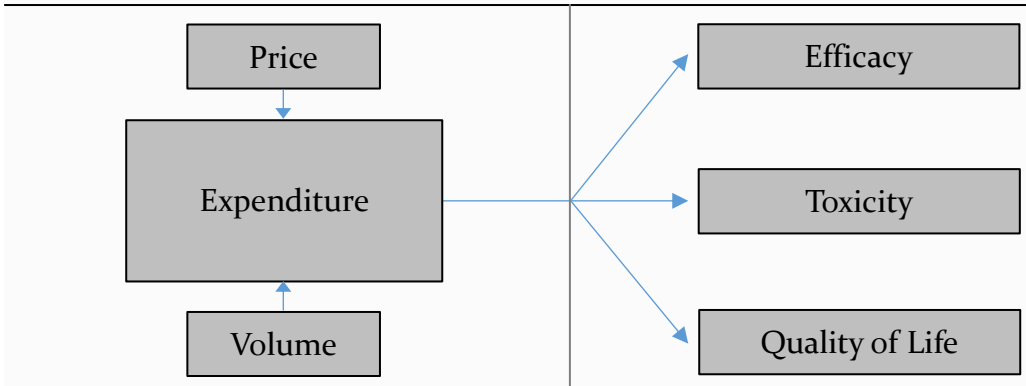
Expected Contributions

By providing and evaluating evidence on the clinical impact, use, and cost of new cancer medicines, this thesis may provide policymakers and clinical practitioners with insights on the issue of value-for-money in cancer drug spending. However, by helping to address the research questions described above, this thesis is expected to primarily make methodological and empirical contributions to the literature.

Figure 2. Overview of Conceptual Framework, Empirical Gaps, Research Questions and Thesis Outline

Overarching Research Question: Is cancer drug spending providing patients and society with value-for-money?

Conceptual Framework (12):



Chapter 3:
Empirical Gap: There is a dearth of publicly available and comparable evidence on the use and cost associated with new cancer medicines.

Research Question: What is the utilization and cost (spending) associated with new cancer medicines?

Chapter 2:
Empirical Gap: Without a conceptual framework in place, it is difficult to systematically assess the clinical impact to cancer patients from new medicines.

Research Question: What are the relative clinical risks and benefits (clinical impact) associated with new cancer medicines?

Chapters 4 & 5:
Empirical Gap: In the absence of information on the clinical impact **(Ch 2)**, utilization or cost **(Ch 3)**, associated with new cancer medicines, it is difficult to assess whether cancer drug spending provides patients and society with value-for-money.

Research Question (Ch 4): Building on data collected from earlier chapters, is the net monetized value of survival gains that can be attributed to cancer drug innovation positive, both at a societal- and drug-level?
Research Question (Ch 5): Building on data collected from earlier chapters, is spending on new cancer medicines associated with measures of their beneficial clinical impact to patients?

2

Clinical Risks and Benefits from New Cancer Medicines

Introduction

There is growing debate about the value of drug expenditures in the US and around the world. Cancer drug prices in particular are growing rapidly, and now may result in annualized treatment costs that exceed $100,000.(44) In response to escalating drug costs, US policymakers have recently launched investigations into drug pricing and price competition.(3) UK policymakers have also recently implemented cutbacks and reforms to a national cancer drug access program, the CDF, over questions of its impact on patient health and concerns of value.(88,89) For their part, clinicians have criticized current cancer drug prices as excessive and unsustainable,(44) and have pointed to evidence suggesting that escalating costs may make it difficult for patients to access, or remain compliant with, life-extending therapies.(44,90)

Discussions of the implications from escalating cancer drug costs however become more nuanced when clinical benefits are considered. Some have argued that high costs may be justified if new cancer treatments are also associated with significant benefits to

patients.(44,46) Even as recent studies point to marginal OS gains from new cancer medicines,(91) efforts to examine the value from related expenditures remain stymied by a dearth of systematic evidence on their clinical risks and benefits. This lack of evidence makes it difficult for the public to demand more from innovation,(92) and, where costs factor into value-based clinical decision-making, for clinicians and patients to balance preferences for the expected impact of treatment against rising drug costs.

Measuring Clinical Benefits

One issue that makes it difficult to systematically assess the value from spending on new cancer medicines is the multiplicity of clinical endpoints that may be used to inform assessments of their clinical impact.

Overall Survival and Surrogate Efficacy Endpoints

OS is generally taken as the gold standard among endpoints that can be used to measure the clinical effectiveness of new cancer medicines.(64,93,94) The US FDA in fact takes OS as a "universally accepted direct measure of benefit" in oncology drug trials.(95) Whereas surrogate clinical endpoints such as PFS may be subject to assessment bias or variability from measurement of radiologic or clinical measures and assessment schedules,(96,97) the interpretation of OS is objective and not prone to investigator bias.(98) This has led some to claim that OS is the "most objective end point to measure patient benefit,"(99) and the FDA itself describes OS as the "most reliable" endpoint in cancer."(95)

In line with these positions, ASCO's Value Framework indicates that OS should be used, if it is reported, to assess the clinical benefit of treatments for advanced or metastatic disease. Only in cases where it is not should assessments of clinical benefit be informed by evidence on treatment-related improvements in PFS or, where also unavailable, RRs. Accordingly, ASCO's Value Framework assigns OS benefits the greatest efficacy weight, and gives drug-related effects on efficacy the most weight—maximum of 80/100 possible points—in NHB scores measuring the overall therapeutic benefit from new cancer treatments. Memorial Sloan Kettering Cancer Center's DrugAbacus Framework adopts a similar approach for assessing the value of cancer therapeutics.(66) Leading value frameworks, including ASCO's Value Framework, reflect the importance that is generally ascribed to OS in measuring treatment efficacy.

There is however a growing body of literature that discusses the potential use of surrogate measures in assessing the impact from cancer treatments on clinical efficacy. This in part owes to the FDA's adoption of *Accelerated Approval* regulations in 1992,(100) which created a fast-track procedure for the evaluation of medicines that treat serious conditions or fill an unmet medical need.(101) To shorten the time required for regulatory evaluation, this procedure allows for the approval of new cancer medicines on the basis of surrogate endpoints, such as PFS and ORRs, that are "reasonably likely to predict clinical benefit".(101) The adoption of this policy has been associated with licensing and coverage decisions for new medicines that increasingly rely on surrogate endpoints: about 16 drugs were approved by the FDA on the basis of surrogate evidence per year between 2010-2014, versus about 6 per year between 1998-2008.(102)

The use of surrogate efficacy endpoints is supported by one stream of evidence indicating that they may predict clinical benefits.(103–106) Oncologists and patients may for instance take PFS, one major surrogate efficacy marker, as prognostic of patient outcomes.(107) Where this is the case, surrogate efficacy endpoints may represent unique dimensions of clinical benefit that could be considered independently of OS.

There are however several challenges in using surrogate endpoints to assess drug-related efficacy benefits to patients.

First, while FDA accelerated approvals provide the manufacturer with full licensing rights, they do not guarantee clinical benefits. Drugs licensed through an accelerated approval procedure are in fact required to complete phase 4 post-marketing trials to confirm clinical benefits.(101) If confirmatory trials are not conducted, or if they fail to demonstrate effectiveness, the FDA can act to remove the drug from the market,(108) as recently happened for bevacizumab's approved use in breast cancer.(73) Fast-track procedures have more recently been supported with the passage of accelerated approval provisions in Sec. 902 of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA), which permits the FDA to fast-track approval of high-need molecules that it considers to be a breakthrough in therapy,(109) as well as the 21st Century Cures Act of 2016, which allows the FDA to consider previously submitted data in its evaluations of precision medicines for serious or rare conditions.(110) Therefore, while accelerated approval procedures may allow for surrogate endpoints, they do not ensure efficacy benefits. By requiring phase 4 post-marketing confirmatory trials, accelerated approvals implicitly suggest that surrogate efficacy data may only unreliably predict clinical benefits.

Second, the evidence supporting an association between OS and PFS varies considerably by cancer type, and may even vary within cancer types.(111) The quality of evidence supporting the existence of an association between surrogate endpoints and OS may also be questionable.(111) For instance, in their review of the evidence examining the relationship between PFS/TTP and OS in advanced or metastatic cancer, Davis and colleagues (2012) find three papers indicating a positive association between PFS and OS in colorectal cancer. The magnitude of this association varied substantially between studies (0.481 to 0.79), and was also inconsistent with the reported association between OS and TTP, with just one of two studies finding a significant association between both outcome variables.(111) Reports of a positive association between individual PFS/TTP and OS outcomes in breast and non-small cell lung cancers also came from a single study for each cancer type.(111) Reviewed studies also lacked a standardized empirical approach that would otherwise make it easier to definitively claim the existence of an association between PFS/TTP and OS.(111) The authors conclude by arguing that studies making strong assumptions regarding the relationship between PFS and OS should therefore be "treated with caution."(111)

Bognar and colleagues (2017) cite growing discomfort among clinicians and payers over the impact from growing use of surrogate endpoints by regulators on the quality of evidence supporting the use of new medical technologies.(102) Surrogates are "imperfectly correlated with the final outcomes of interest" and "imperfectly predict clinical benefits," the authors charge.(102) They therefore provide "weaker evidence of the benefit value than … 'hard' or final outcome evidence."(102) With respect to clinical

practice, PFS may be correlated with survival in oncology, but it "might not [reflect] intrinsically valuable" benefits to patients.(102)

There is in fact a lack of consensus on whether PFS is indeed a "true measure of outcome due to treatment,"(112) and similar arguments may apply to other surrogate efficacy markers. While this may simply reflect limitations in the available evidence, it remains the case that consensus has not been reached on whether surrogate measures of efficacy, including PFS, are valid indicators of clinical benefit. This may be why the FDA states that surrogate efficacy endpoints are potentially "[predictive of] clinical benefit, but [are not themselves] a measure of clinical benefit".(108)

Second, while the use of surrogate endpoints has recently increased, they continue to be used as a primary endpoint in a minority of cancer drug evaluations.(113) Even if clinical efficacy is established through surrogate measures in accelerated approvals,(64) the FDA states that "overall survival should be evaluated in randomized controlled trials",(95) indicating that this parameter should be collected during the oncology drug development process. In contrast, FDA guidance documentation for industry does not explicitly recommend that manufacturers collect data on particular surrogate endpoints for all new cancer drugs.(95) Therefore, even if surrogate efficacy measures were indicative of objective clinical benefits, the non-systematic nature of their collection and evaluation during drug evaluations prevents researchers from using them to measure clinical benefits across multiple cancer drug approvals.

Quality of Life and Safety

Finally, regulators also often examine the impact from treatment on QoL and safety to evaluate the clinical risks and benefits from treatment.(114,115)

The FDA's enabling legislation—the Federal Food, Drug, and Cosmetic Act of 1938, and the Kefauver-Harris Amendments of 1962—requires that the agency evaluate both the safety and efficacy of new medical products in the Unites States.(114,116) In particular, for an oncology approval to occur, there must be "substantial evidence of efficacy from adequate and well-controlled trials," and drugs must also be "safe for their intended use."(114) These requirements have since been informally broadened to include considerations of QoL. Coordinating with internal experts from the Oncologic Drugs Advisory Committee, the FDA determined in the 1980s that cancer drug approvals should also be based on direct evidence of clinical benefits, which was defined in terms of improvements in survival, physical functioning, symptoms, as well as in QoL.(95) Though this is not codified, regular oncology approvals may therefore consider drug-related effects on QoL alongside OS and safety.

In other countries, HTA agencies—including England's NICE, France's HAS, and Australia's PBAC—may consider clinical efficacy, QoL and safety when evaluating new medicines prior to decision-making on coverage, pricing, and reimbursement.(117–119) One key distinction, however, is that FDA approvals do not require an evaluation of comparative benefits from treatment,(120) or late-stage clinical trial evidence under accelerated licensing procedures.(109) HTA agencies—including NICE, HAS, and the PBAC—may however require the submission of clinical evidence comparing the clinical

performance of new medicines with that of main therapeutic comparators, defined as the therapy that would most likely be replaced by the new intervention.(121–123)

Context and Empirical Gaps

As healthcare debates focus on the issue of rising drug costs, there is a growing need to systematically evaluate how new cancer medicines have impacted patient health. A handful of recent studies have started to address this gap by measuring the survival benefits associated with newly licensed cancer medicines.(46,73) However, this evidence should be evaluated alongside other clinical features that are known to impact the well-being of patients, including QoL and safety. Such an exercise is particularly timely given the recent emergence of evidence-based value frameworks for cancer that identify the outcome measures—efficacy, toxicity, and QoL—that matter to patients, and, when considered alongside convenience and cost, help patients define the value to them from new therapies.(12) The current lack of evidence on these outcome measures otherwise makes it difficult for the public to demand more from innovation,(92) and, where costs factor into the decision-making process, for clinicians and patients to balance personal preferences on the expected impact of treatment against rising drug costs.

Summary of Research

To shed light on the clinical risks and benefits from new cancer medicines, a narrative synthesis approach was taken within the context of a systematic review of health technology assessments. All NMEs approved by regulatory authorities in the US (FDA) and Europe (EMA) between 2003-2013 with a primary indication for oncology were considered. Since US licensing decisions do not require proof of comparative efficacy and

may not consider OS benefits under accelerated licensing procedures,(109,124) summary conclusions of drug-related effects on OS, QoL, and safety were extracted and analyzed from appraisals that had been published by leading HTA agencies in Australia (PBAC), England (NICE), and France (HAS). These countries were selected because they publish English-language HTA appraisals, and also have comparable economic conditions and pharmaceutical systems.(77)

This analysis finds that the magnitude of clinical benefits varies widely across all newly licensed cancer medicines and indications, improvements in OS and QoL often come at the cost of safety, and there are reasons to doubt whether clinical efficacy has been matched by effectiveness in real-world clinical settings. This study provides additional clarity on the potential risks and benefits of new cancer medicines, and therefore provides an additional resource for clinical decision-making by patients and physicians. It also raises questions about how clinical impact is measured by regulators as part of the drug review process, how the scientific evidence is used to inform clinical practice, and how much value is generated from cancer drug spending.

Methods

Sample Selection

The methods used by Roberts and colleagues (125) were adapted to this study to identify all initial cancer drug approvals by the US FDA and EU EMA occurring between 2003-2013. All NMEs approved by the FDA or EMA over this period with a primary indication for oncology were eligible for inclusion. Primary indication is defined within this context

as the first FDA- or EMA-approved indication for new NMEs (initial approvals).(125) EMA-approved indications were used only if an FDA approval was not available. Any molecule that did not receive licensure by either of the FDA or EMA between 2003-2013, and which did not have an initial, primary anticancer indication was therefore excluded. This analysis also focused on primary indications exclusively, which are likely to reflect their main intended use after initial licensure. Drugs that could be prescribed to cancer patients, but which were indicated for uses other than to actively treat the disease—e.g. to manage symptoms or side effects from active treatment—were excluded.

Initial approvals for oncology medicines that met these selection criteria and which were approved by the FDA between 2003-2010 were obtained from Roberts and colleagues,(125) while those that were approved by the FDA between 2011-2013 were identified through the FDA's annual lists of novel drug approvals and its Drugs@FDA registry.(126–129) EMA initial anti-cancer drug approvals occurring between 2003-2013 were identified by applying the above selection criteria to the EMA's EPAR search engine.(130) Of those medicines that were identified by Roberts and colleagues,(125) this analysis excluded plerixafor and palifermin—both are indicated for use in cancer patients, but they have no direct anticancer effect (Table 2). Medicinal inclusion was confirmed by an anonymous medical reviewer at the US FDA. A flow diagram depicting this process is provided in Figure 4.

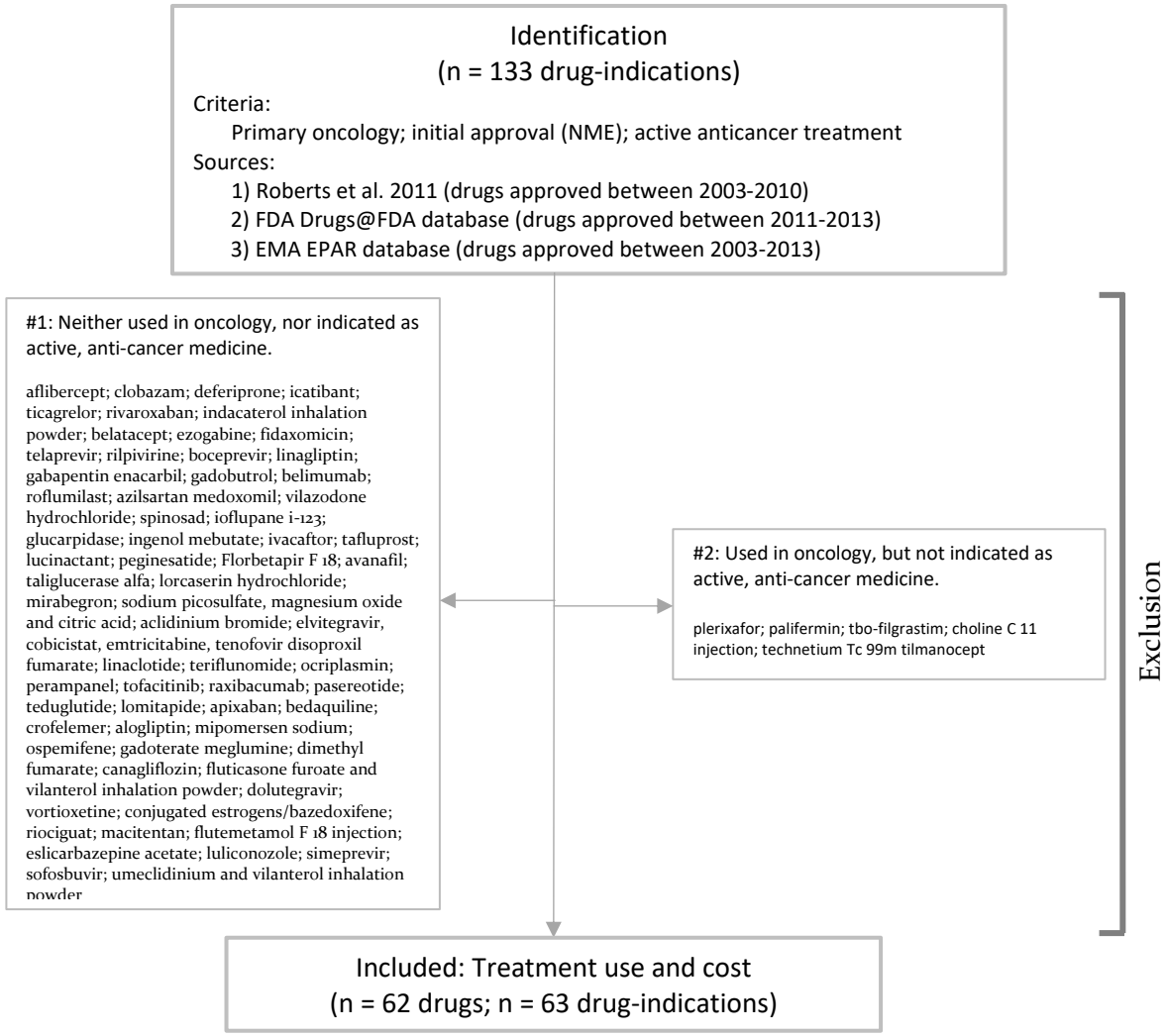
Table 2. Cancer Drug Exclusions

Drug Name	Reason for Exclusion	FDA 1° Indication – Initial Approval	Approval Date
plerixafor	**1° indication is not for anticancer therapy.**	**"Mozobil™, a hematopoietic stem cell mobilizer, is indicated in combination with granulocyte-colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma and multiple myeloma."**	**2008**
palifermin	**1° indication is not for anticancer therapy.**	**"Kepivance™ is indicated to decrease the incidence and duration of severe oral mucositis in patients with hemtologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support."**	**2004**

Source:

Authors' analysis of data, as described in Methods section.

Figure 4. Drug Sample Inclusion/Exclusion Criteria



Source:

Authors' analysis of data, as described in Methods section.

Technology Appraisals

This study based its analysis of the comparative clinical risks and benefits of new cancer medicines on regulatory summaries of the impact from new treatments, as reported in Australian, English, and French HTA agency appraisals. This approach was taken for three reasons:

First, it is often difficult to systematically assess the comparative harms and benefits of new cancer medicines based solely on FDA drug reviews. While the agency publishes an extensive amount of information in its medical, statistical, chemistry, pharmacology, microbiology, clinical pharmacology biopharmaceutics, risk assessment and risk mitigation reviews of new medicines, they are often published with non-rendered or scanned text. FDA reviews may also often be structured differently, which may make it difficult to systematically assess the clinical risks and benefits of new treatments. Finally, FDA reviews may sometimes be heavily redacted, even where non-economic information (e.g. comparative effectiveness and harms) is discussed (e.g. (131)).

Second, the FDA's enabling legislation—the Federal Food, Drug, and Cosmetic Act of 1938, and the Kefauver-Harris Amendments of 1962—requires that the agency evaluate the safety and efficacy of new medical products in the US.(114,116) New approvals are not required to prove comparative effectiveness, resulting in "relatively few serious attempts [at its] assessment".(120) However, under certain circumstances—for example, if it would ethically unacceptable to use placebo controls to seriously ill patients (132)—it may only be possible to prove efficacy and safety in relation to an active comparator. As a consequence, although many clinical trials submitted in support of a new drug

application include both active and placebo controls, the "FDA's experience with comparative effectiveness claims is relatively limited."(120)

Third, this approach helps eliminate any bias that could occur from the independent review and interpretation of the primary clinical evidence. There is no large-scale, patient-level registry that provides information on patient characteristics, treatment and outcomes before and after entry of new cancer medicines. There are indications that this may change in the near future with, for instance, the emergence of the US National Cancer Institute's National Cancer Knowledge System, a component of the US Precision Medicine Initiative® that will integrate genomic information with clinical response data and outcomes information. Future studies may be able to leverage data from this system to assess the real-world clinical impact from newly developed cancer medicines.

Nevertheless, since this information is not available today, this study used a systematic process to assess the expected clinical impact on therapy from recent cancer drug innovations. This involved reviewing and extracting trial-based HTA agency summary evaluations of new medicines. One alternative might have been to evaluate the primary clinical evidence directly. However, results from clinical trials may go unpublished,(133) and primary clinical trial data is often not available for secondary analysis by independent researchers.

HTA agencies, in contrast, may have the authority to require submission of all applicable clinical data, published and unpublished,(121,134,135) in theory minimizing the level of bias that could occur in their evaluations of treatment-related clinical risks and benefits.

By drawing from HTA agency evaluations, this study synthesizes regulatory evaluations of all relevant scientific evidence, and expert opinions regarding the expected clinical impact from new cancer medicines.

Fourth, even if access to all of primary scientific data were not an issue, it is unclear whether an independent evaluation of the drug-related clinical risks and benefits would consistently correspond with those of regulators and other public authorities. Regulatory conclusions of drug-related clinical benefits are often used to define value-based decision-making on issues such as drug coverage, pricing and reimbursement. For instance, assessments of the absolute (SMR) and comparative (ASMR) clinical benefit from France's HAS are used to determine whether to publicly reimburse for new health technologies (SMR), what the level of reimbursement should be (SMR), and in the pricing of new therapies (ASMR). Therefore, by relying on these sources of information rather independent evaluations of the primary evidence, subsequent chapters can test the value-based proposition that (12):

> "the cost of a given intervention [based on accepted pricing] … bears a relationship to the beneficial impact it has for patients who receive that treatment."

Finally, although OS has traditionally been taken as a universal marker of clinical efficacy in oncology drug trials, licensing approvals are increasingly based on surrogate measures.(136) This is reflected most prominently by the FDA's accelerated approval pathway for serious or life-threatening diseases, which is designed to help expedite drug

development and availability in cases where few alternative treatment options exist. To do so, accelerated approvals may be based on surrogate measures of efficacy from Phase II trials.(64) Surrogate efficacy markers can be measured sooner than OS,(137) may be used to justify reimbursement, and may be "reasonably likely" to predict longer-term clinical benefits in certain circumstances.(95,138)

Molecules that are approved under an accelerated procedure are nevertheless required to conduct post-marketing confirmatory clinical trials to verify the effect on IMM. As a result, the purpose of early phase clinical trials is often to "evaluate safety and identify evidence of biological drug activity, such as tumor shrinkage", while later phase, confirmatory efficacy studies may instead "evaluate whether a drug provides a clinical benefit such as prolongation of survival or an improvement in symptoms."(136) Reflecting this, Johnson and colleagues (2003) find that, unlike regular approvals, assessments of clinical effectiveness of oncology medicines approved under an accelerated pathway are often not based on OS benefits, but on surrogate measures, including objective response rates.(114)

Perhaps particularly where there is an outstanding medical need, it is therefore unlikely for FDA reviews underlying initial cancer drug approvals to systematically evaluate the full clinical impact of new cancer medicines. At the same time, high failure rates of Phase III clinical trials in oncology may indicate that Phase II clinical trials alone are insufficiently informative on the clinical effectiveness of new medicines,(139) at least in how they are currently designed.

Sources

Appraisals from English (NICE), French (HAS), and Australian (PBAC) HTA agencies published through May 2015 were therefore used to assess the clinical impact from cancer drug treatment. These organizations are required to evaluate the clinical risks and benefits of new medicines in relation to existing clinical standards that are used for the same indication,(121–123) and their assessments are often used in value-based decision-making on issues including coverage, pricing, and reimbursement.

Although new cancer drug molecules are often first approved in the US,(125) they often gain licensure in other settings. Any delay in market entry may make it more likely for evidence from confirmatory clinical trials to be incorporated into the evaluation by international HTA agencies. These agencies also operate within countries that are similar to the US in terms of their populations and degree of economic development, and they regularly publish comprehensive, and consistently structured, HTA reports in the English language.

From a clinical perspective, the available comparative evidence suggests that clinical practice guidelines for cancer treatment often coincide across developed healthcare settings.(140–142) At least within the case of metastatic breast cancer, this may reflect the notion that there are relatively few differences in individual and tumor characteristics across independently selected patients in industrialized nations.(143)

Where a HAS appraisal could not be found using the agency website's native search engine, an additional search was performed for HAS reports using an online search

engine (Google) that included the drug's active ingredient and "HAS Santé" (e.g. "Bortezomib HAS Santé"). In the few cases where French TAs were not available in English, the documents were translated. Discussions of drug costs were not considered in this chapter. EU orphan drug status were obtained for each FDA-approved cancer drug indication from www.orpha.net.

Selection Process

HTA appraisals were selected for review if they pertained to the same target condition (e.g. colorectal cancer) as of the first FDA-approved indication. If multiple reports evaluated the same target condition, this analysis selected the latest report that most closely matched the first FDA-approved indication with respect to any treatment restrictions (e.g. cancer staging). In ambiguous cases, determinations were made in consultation with a medical expert. If the FDA approved two indications in its first evaluation of a new cancer drug (e.g. sunitinib), appraisals for both primary indications were extracted. Initial EMA-approved indications were used if the drug had not been approved by the US FDA through May 2015.

Data Extraction

The patient, intervention, comparator, outcomes process was used as a structured approach to review technological appraisals and evaluate the clinical benefits from new interventions.(144) For this, information on recommended patient populations and novel interventions were extracted from each drug appraisal. Therapeutic comparators were also extracted alongside data pertaining to outcome measures. This approach was used

to systematically identify trial design parameters that could influence regulatory assessments of treatment-related clinical outcome measures.

Systematic Review with Narrative Synthesis

Two reviewers independently adopted the patient, intervention, comparator, outcomes process within the context of a systematic review with narrative synthesis of HTA assessments of the clinical impact from new cancer medicines. Two reviewers were needed to minimize any bias from the qualitative synthesis of HTA assessments. Summary HTA assessments of clinical impact were typically characterized by explicit value judgments of the supporting evidence or an acknowledgement of the significance of clinical trial results.[2] Accepted gains in OS were typically given as discrete, one-sided directional, or a range of values.[3] Manufacturer-submitted data was not considered unless it had been accepted by the HTA agency in its summary assessment. For an overview of narrative syntheses, and how the procedure was used in this study, please refer to Box 1.

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[2] For example, England's NICE accepted that sunitinib was associated with a more than 3-month increase in overall survival for its first-line RCC indication, specifically acknowledging an increase of 10 months according to the model that reflected the "Committee's preferred assumptions."

[3] England's NICE, for instance, determined that bevacizumab was associated with a 4.7-month increase in median OS compared to IFL (irinotecan, bolus 5-FU and leucovorin), but no significant difference in OS compared to 5-FU/LV.

Box 1. Overview of Review with Narrative Syntheses in Qualitative Research

Literature reviews represent a "systematic, explicit, comprehensive and reproducible method for identifying, evaluating, and interpreting the existing body of original work produced by researchers and scholars."(357) Within this context, narrative synthesis exists as a flexible analytical tool that can be used to synthesize and extract meaning from quantitative and qualitative evidence, and to "[aggregate] information into a new and unified whole".(358) There has traditionally been no 'codified' procedure for the narrative synthesis of qualitative evidence—there are a number of different approaches to narrative data synthesis.(359) Still, a general set of practices should be followed to ensure that the synthesis of data occurs through a rigorous and transparent manner. These general practices are reviewed here; further detail can be found elsewhere.(359) In addition, a brief methodological description is provided to explain the procedures that were used in this study to comply with these general practices.

- Develop a theory of how the intervention works, why and for whom.(359) This study reviewed the clinical endpoints that may be used in oncology drug trials, and collected PICO parameters.
- Conduct a preliminary synthesis of the studies that are included to inform the collection and synthesis of research findings.(359) Here, two researchers performed an initial review of technological appraisals to develop a coding system that could systematically and comprehensively synthesize HTA agency conclusions regarding drug-related effects on OS, QoL, and safety.
- Narrative data analyses should subsequently explore relationships in the data to consider the impact from heterogeneity in the studies that are used.(359) This study evaluates relationships in the evidence that is disseminated by HTA agencies, and it considers the impact from defining features of the drug assessment process.
- Finally, the research should assess the robustness of the synthesis, which is itself dependent on the amount and quality of the evidence and the methods used to synthesize the evidence.(359) This study pre-specified the process for reviewing evidence; it was carried out with a priori knowledge of the parameters that could be used by HTA agencies to evaluate OS, QoL, and safety benefits (Table 3); and internal validation was sought through a consensus-seeking procedure.

Information on recommended patient populations (treatment indications, usage restrictions), novel interventions [ATC code, therapeutic target], and therapeutic comparators were extracted from each drug appraisal, as were evaluations of the impact on OS, QoL, and safety from drug treatment. Table 3 provides an overview of the classes of evidence that may have been evaluated and reported by Australian, English, and French authorities to assess OS, QoL, and safety.

Table 3. Evidence Generally Reported by HTA Agencies to Evaluate Drug-Related Effects on Key Outcome Measures

Outcome Measure	Evidence
Overall Survival	Median OS,[1,2,3] mean OS, [1,3] survival probability (%),[2,3] OS (mean/median, NOS),[2,3] expectations of impact on mortality (NOS)[2]
Quality of Life	Symptom improvement, [1,2] time to change (deterioration/improvement) in functioning or symptoms,[1,2,3] QoL instruments,[1,2,3,4] impact on utility,[1] patient representative/clinical expert inputs,[1,2,5] expectations of impact on QoL (NOS)[1,2,3,6]
Safety	Incidence of AEs,[1,2,3,7] incidence of severe or serious AEs,[1,2,3,8] time to first AE (≥ grade III),[1] treatment discontinuation or dose reduction,[1,2,3] overall tolerance and safety profile (NOS),[1,2,3,9] treatment-related deaths,[1,2,3,10] patient representative/clinical expert inputs [1,2,3,11]

Notes:

[1] NICE

[2] HAS

[3] PBAC

[4] For example, FACT-An questionnaire, time without symptoms and toxicity (TwiST) and quality-adjusted survival and toxicity (Q-TwiST); SF12 v2, EQ-5D, EQ-5D-VAS; FACT-G; BPI-SF; FACT-Lym; FKSI-DRS index; FKSI-15 Index; FACT-P; QLQ-C30; QLQ-MY20; CTSQ; EORTC-QLQ; Karnofsky performance status; ECOG performance status; LCSS

[5] May include inputs on preference for oral/IV administration, amount of time in hospital, number of hospitalizations, meaningfulness of improvements in symptoms (e.g. fatigue, pain), and ability to perform daily activities

[6] Internal HTA agency opinion or expectation regarding aspects of clinical impact, not directly informed by the available evidence.

[7] Described as AEs (NOS), TEAEs without specification of serious grade, grade I/II AEs, AEs of mild to moderate intensity

[8] Described as SAEs, grade III/IV AEs, treatment-related syndromes (e.g. systemic inflammatory response syndrome)

[9] For example, discussion of overall tolerance and safety profile without reporting of primary evidence in assessment.

[10] Including grade V AEs.

[11] Examples of inputs from patients, patient representatives, or clinical experts included comments on patient willingness to accept side effects given benefits of treatment, and comparability of adverse reaction profiles.

A rules-based process was undertaken to evaluate evidence reported by HTA agencies. For this, the following were considered from HTA agencies: overall judgements of the available evidence on OS, QoL, and safety from summary sections; acknowledgement of the significance of clinical trial results; or referral to prior evaluations of the primary evidence. If these were absent, or if an HTA agency concluded that clinical benefits could not be assessed, corresponding extraction parameters were marked as missing. Disagreement on how to interpret HTA agency summaries of the clinical impact from treatment were resolved through consensus.

Defining features of each drug appraisal, including FDA approval date, first FDA-approved indication, FDA Accelerated Approval status, HTA appraisal date, type of supporting evidence, comparison type, EU orphan status, biologic status, and comparator, were also recorded. A clinical expert also used FDA-approved primary indications to classify all new cancer medicines by their therapeutic target. Across the entire sample, medicines were classified as being indicated for malignant ascites, soft tissue sarcoma, thyroid cancers, GI cancers, lung cancers, hematological malignancies, prostate cancers, skin cancers, renal cancers, and breast cancers.

The narrative synthesis approach was particularly useful for this study: though they may be consistently structured, appraisals are meant as critical evaluations by HTA agencies of the clinical and economic evidence. The evidence that is therefore discussed within appraisals can vary and may depend on what is submitted, the availability of quantitative or qualitative evidence, as well as its acceptability and pertinence to the review. This approach also captured key outcome measures that are regularly considered during formal drug reviews, and which are reflected in ASCO's recently published conceptual

framework for measuring the value of cancer treatment options.(12) An overview of the regulatory evidence used in this analysis is provided in Appendix 2.1.

Overall Survival

Both reviewers independently identified and extracted OS estimates for the first approved indication of each newly licensed cancer drug. To do so, this study considered summary judgments of the available evidence on OS, acknowledgment of the significance of clinical trial results, or referral to prior evaluations of the supporting evidence. An overview of the OS evidence that was considered by each HTA agency is given in Table 3. The second, independent reviewer assisted with data collection. I conceived and designed studies, acquired, analyzed, and interpreted data, and drafted this chapter, as well as the associated publication.

Quantitative measures of the drug-related impact on OS were also coded as a categorical variable. HTA documents, particularly those from NICE, take drug-related improvements in OS of greater than or less than 3 months over best alternative treatments (145) as an indicator of the likelihood of benefit. According to England's HTA agency, OS benefits of at least three months provide "sufficient evidence to indicate that the treatment offers an extension to life."(117) This approach also reflected the magnitude of OS benefits that are considered large enough by English authorities to justify additional expense in end-of-life care,(146) and used at times by Australian authorities to assess new health technologies.(147) In other instances, agencies may also conclude that drugs are associated with an unquantifiable increase, or no demonstrable improvement, in OS.

On this basis, drugs were classified as having a known OS benefit of ≥3 months if HTA agencies concluded that the drug was associated with a OS gain of ≥3 months (discrete value), or if one-sided directional or range estimates fell within this space. Other possible categories of OS benefits included: certain or uncertain increases of <3 months; an increase in survival, but of unknown magnitude; and no demonstrated increase in OS. After independent analysis, both researchers compared results and sought consensus if there was any disagreement in the extracted parameters. Inputs from a third researcher were sought if consensus could not be reached (this did not become necessary).

To conservatively measure the therapeutic potential of new treatments, a composite measure of drug-related OS benefits corresponding to the maximum possible OS benefit from treatment was developed by aggregating data from the HTA agency appraisals that were available for each medicine. To do this, a hierarchical process was followed: if only one HTA agency evaluated a given drug, its assessment of gains in OS was taken. If drug appraisals were available from multiple HTA agencies, the largest estimate of the drug-related survival benefit was taken to measure the clinical benefits that may be possible from treatment. If no difference in OS could be established by any of the three agencies, then the drug was taken to produce no measurable change in OS. Summary assessments of the clinical risks and benefits associated with new cancer medicines did not vary to any great extent across the three HTA agencies considered in this analysis (Appendix 2.1). This may in part reflect the finding that assessments were often based on the same set of comparators (Appendix 2.1).

Treatment standards can also change over time as new medicines enter the market. To calculate the total average increase in OS between 2003-2013, the following approach was taken: where cancer drugs were associated with a composite gain in OS that was given as a range—representing a range in the maximum OS benefit that was accepted by English, French, and Australian HTA agencies—the midpoint was taken. New cancer drugs were then mapped against the treatment comparators that they would replace, as identified by HTA assessments. For this, it was necessary for primary treatment indications to be consistent across the new intervention and the mapped comparator. Drug-specific gains in OS were then summed across the mapped comparators.

The following are two examples of how this process was carried out: subsequent to its approval by the FDA in 2004 for the treatment of malignant pleural mesothelioma, pemetrexed was used by French and Australian HTA agencies to evaluate the clinical effectiveness of crizotinib (approved by the FDA in 2011 for locally advanced or metastatic non-small cell lung cancer). While these two drugs were compared against each other, the first FDA-approved indication for each of these medicines was not identical. The FDA eventually granted pemetrexed a licensing extension in 2006 so that it could be used for the same indication as crizotinib, but this analysis did not consider non-primary indications in this study. Since pemetrexed and crizotinib therefore did not have an equivalent primary indication for use, their OS benefits were considered independently. In contrast, erlotinib was approved by the FDA in 2004 for patients with locally advanced or metastatic non-small cell lung cancer and evaluated against placebo and BSC. Afatinib was approved by the FDA in 2013 for the same clinical indication, and its clinical efficacy was compared against that of erlotinib and gefitinib by HTA agencies.

Since both afatinib and erlotinib were indicated for the same purpose, this analysis directly compared the OS benefits associated with each medicine.

This exercise allowed for the mapping of changing clinical standards as new drugs entered the market, and to therefore estimate the total gain OS between 2003-2013 within and across treatment indications. If a drug was approved by the FDA for two primary indications (sunitinib), the OS benefits associated with each indication was considered separately, since each pertained to different patient populations. Finally, average gains in OS were calculated by therapeutic target indications (malignant ascites, bladder, soft tissue, hematologicals, lung, GI, renal, breast, prostate, thyroid, skin).

Quality of Life

HTA summary evaluations of drug-related changes in QoL and safety were, in general, qualitative. Preliminary analysis revealed that, where discussed, HTA agency conclusions regarding QoL could be classified into four categories: an overall improvement or reduction in QoL, mixed evidence, or no established difference relative to best alternative treatments. A detailed description of the QoL-related evidence that was generally considered by each HTA agency is given in Table 3.

To classify the overall effect on QoL from each drug, two researchers independently highlighted and synthesized all text on drug-related effects on QoL that was published within appraisal summary sections. In the few instances where multiple primary indications were evaluated concomitantly by any one HTA agency (e.g. renal cell carcinoma and gastrointestinal stromal tumor), or if conclusions were based on multiple

comparators, both reviewers took the most positive estimate of drug-related changes in QoL. For example, if one evaluation found there to be an improvement in QoL, but a second found no change, both reviewers marked the drug as producing an improvement in patient QoL. If there were two opposing conclusions—e.g. if QoL improved for one primary indication, but worsened in another—then both reviewers marked the drug as producing mixed evidence. Given the potential implications for clinical practice, this approach was designed to capture the maximum clinical benefit to patients that may be possible from treatment with new cancer medicines. Both researchers then compared results and sought consensus where disagreement existed. Inputs from a third researcher were sought if consensus could not be reached.

A rules-based process was used to synthesize all available HTA agency assessments and generate a composite, qualitative rating of the impact on QoL from treatment with each drug-indication. If summary assessments from one HTA agency described an overall improvement in QoL, while another found no change, the drug was classified as being associated with improvements in QoL. If opposing interpretations of the available evidence existed—e.g. if one agency found an overall improvement in QoL, while another concluded that the drug-indication worsened QoL—the drug-indication was classified as being associated with mixed evidence. If no difference in QoL was established by any of the three agencies due to a lack or insufficiency of evidence, then the drug-indication was classified as having no established impact on QoL. For more information on the parameters typically used by HTA agencies to assess QoL, please refer to Table 3.

Safety

HTA agency summaries regarding the effect on safety from drug treatment were also extracted from appraisals and sythesized. Discussions of treatment effects on the incidence of individual types of adverse events were not considered, unless HTA agencies explicitly stated that these were of significant concern. Instead, HTA summary assessments of the overall impact on safety from drug treatment were typically based on a review of the following types of evidence: treatment effect on incidence of all AEs, incidence of serious AEs, adverse drug reactions, treatment-related AEs, treatment discontinuations or required dose reductions due to AEs (Table 3). While EMA EPARs or TGA assessments of safety could have also been used for this analysis, their interpretations of the data are less relevant for pricing and coverage decisions than HTA agency reviews. Both reviewers compared results after independent analysis and sought consensus if there was disagreement on how to interpret summary HTA agency evaluations of the impact from treatment on patient safety. Inputs from a third researcher were sought where consensus could not be reached.

A rules-based process was used to generate a composite, qualitative rating of the expected impact on patient safety from treatment with each drug-indication. This process followed the one that was described above to assess drug-related effects on QoL. Specifically, if summary assessments from one HTA agency described an overall improvement in safety, while another found no change, the drug was classified as being associated with improvements in safety. If opposing interpretations of the available evidence existed—e.g. if one agency found an overall improvement in safety, while another concluded that the drug-indication worsened patient safety (i.e. an overall increase in toxicity)—the drug-indication was classified as being associated with mixed

evidence. If no difference in safety was established by any of the three agencies due to a lack or insufficiency of evidence, then the drug-indication was classified as having no established impact on safety. For more information on the parameters typically used by HTA agencies to assess safety, please refer to Table 3.

Analysis

Overall Survival, Quality of Life, and Safety

Descriptive statistics were used to analyze the composite classifications of clinical benefits across the entire sample of recently approved cancer drugs. For more information on how composite classifications of clinical benefits were constructed, please refer to the previous section. Secondary analyses also examined the association between defining features of the supporting clinical trial evidence—as reported within HTA agency appraisals—and summary conclusions of drug-related clinical benefits.

Krippendorff's alpha coefficient (α) was used to assess interagency agreement of summary assessments of drug-related effects on OS, QoL and safety, and to inform the wider interpretation of results.(148) The α statistic was computed using the krippalpha package in Stata 13 (College Station, TX: StataCorp LP).(149) Composite measures of OS benefits were categorized as clinically significant gains of ≥3 months, marginal gains of <3 months, an increase in OS but of uncertain magnitude, and no increase. Composite measures of the impact on QoL and safety were also coded as improvement, mixed evidence, reduction, and no difference. Base case analyses calculated Krippendorff's alpha coefficient with rank-ordered data. To nevertheless check for robustness,

sensitivity analyses also modeled clinical benefits as nominal variables. A brief overview of this statistic is provided in Box 2, along with a justification of its use in this study.

Clinical Benefits from Treatment

Finally, descriptive statistics were used to summarize composite measures of the impact on OS, QoL, and safety associated with all medicines that were considered in this analysis. Drugs were considered to be associated with at least some evidence of an improvement in OS if their composite classification of the impact on OS was: an increase of ≥3 months, <3 months, or an unquantifiable increase. Drugs were considered to be associated with at least some evidence of an improvement in QoL or safety if their composite classification of the impact on QoL or safety was: improvement in QoL or safety, or mixed evidence.

Box 2. Overview of Krippendorf's Alpha Coefficient to Measure Interrater Agreement

IRA is defined as "the extent to which different raters assign the same precise value for each item being rated."(360) Several measures exist to measure IRA, including Cohen's unweighted kappa, weighted kappa, Fleiss' kappa, Krippendorff's alpha, Kendall's W, and intraclass correlation coefficients.(360) Which statistic is used to measure IRA should reflect the nature of the data that is being evaluated. Specifically, selection of an IRA measure should be based on the purpose of the analysis, the importance of the absolute value or trend in ratings, the type of variable that is being analyzed, and the number of raters involved.(360) Some may only be appropriate for use when there are 2 raters (k = 2; Cohen's unweighted kappa, weighted kappa), while others can be used in analyses that include a larger number of raters (e.g. Fleiss' kappa, Krippendorff's alpha, Kendall's W, intraclass correlation coefficients). Measurement scales should also factor into the selection of an IRA statistic: some indices—such as Cohen's unweighted kappa, Fleiss' kappa—should only be used when working with nominal, non-ordered data, while more flexible alternatives—including the unweighted kappa and Krippendorff's alpha—can also accommodate ordinal data. Kendall's W can be used with ordinal data, while intraclass correlations can be used when observations exist on an interval/ratio scale.

Krippendorff's alpha has several features that make it particularly useful for this analysis. First, it is a generalization of several known reliability indices.(361) It can be applied to contexts that have any number of observers—useful here, as this analysis evaluates data from three HTA agencies—any number of categories or measures—each of the measures of clinical benefit includes four categories—any metric or level of measurement—including, nominal, ordinal, interval, ratio—settings that have incomplete or missing data—useful in this analysis since clinical effectiveness may not have been evaluated for each drug by all three HTA agencies—and for large and small samples. (361) Krippendorff's alpha was therefore chosen to measure agreement between categorical measures of the overall survival, quality of life, and safety benefit assigned to each drug on the basis of English, French, and Australian HTA appraisals.(361)

Krippendorff (2004) provides both an in-depth discussion on the logic behind Krippendorff's alpha, as well as details on how to calculate the statistic—an overview of this publication is provided below.(361) Briefly, Krippendorff's alpha in general form is given as:

$$\alpha = 1 - \frac{D_o}{D_e}$$

Where D_o represents the observed disagreement among raters for values assigned to units of analysis u:

$$D_o = \frac{1}{n}\sum_c \sum_k o_{ck\,metric}\delta^2_{ck}$$

$o_{ck\,metric}$ represents the frequency of observed coincidences within units of analysis for values c and k, as tabulated in reliability data matrices, and δ^2_{ck} is a difference function (representing the squared difference between coinciding values) that serves to weight observed and expected coincidences and to therefore account for different metrics or levels of measurement.D_e represents the disagreement that would be expected when values are assigned to units by chance, rather than unit properties:

$$D_e = \frac{1}{n(n-1)}\sum_c \sum_k n_c \times n_{k\,metric}\delta^2_{ck}$$

To interpret his coefficient, Krippendorff indicates that it is "customary to require α ≥ .800. Where tentative conclusions are still acceptable, α≥ .667 is the lowest conceivable limit".(362)

Limitations

Surrogate measures of efficacy were not considered in this analysis. This approach was taken to reflect the fact that surrogate efficacy measures: are not consistently weighed during regulatory evaluations;(95) may be subject to assessment bias or variability from

measurement of radiologic or clinical measures and assessment schedules;(96,97) should not be used to assess efficacy within value studies if OS is reported;(12) have been inconsistently associated with objective measures of clinical benefit in the literature, with reported associations between OS and PFS varying considerably by cancer type, and even within cancer types;(111) and since their predictive value in measuring clinical outcomes remains debated.(111) Indeed, Bognar and colleagues (2017) take this to argue that surrogates "imperfectly predict clinical benefits," and therefore offer "weaker evidence of benefit than … 'hard' or final outcome evidence."(102) Even if they did, *surrogacy* implies that these measures proxy for the efficacy measure that is considered in this analysis, OS.

This approach was also designed to reflect guidance to healthcare professionals on the use of surrogate efficacy measures, ongoing clinical discussions related to their use, as well as guidance from ASCO on measuring the value of new cancer treatments. The FDA states that while surrogate markers of efficacy may be predictive of clinical benefits, they are "not themselves a measure of clinical benefit".(108) For their part, Bognar and colleagues (2017) report growing discomfort among clinicians and payers over the impact from growing use of surrogate endpoints by regulators on the quality of evidence supporting the use of new medical technologies.(102) Moreover, ASCO's recently published Value Framework for cancer treatment options recommends that efficacy benefits be measured through two surrogate efficacy endpoints—PFS and RRs—only if OS is not reported.(12)

Within this backdrop, this analysis assessed clinical efficacy benefits by reviewing regulatory assessments of drug-related effects on OS, an unambiguous marker of clinical

efficacy in oncology drug trials.(64,93,94) If, however, surrogate markers of clinical efficacy do in fact represent unique dimensions to the clinical benefit from new treatments, then their absence would mean that this analysis is incomplete. Further studies may wish to extend this analysis to include surrogate efficacy markers, particularly as consensus is reached on how well they reflect objective clinical benefits to patients.

The clinical impact of prescribed treatments may vary across cancer stages. This study reviewed HTA reports to assess the clinical risks and benefits from the use of new medicines that corresponded to the first approved indication, which often includes a recommended stage for use. The approved indication for new cancer medicines typically pertained to advanced or metastatic disease, with the exception of hematologicals (Appendix 2.1). Due to an insufficient sample, this study therefore did not assess whether there is an association between OS benefits and disease staging. Practically-speaking, real-world clinical practice may also employ new therapies outside of their recommended indication. In the absence of internationally comparable data on actual, patient-level drug consumption,(75) this study is unable to explore the impact from preferences and timing for treatment across cancer stages. Future studies should nevertheless leverage real-world data to evaluate whether and to what extent value assessments are affected by disease staging.

This analysis examines the clinical risks and benefits associated with new cancer medicines by reviewing HTA agency appraisal summaries of the scientific evidence. To provide an estimate of the clinical impact that would be expected in practice, HTA agencies synthesize and evaluate the published and unpublished clinical trial evidence

and report their conclusions in appraisals. Still, trial-based summary assessments of clinical impact do not always translate to the real-world, and may not adequately reflect the clinical risks and benefits to individual patients. To more precisely measure the clinical risks and benefits from treatment, future studies should extend this analysis by also incorporating post-marketing studies,(150) or using observational data or pragmatic clinical trial evidence, as it becomes available. Future academic initiatives may be able to leverage data from the National Cancer Institute's upcoming National Cancer Knowledge System—a component of the US Precision Medicine Initiative® that will integrate genomic information with clinical response data and outcomes information—to assess the real-world clinical impact from newly developed cancer drugs. Such analyses may help further inform value-based decision-making on cancer drug use, coverage, pricing, and reimbursement.

On this point, there is no known large-scale, international, patient-level registry on cancer treatment and outcomes occurring prior to and following entry of new cancer medicines. In its absence, this study undertook a systematic process to review regulatory assessments and to examine the impact on therapy that would be expected from recent cancer drug innovations. Results from clinical trials may go unpublished, and primary clinical trial data is often not available for secondary analysis. HTA agencies, in contrast, may have the authority to require submission of all applicable clinical data, published and unpublished,(151) in theory minimizing the level of bias in their assessment. By drawing on these, and in the absence of observational data, this synthesis reflects the frontier of regulatory thinking on the clinical risks and benefits from new cancer drug treatments.

Finally, this study focused on the first FDA- or EMA-approved anticancer indication for NMEs. Following initial approval, medicines may receive licensing extensions for other indications. This thesis did not consider the survival benefits associated with secondary indications. This approach was consistent with the available literature: the benefits associated with these indications may be unknown to manufacturers at the time of market launch, and are therefore unknown to regulators and HTA authorities, making them difficult to incorporate into intial pricing decisions.(73) This however does not bias the analyses that are carried out in this thesis, since it focuses on drug-indications pertaining to initial approvals. Future studies should however incorporate clinical and economic data pertaining to secondary licensures to assess the value from spending on these indications.

Results

A total of 62 new active molecules were approved by the FDA or EMA between 2003-2013 with a primary anticancer indication. Molecule descriptors for each of these medicines—including name of active ingredient, FDA/EMA licensure status, primary FDA or EMA indication, date of initial approval, ATC code, orphan status, and clinical target—are provided in Table 4.

Table 4. Sample of Cancer Medicines

Active Ingredient	Licensure	FDA or EMA Primary Indication[1]	Initial Approval[2]	ATC Code	Orphan Status	Target Organ
abiraterone acetate	FDA / EMA	A CYP17 inhibitor indicated for use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel.	Apr-11	L02BX03	-	Prostate
afatinib	FDA / EMA	A kinase inhibitor indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.	Jul-13	L01XE13	-	Lung
asparaginase E. chrysanthemi	FDA	An asparagine specific enzyme indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to E. coli-derived asparaginase.	Apr-11	L01XX02	EU	Hemat.
axitinib	FDA / EMA	A kinase inhibitor indicated for the treatment of advanced renal cell carcinoma after failure of one prior systemic therapy.	Jan-12	L01XE17	EU (w)	Renal
azacitidine	FDA / EMA	Indicated for treatment of patients with the following myelodysplastic syndrome subtypes: refractory anemia or refractory anemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia.	May-04	L01BC07	US / EU	Hemat.
bendamustine	FDA / EMA	An alkylating drug indicated for the treatment of patients with chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established.	Oct-08	L01AA09	US	Hemat.
bevacizumab	FDA / EMA	In combination with intravenous 5-fluorouracil–based chemotherapy, indicated for first- line treatment of patients with metastatic carcinoma of the colon or rectum.	Feb-04	L01XC07	-	GI
bortezomib	FDA / EMA	Indicated for the treatment of multiple myeloma patients who have received at least two prior therapies and have demonstrated disease progression on the last therapy. The effectiveness of VELCADE is based on response rates (see CLINICAL STUDIES section). There are no controlled trials demonstrating a clinical benefit, such as an improvement in survival.	May-03	L01XX32	US	Hemat.
bosutinib	FDA / EMA	A kinase inhibitor indicated for the treatment of adult patients with chronic, accelerated, or blast phase Ph+ chronic myelogenous leukemia (CML) with resistance or intolerance to prior therapy.	Sep-12	L01XE14	US / EU	Hemat.
brentuximab vedotin	FDA / EMA	A CD30-directed antibody-drug conjugate indicated for: a) The treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates. b) The	Aug-11	L01XC12	US / EU	Hemat.

		treatment of patients with systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen. These indications are based on response rate.				
cabazitaxel	FDA / EMA	A microtubule inhibitor indicated in combination with prednisone for treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen.	Jun-10	L01CD04	-	Prostate
cabozantinib	FDA / EMA	A kinase inhibitor indicated for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC).	Nov-12	L01XE26	US	Thyroid
carfilzomib	FDA / EMA	A proteasome inhibitor indicated for the treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate.	Jul-12	L01XX45	US / EU	Hemat.
catumaxomab	EMA	Indicated for the intraperitoneal treatment of malignant ascites in adults with EpCAM-positive carcinomas where standard therapy is not available or no longer feasible.	Apr-09	L01XC09	US / EU	Ascites
cetuximab	FDA / EMA	Used in combination with irinotecan for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy. // cetuximab administered as a single agent is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy.	Feb-04	L01XC06	-	GI
clofarabine	FDA / EMA	Treatment of pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens. This use is based on the induction of complete responses. Randomized trials demonstrating increased survival or other clinical benefit have not been conducted.	Dec-04	L01BB06	US / EU	Hemat.
crizotinib	FDA / EMA	A kinase inhibitor indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test. This indication is based on response rate.	Aug-11	L01XE16	-	Lung
dabrafenib	FDA / EMA	A kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.	May-13	L01XE23	-	Skin
dasatinib	FDA / EMA	Indicated for the treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib. // dasatinib is also indicated for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia with resistance or intolerance to prior therapy.	Jun-06	L01XE06	US / EU	Hemat.
decitabine	FDA / EMA	Indicated for treatment of patients with myelodysplastic syndromes (MDS) including previously treated and untreated, de novo and secondary MDS of	May-06	L01BC08	US / EU	Hemat.

		all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.				
degarelix	FDA / EMA	A GnRH receptor antagonist indicated for treatment of patients with advanced prostate cancer.	Dec-08	L02BX02	-	Prostate
enzalutamide	FDA / EMA	An androgen receptor inhibitor indicated for the treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel.	Aug-12	L02BB04	-	Prostate
eribulin	FDA / EMA	A microtubule inhibitor indicated for the treatment of patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting.	Nov-10	L01XX41	-	Breast
erlotinib	FDA / EMA	Indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen.	Nov-04	L01XE03	-	Lung
everolimus	FDA / EMA	A kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.	Mar-09	L01XE10	EU (w)	Renal
gefitinib	FDA / EMA	Indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutation of EGFR-TK.	May-03	L01XE02	-	Lung
ibrutinib	FDA / EMA	A kinase inhibitor indicated for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. This indication is based on overall response rate.	Nov-13	L01XE27	US / EU	Hemat.
ipilimumab	FDA / EMA	A human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody indicated for the treatment of unresectable or metastatic melanoma.	Mar-11	L01XC11	-	Skin
ixabepilone	FDA	A microtubule inhibitor, in combination with capecitabine is indicated for the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline and a taxane. // ixabepilone as monotherapy is indicated for the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline, a taxane, and capecitabine.	Oct-07	L01DC04	-	Breast
lapatinib	FDA / EMA	A kinase inhibitor, indicated in combination with capecitabine, for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.	Mar-07	L01XE07	-	Breast
lenalidomide	FDA / EMA	Indicated for the treatment of patients with transfusion-dependent anemia due to Low- or Intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.	Dec-05	L04AX04	US / EU	Hemat.

nelarabine	FDA / EMA	Indicated for the treatment of patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens. This use is based on the induction of complete responses. Randomized trials demonstrating increased survival or other clinical benefit have not been conducted.	Oct-05	L01BB07	US / EU	Hemat.
nilotinib	FDA / EMA	A kinase inhibitor indicated for the treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia (CML) in adult patients resistant to or intolerant to prior therapy that included imatinib.	Oct-07	L01XE08	US / EU	Hemat.
obinutuzumab	FDA / EMA	A CD20-directed cytolytic antibody and is indicated, in combination with chlorambucil, for the treatment of patients with previously untreated chronic lymphocytic leukemia.	Nov-13	L01XC15	US / EU	Hemat.
ofatumumab	FDA / EMA	A CD20-directed cytolytic monoclonal antibody indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab. The effectiveness of ofatumumab is based on the demonstration of durable objective responses.	Oct-09	L01XC10	US / EU	Hemat.
omacetaxine mepesuccinate	FDA / EMA	Indicated for the treatment of adult patients with chronic or accelerated phase chronic myeloid leukemia (CML) with resistance and/or intolerance to two or more tyrosine kinase inhibitors (TKI). This indication is based upon response rate.	Oct-12	L01XX40	US	Hemat.
panitumumab	FDA / EMA	Indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.	Sep-06	L01XC08	-	GI
pazopanib	FDA / EMA	A kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma.	Oct-09	L01XE11	EU (w)	Renal
pemetrexed	FDA / EMA	In combination with cisplatin is indicated for the treatment of patients with malignant pleural mesothelioma whose disease is either unresectable or who are otherwise not candidates for curative surgery.	Feb-04	L01BA04	US / EU (w)	Lung
pertuzumab	FDA / EMA	A HER2/neu receptor antagonist indicated in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.	Jun-12	L01XC13	-	Breast
pomalidomide	FDA / EMA	A thalidomide analogue indicated for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate.	Feb-13	L04AX06	US / EU	Hemat.
ponatinib	FDA / EMA	A kinase inhibitor indicated for the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) that is resistant or intolerant to prior tyrosine kinase inhibitor therapy or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL)	Dec-12	L01XE24	EU	Hemat.

		that is resistant or intolerant to prior tyrosine kinase inhibitor therapy. This indication is based upon response rate.				
pralatrexate	FDA / EMA	A folate analogue metabolic inhibitor indicated for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). This indication is based on overall response rate.	Sep-09	L01BA05	EU	Hemat.
radium Ra 223 dichloride	FDA / EMA	An alpha particle-emitting radioactive therapeutic agent indicated for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease.	May-13	V10XX03	-	Prostate
regorafenib	FDA / EMA	A kinase inhibitor indicated for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.	Sep-12	L01XE21	-	GI
romidepsin	FDA / EMA	A histone deacetylase (HDAC) inhibitor indicated for: Treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy.	Nov-09	L01XX39	US / EU	Hemat.
ruxolitinib	FDA / EMA	A kinase inhibitor indicated for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.	Nov-11	L01XE18	US / EU (w)	Hemat.
sipuleucel-T	FDA / EMA	An autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.	Apr-10	L03AX17	-	Prostate
sorafenib	FDA / EMA	Indicated for the treatment of patients with advanced renal cell carcinoma.	Dec-05	L01XE05	US / EU	Renal
sunitinib	FDA / EMA	Indicated for the treatment of gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate. // sunitinib is indicated for the treatment of advanced renal cell carcinoma. Approval for advanced renal cell carcinoma is based on partial response rates and duration of responses. There are no randomized trials of sunitinib demonstrating clinical benefit such as increased survival or improvement in disease-related symptoms in renal cell carcinoma.	Jan-06	L01XE04	EU	Renal
tegafur / gimeracil / oteracil	EMA	Indicated in adults for the treatment of advanced gastric cancer when given in combination with cisplatin.	Mar-11	L01BC53	EU (w)	GI
temsirolimus	FDA / EMA	A kinase inhibitor indicated for the treatment of advanced renal cell carcinoma.	May-07	L01XE09	US / EU	Renal
tositumomab	FDA / EMA	Indicated for the treatment of patients with CD20 positive, follicular, non-Hodgkin's lymphoma, with and without transformation, whose disease is refractory to Rituximab and has relapsed following chemotherapy.	Jun-03	V10XA53	US / EU (w)	Hemat.
trabectedin	EMA	Indicated for the treatment of adult patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents.	Sept-07	L01CX01	-	Soft Tissue

trametinib	FDA / EMA	A kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.	May-13	L01XE25	-	Skin
trastuzumab emtansine	FDA / EMA	HER2-targeted antibody and microtubule inhibitor conjugate indicated, as a single agent, for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: a) Received prior therapy for metastatic disease, or b) Developed disease recurrence during or within six months of completing adjuvant therapy.	Feb-13	L01XC14	-	Breast
vandetanib	FDA / EMA	A kinase inhibitor indicated for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease.	Apr-11	L01XE12	US / EU (w)	Thyroid
vemurafenib	FDA / EMA	A kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAFV600E mutation as detected by an FDA-approved test.	Aug-11	L01XE15	-	Skin
vinflunine	EMA	Indicated in monotherapy for the treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen.	Sept-09	L01CA05	-	Bladder
vismodegib	FDA / EMA	A hedgehog pathway inhibitor indicated for the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation.	Jan-12	L01XX43	-	Skin
vorinostat	FDA / EMA	A histone deacetylase (HDAC) inhibitor indicated for: treatment of cutaneous manifestations in patients with cutaneous T- cell lymphoma (CTCL) who have progressive, persistent or recurrent disease on or following two systemic therapies.	Oct-06	L01XX38	US	Hemat.
ziv-aflibercept	FDA / EMA	In combination with 5-fluorouracil, leucovorin, irinotecan- (FOLFIRI), indicated for patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen.	Aug-12	L01XX44	-	GI

Source:

Authors' analysis of data, as described in Methods section.

Notes:

[1] EMA indication given if FDA had not issued marketing license through end of study period.

[2] Date of initial approval given for the EMA only if FDA had not issued marketing license through end of study period.

The number of new cancer molecules receiving licensure per year in the US slowed between 2006-2009, but has more recently increased (Table 4). Of the 62 initial FDA or EMA approvals with a primary anticancer indication, the largest share (n = 24, 39%) were indicated for treatment of hematological malignancies. Representation across the remaining indications was fairly evenly distributed: 1 of the 62 new cancer molecules (2%) was indicated to treat malignant ascites; 1 (2%) was indicated to treat bladder cancer; 5 (8%) for breast cancer; 6 (10%) for gastrointestinal cancer; 1 (2%) for both gastro-intestinal and renal cancers (two primary anticancer indications); 5 (8%) for lung cancer; 6 (10%) for prostate cancer; 5 (8%) for renal cancer; 5 (8%) for skin cancer; 1 (2%) for soft tissue sarcomas; and 2 (3%) for thyroid cancer. There were no initial drug approvals for a variety of other cancer types, including cervical, bladder, and nervous system cancer.

Of the 62 new active cancer medicines approved by the FDA or EMA between 2003-2013, 35 (56%) have an active or withdrawn orphan designation. The proportion of newly licensed cancer medicines receiving orphan designation has remained fairly stable over time (Table 4). A majority of orphan medicines (24/35, or 69%) were indicated for hematological malignancies. A far smaller proportion were indicated for renal cancer (6/35, or 17%), thyroid cancer (2/35, or 6%), ascites (1/35, or 3%), GI cancer (1/35, or 3%), and lung cancer (1/35, or 3%). Of the 58 new active cancer molecules approved by the FDA between 2003-2013, 17 were approved under the Accelerated Approvals program.

4 of the 62 molecules were approved by the EMA but not the FDA through May 2015. Of the 62 drugs, 52 (85%) were assessed for OS by at least 1 of the 3 HTA agencies that were

considered in this study, Australia's PBAC, France's HAS, or England's NICE. The remaining 9 molecules may have had evaluations published after May 2015; may not have been reviewed by HTA agencies if considered low-priority therapies;(152) or may have been rejected by European (EMA) or national licensing authorities. Of the 53 drugs that were therefore included in this study, 35 were assessed by all 3 agencies, 7 were assessed by 2, and 11 were assessed by 1 HTA agency. In most cases HTA agency assessments were based on the same set of comparators (Appendix 2.1).

Clinical Benefits

A summary of the composite, drug-related effects on OS, QoL, and safety is provided in Table 5.

Table 5. Therapeutic Profile of All Cancer Medicines Approved by the FDA or EMA between 2003-2013 for a Primary Anti-cancer Indication

Active ingredient	FDA- or EMA-approved indication[2]	Appraisal dates	Comparator(s)	OS effect (months)[3]	QoL effect	Safety effect
Ascites						
catumaxomab	Ascites (EMA)	Dec-09	paracentesis	NE	NE	NE
Bladder						
vinflunine	Carcinoma of the urothelial tract (EMA)	Dec-09–Jan-13	BSC	Exact magnitude uncertain	NE	Reduction
Breast						
trastuzumab emtansine	Breast cancer	Mar-14–Nov-14	lapatinib + capecitabine	≥ 3 (5.8)	Improvement	Mixed evidence
eribulin	Breast cancer	Jul-11–Nov-13	TPC	< 3 (2.5–2.7)	NE	Reduction
ixabepilone	Breast cancer	n/a	n/a	n/a	n/a	n/a
lapatinib	Breast cancer	Nov-07–May-10	capecitabine monotherapy	< 3 (0.3–2.4)	NE	Reduction
pertuzumab	Breast cancer	Jul-13–Mar-14	trastuzumab + docetaxel	≥ 3 (15.7)	Improvement	Reduction
Gastro-intestinal						
bevacizumab	Colorectal carcinoma	Jun-05–Jul-08	IFL/5-FU/LV	≥ 3 (3.0–4.7)	NE	Reduction
cetuximab	Colorectal carcinoma	Mar-05–Mar-09	BSC	Exact magnitude uncertain	NE	Reduction
panitumumab	Colorectal carcinoma	Apr-08–Nov-13	BSC/cetuximab (safety)	≥ 3 (2.7–3.2)	NE	NE
regorafenib	Colorectal cancer	May-14–Jul-14	placebo	< 3 (1.4)	NE	Reduction
tegafur/gimeracil/oteracil	Gastric cancer (EMA)	Oct-12–Mar-13	5-FU/cisplatin	NE	NE	NE
ziv-aflibercept	Colorectal cancer	Jul-13–Mar-14	placebo	< 3 (1.4)	Improvement	Reduction
Gastro-intestinal/Renal						
sunitinib	Gastrointestinal stromal tumor / Renal cell carcinoma	Sep-06–Sep-09 / May-07–Mar-09	BSC/interferon-alfa	≥ 3 (7.8) / ≥ 3 (10.0)	Improvement	Reduction
Hematological						
asparaginase E. chrysanthemi	Acute lymphoblastic leukemia	n/a	n/a	n/a	n/a	n/a
azacitidine	Myelodysplastic syndromes	Jul-09–Mar-11	conventional care	≥ 3 (9.4–9.6)	Improvement	Reduction
bendamustine	Lymphocytic leukemia	Oct-10–Feb-11	chlorambucil	NE	Reduction	Reduction
bortezomib	Multiple myeloma	Oct-04–Oct-07	high-dose dexamethasone	≥ 3 (6.1–11.5)	Improvement	Mixed evidence
bosutinib	Chronic myelogenous leukemia	Nov-13–Feb-14	BSC	≥ 3 (exact gain uncertain)	NE	Improvement
brentuximab vedotin	Hodgkin lymphoma / Systemic lymphoma	Mar-13–Mar-14	multi-agent salvage chemotherapy	Exact magnitude uncertain	NE	Mixed evidence
carfilzomib	Multiple myeloma	n/a	n/a	n/a	n/a	n/a

clofarabine	Acute lymphoblastic leukemia	Dec-06	non-comparative	NE	NE	NE
dasatinib	Chronic myeloid leukemia // Acute lymphoblastic leukemia	Mar-07–Jan-12	non-comparative	NE	NE	Mixed evidence
decitabine	Myelodysplastic syndromes	n/a	n/a	n/a	n/a	n/a
ibrutinib	Mantle cell lymphoma	n/a	n/a	n/a	n/a	n/a
lenalidomide	Transfusion-dependent anemia due to myelodysplastic syndromes	Mar-13–Nov-14	placebo	Exact magnitude uncertain	Improvement	Reduction
nelarabine	Acute lymphoblastic leukemia / Lymphoblastic lymphoma	Dec-07	non-comparative	NE	NE	NE
nilotinib	Chronic myelogenous leukemia	Feb-08–Jan-12	non-comparative	NE	NE	Improvement
obinutuzumab	Chronic lymphocytic leukemia	Jul-14–Mar-15	chlorambucil	Exact magnitude uncertain	Mixed evidence	Mixed evidence
ofatumumab	Chronic lymphocytic leukemia	Oct-10–Nov-14	chlorambucil	NE	NE	NE
omacetaxine mepesuccinate	Chronic myeloid leukemia	n/a	n/a	n/a	n/a	n/a
pomalidomide	Multiple myeloma	Jan-14–Mar-15	standard care / high-dose dexamethasone (safety)	≥ 3 (exact gain uncertain)	Improvement	Reduction
ponatinib	Chronic myeloid leukemia / Acute lymphoblastic leukemia	Nov-14–Jan-15	dasatinib/nilotinib	NE	NE	Reduction
pralatrexate	Peripheral lymphoma	n/a	n/a	n/a	n/a	n/a
romidepsin	Cutaneous lymphoma	n/a	n/a	n/a	n/a	n/a
ruxolitinib	Myelofibrosis	Jan-13–Jul-13	BSC	Exact magnitude uncertain	Improvement	Reduction
tositumomab	Non-Hodgkin's lymphoma	n/a	n/a	n/a	n/a	n/a
vorinostat	Cutaneous lymphoma	Mar-11	BSC	NE	NE	Mixed evidence
Lung						
afatinib	Non-small cell lung cancer	Jul-13–Apr-14	erlotinib/gefitinib	NE	Improvement	Reduction
crizotinib	Non-small cell lung cancer	Sep-13–Nov-14	pemetrexed	≥ 3 (3.1–3.5)	Improvement	NE
erlotinib	Non-small cell lung cancer	Mar-06–Nov-08	placebo/BSC	< 3 (2.0)	Improvement	Mixed evidence
gefitinib	Non-small cell lung cancer	Nov-09–Jul-13	paclitaxel + carboplatin	NE	Improvement	Improvement
pemetrexed	Pleural mesothelioma	Mar-05–Jan-08	cisplatin	≥ 3 (2.8–3.3)	Improvement	Reduction
Prostate						
abiraterone acetate	Prostate cancer	Feb-12–Jul-12	BSC (prednisolone)	≥ 3 (3.9–4.6)	Improvement	Improvement
cabazitaxel	Prostate cancer	Nov-11–Oct-12	mitoxantrone	≥ 3 (2.4–4.2)	NE	Reduction
degarelix	Prostate cancer	Sep-09–Apr-14	leuproprelin + LHRH agonists	NE	NE	Reduction
enzalutamide	Prostate cancer	Nov-13–Jul-14	placebo	≥ 3 (4.5–4.8)	Improvement	Mixed evidence
radium-223 dichloride	Prostate cancer	Apr-14	placebo	< 3 (2.8)	NE	NE
sipuleucel-T	Prostate cancer	Feb-15	BSC	≥ 3 (4.0)	Improvement	Improvement

Renal						
axitinib	**Renal cell carcinoma**	**Jan-13–Feb-15**	**BSC**	**≥ 3 (exact gain uncertain)**	**NE**	**Mixed evidence**
everolimus	**Renal cell carcinoma**	**Nov-09–Apr-11**	**BSC**	**≥ 3 (5.2)**	**Improvement**	**Reduction**
pazopanib	**Advanced renal cell carcinoma**	**Feb-11–Jun-13**	**BSC/interferon-alfa**	**≥ 3 (exact gain uncertain)**	**NE**	**Mixed evidence**
sorafenib	**Renal cell carcinoma**	**Sep-06–Aug-09**	**BSC**	**≥ 3 (exact gain uncertain)**	**Improvement**	**Reduction**
temsirolimus	**Renal cell carcinoma**	**Feb-08–Aug-09**	**interferon-alfa**	**≥ 3 (3.6)**	**Improvement**	**Improvement**
Skin						
dabrafenib	**Melanoma**	**Oct-14**	**dacarbazine/vemurafenib (safety)**	**Exact magnitude uncertain**	**Reduction**	**Improvement**
ipilimumab	**Melanoma**	**Nov-12–Nov-14**	**dacarbazine**	**≥ 3 (5.7)**	**NE**	**Reduction**
trametinib	**Melanoma**	**Nov-14**	**dabrafenib**	**Exact magnitude uncertain**	**Improvement**	**NE**
vemurafenib	**Melanoma**	**Oct-12–Mar-13**	**dacarbazine**	**≥ 3 (3.3–3.9)**	**Improvement**	**Reduction**
vismodegib	**Basal cell carcinoma**	**Dec-13**	**non-comparative**	**NE**	**NE**	**NE**
Soft tissue						
trabectedin	**Soft tissue sarcoma (EMA)**	**Apr-08–Feb-10**	**BSC**	**≥ 3 (exact gain uncertain)**	**NE**	**Improvement**
Thyroid						
cabozantinib	**Medullary thyroid cancer**	**Dec-14**	**placebo**	**NE**	**NE**	**Reduction**
vandetanib	**Medullary thyroid cancer**	**Jun-12**	**placebo**	**NE**	**NE**	**NE**

Source:

Authors' analysis of data, as described in Methods section.

Notes:

[1] Change in OS, QoL, and safety is given as a composite score of the therapeutic improvement from each new drug relative to therapeutic comparators.
n/a = no appraisal available from Australian (PBAC), French (HAS), or English HTA agencies through May 2015.
NE = none established

[2] EMA indication used in instances where FDA approval was not available.

[3] OS benefits are classified as a categorical variable. Where multiple evaluations were available across Australian (PBAC), French (HAS), and English (NICE) HTA agencies, a range (in parentheses) was also developed to reflect the maximum OS benefit acknowledged by the HTA agencies that were able to quantify the magnitude of benefit.

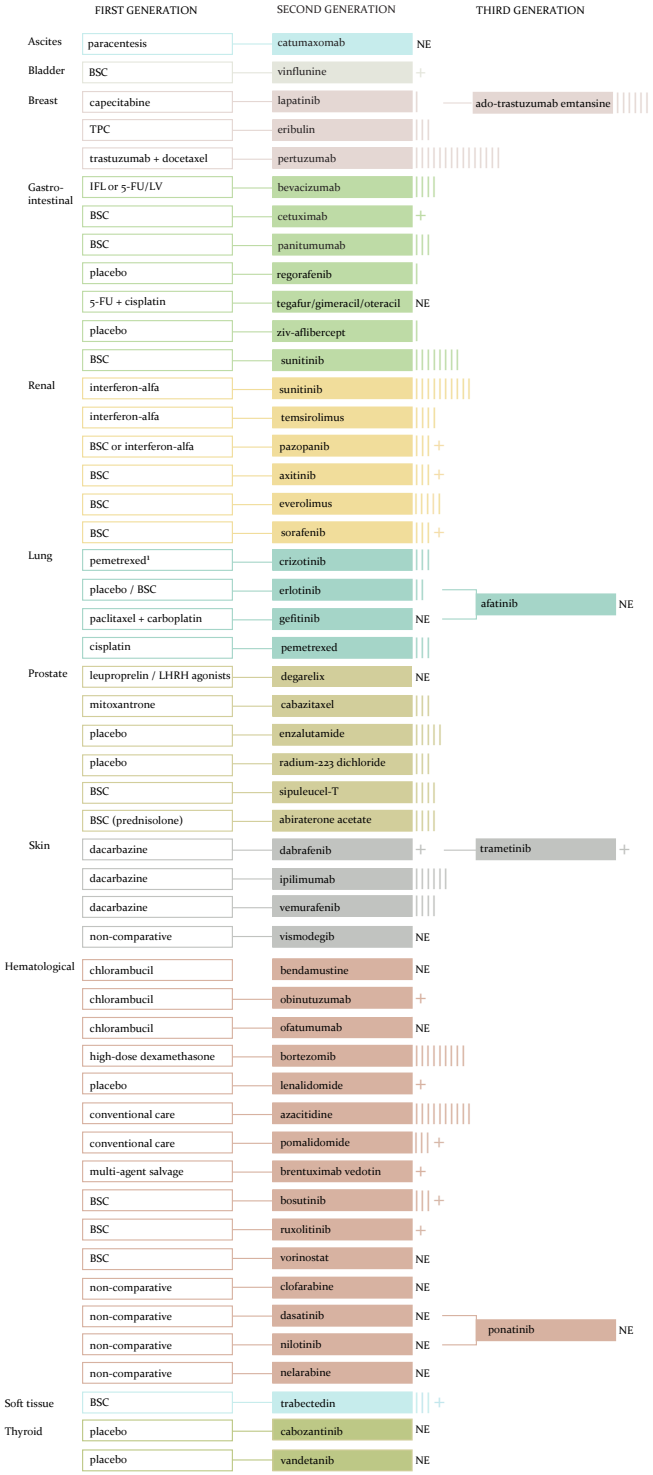
Overall Survival

23 of the 53 drugs that were analyzed in this study (43%) were confirmed by at least one HTA agency to increase OS by at least three months. HTA agencies were however unable to quantify an exact magnitude of increase for 6 of these 23 medicines. 6 of the 53 drugs (11%) increased OS by less than 3 months, and 8 (15%) produced an increase in OS of unknown magnitude. The remaining 16 (30%) cancer medicines did not demonstrate an increase in OS over alternative treatments, either because no difference was found or because a determination was not or could not be made by HTA agencies on the basis of the available evidence (Table 5). There was no clear association between expected OS benefits from treatment and disease stage.

Total increases in OS over the last decade were examined by mapping new interventions against the treatment comparators that would be replaced, as identified in HTA assessments (Figure 5). In all cases where comparative differences in OS could be quantified, the average OS benefit from all new cancer medicines was 3.43 ± 0.63 months (0.29 ± 0.05 years) relative to 2003 treatment standards.

These benefits, however, varied significantly across and within treatment indications: drugs indicated for thyroid cancers produced an average (SEM) increment of 0 (0) months in OS; ascites, 0 (0) months; lung cancers, 2.09 (0.75) months; hematological cancers, 2.61 (1.69) months; gastrointestinal cancers, 2.90 (1.12) months; prostate cancers, 3.17 (0.69) months; skin cancers, 4.65 (1.05) months; renal cancers, 6.27 (1.92) months; and breast cancers, 8.48 (3.84) months.

Figure 5. Improvements in Overall Survival from Anti-Cancer Medicines Newly Licensed between 2003-2013



Source:

Authors' analysis of data, as described in Methods section.

Notes:

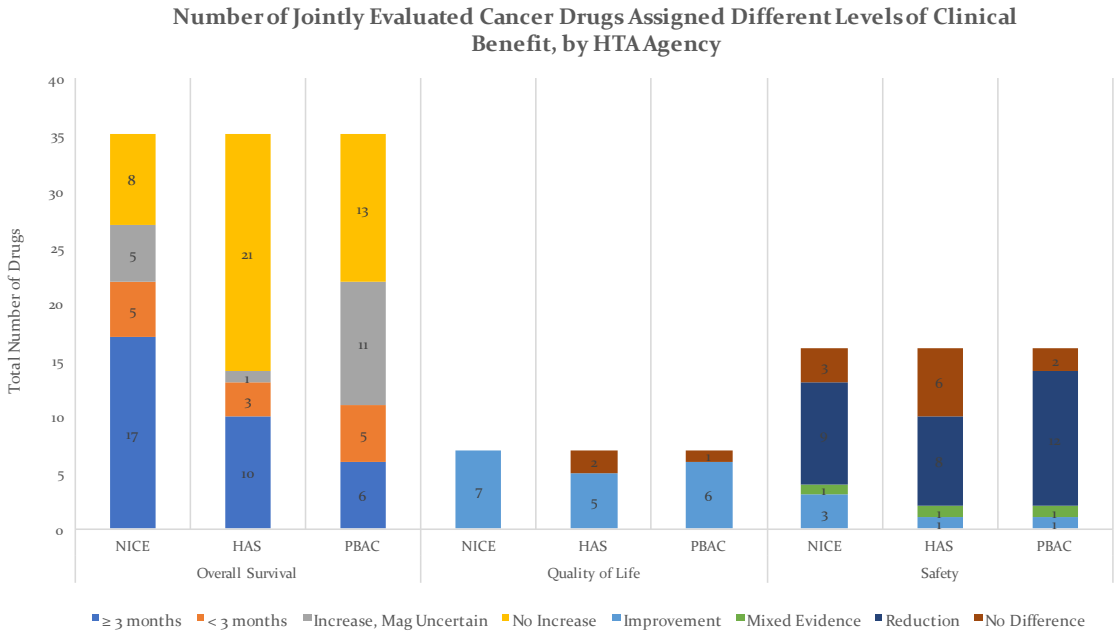
[1] Pemetrexeda represents use for a nonprimary indication—it is therefore considered independently of the pemetrexed indication that is evaluated in this study.

[2] Development of new cancer medicines (2003-2013), mapped according to therapeutic comparator used by health technology appraisal agencies in appraisal documents to assess therapeutic value. "First generation" drugs are the set of comparators not approved between 2003 and 2013, whereas "third generation" drugs are those that were evaluated against medications that were newly licensed in the study period ("second generation").

[3] Survival benefits associated with parallel treatment pathways (afatinib-erlotinib/gefitinib; ponatinib-nilotinib/dasatinib) are considered independently of each other, as are those associated with multiple primary indications (sunitinib). The gain in overall survival (OS) relative to initial standards of care, for all drugs where marginal increases in OS could be quantified, is provided with the use of bars that represent the number of months gained (rounded to nearest integer). If a range of values corresponding to OS benefits were available across health technology appraisal agencies, an average was taken. Uncertain increase in OS is represented with a "+"; NE indicates no established increase in OS.

For the drugs that were evaluated by all three HTA agencies, England's HTA agency was most likely to attribute significant OS improvements to new medicines (Figure 6). This contrasted with Australia's HTA agency, which appeared to be more cautious in its acceptance of significant OS-related benefits (Figure 6). HTA agencies may rely on different sources of evidence, including RCTs, extension trials, RWE, and indirect comparisons, to assess the clinical impact from treatment. For a detailed description of the evidence used by HTA agencies to inform these assessments, please refer to Appendix 2.1. Future studies should thoroughly compare and contrast the evidence used by the three HTA agencies to inform clinical impact assessments, and how assessments of drug clinical benefits translate to listing recommendations.

Figure 6. Number of Jointly Evaluated Cancer Drugs Assigned Different Levels of Clinical Benefit, by HTA Agency



Source:

Authors' analysis of data, as described in Methods section.

Across all available drug-specific assessments of OS, Krippendorff's alpha (α) equaled 0.38, suggesting a low- to moderate-level of agreement in assessments of OS benefits among all 3 HTA agencies (Table 6). Interagency agreement was however higher when English evaluations (α=0.62) and drugs that produced large improvement in OS (α=0.63) were excluded. This may suggest that regulators take different approaches to the evaluation of new cancer medicines, and that regulators become increasingly uncertain about claims of drug-related survival benefits as the magnitude of those claims increases.

Table 6. Interagency Agreement – Krippendorff's Alpha Coefficients

Rater	OS		QoL		Safety	
	Entire Sample	! = ≥3 months	Entire Sample	! = Improvement	Entire Sample	! = Improvement
Ordinal						
NICE + HAS + PBAC	0.380235	0.632742	0.608365	0	0.230789	-0.143208
NICE + HAS	0.316244	0.525054	0.608365	0	0.592507	0.127778
NICE + PBAC	0.233290	0.775789	0.055263	-	-0.033927	-0.439335
HAS + PBAC	0.618591	0.560272	0.547619	1	0.046384	0.081633
Nominal						
NICE + HAS + PBAC	0.354930	0.475309	0.535817	0	0.285894	0.126514
NICE + HAS	0.319274	0.412811	0.549839	0	0.508850	0.396648
NICE + PBAC	0.343593	0.618462	0.027027	-	0.205556	0.080808
HAS + PBAC	0.403390	0.354115	0.547619	1	0.174041	0.080808
Units	186	117	186	117	186	147

Source:

Authors' analysis of data, as described in Methods section.

Notes:

[1] Krippendorff's alpha coefficients were used to measure interagency agreement on the level of clinical benefit assessed by each agency. Krippendorff's alpha coefficients were measured for different agency pairings (left) and for either the entire sample ("Entire Sample") or for drugs that were not associated with an increase in OS of greater than or equal to 3 months ("!= ≥ 3 months") or with an improvement in QoL or safety ("!= Improvement"). Given the inherent order in the clinical benefit classifications used (OS: ≥3 months, <3 months, increase but magnitude uncertain, no increase; QoL, safety: improvement, mixed evidence, reduction, no difference), base case Krippendorff's alpha coefficient were calculated by modeling clinical benefit data as an ordinal variable (top). To test for robustness, sensitivity analyses modelled the data as a nominal variable (bottom).

Indeed, this points to the question of whether trial-based HTA assessments may translate to real-world clinical practice. HTA agency conclusions for 10 of the 23 drugs that were deemed to increase OS by ≥3 months (axitinib, bosutinib, crizotinib, everolimus, panitumumab, pazopanib, pomalidomide, sorafenib, sunitinib and trabectedin) were based on modeled data, indirect comparisons, or agency opinions. Axitinib, for example, was classified as increasing OS by ≥3 months relative to BSC based on an evaluation from NICE, which concluded that a gain of >3 months was "likely". The agency's conclusion however was based on indirect and simulated treatment comparisons, and it did not provide an exact magnitude of increase.

Furthermore, for 5 of the 23 drugs (axitinib, crizotinib, enzalutamide, panitumumab and pazopanib), significant OS benefits were found relative to one treatment comparator, but were not established in relation to other possible comparators. England's NICE, for instance, determined that bevacizumab was associated with a 4.7-month increase in median OS compared to IFL (irinotecan, bolus 5-FU and leucovorin), but no significant difference in OS compared to 5-FU/LV. Elsewhere, 5 of the 53 drugs that were assessed for OS (clofarabine, dasatinib, nelarabine, nilotinib, vismodegib) were based exclusively on non-comparative trials that could not estimate gains in OS, making it difficult to quantify their impact on therapy.

Quality of Life

Of the 53 drugs that were evaluated by at least one HTA agency, 22 (42%) improved QoL, 2 (4%) reduced QoL, 1 (2%) was associated with mixed evidence, and 28 (53%) did not demonstrate a difference in QoL relative to best alternative treatments (Table 5). For

more information on the quality of life parameters that were evaluated by HTA agencies to summarize the clinical impact from treatment, and which are therefore reflected in this chapter, please refer to Table 3.

As for OS, England's HTA agency was most likely to find an improvement in QoL from new cancer medicines. Across the entire sample, there was a moderate to high level of agreement among HTA agencies in the assessed level of QoL benefit from new cancer drugs (α=0.61)(Table 6). This suggests that HTA agencies tend to similarly interpret the QoL evidence—more so than that of OS—and may therefore lend confidence to the notion that new cancer drugs are providing QoL benefits to patients.

Still, regulatory opinions of treatment-related effects on QoL were not always based on empirical data. Of the 22 drugs that were deemed to improve QoL, evaluations for 17 were based on a review of empirical evidence, including data from validated QoL instruments. The QoL benefits associated with the remaining 5 drugs (pertuzumab, trametinib, ziv-aflibercept, sipuleucel-T, vemurafenib) were based exclusively on comments or testimony from patients and clinical experts. For example, HAS and PBAC both published evaluations of pertuzumab through May 2015. In their appraisals, based on evidence from the FACT-B questionnaire, HAS concluded that pertuzumab was not expected to have any impact on patients' QoL. The PBAC, in contrast, noted strong support for pertuzumab from the consumer comments facility describing a range of benefits from treatment, including in QoL.

Safety

Eight (15%) of the 53 drugs that were evaluated by HTA agencies were found to improve safety. A far larger share (24, or 45%), however, reduced patient safety. Ten (19%) were associated with mixed evidence and 9 (21%) failed to demonstrate any difference in safety compared to alternative treatments (Table 5). For more information on the safety parameters that were evaluated by HTA agencies to summarize the clinical impact from treatment, and which are therefore reflected in this chapter, please refer to Table 3.

Mirroring earlier trends for OS, English and Australian authorities were least and most likely to determine that new cancer medicines reduced patient safety, respectively. Across the entire sample, there was low level of interagency agreement between all HTA agencies on the impact on safety from new cancer medicines (α=0.23)(Table 6). This was however driven by a lack of consensus with Australia's HTA agency: interagency agreement was moderate to high when limited to English and French assessments (α=0.59).

Joint Benefits from Treatment

Of the 23 drugs that significantly increased OS by at least three months, 15 (65%) were also found to improve QoL, while the remaining 8 (35%) produced no measurable change. In contrast, of the 23 drugs that significantly extended OS, 5 (22%) improved safety, 11 (48%) reduced safety, 5 (22%) were associated with mixed evidence, and 2 (9%) produced no difference in safety relative to existing standards of care. Most new cancer medicines that significantly extend life therefore also improve QoL, but reduce patient safety (Table 3).

There was a noticeably smaller improvement in QoL in the set of drugs that produced a marginal to no improvement in OS. Of the 30 evaluated drugs that did not increase OS by at least 3 months, 7 (23%) were found to improve QoL, 2 (7%) worsened QoL, 1 (3%) had a mixed effect, and 20 (67%) did not demonstrate any change in QoL. Safety nevertheless remained a concern. Of the 30 drugs that did not increase OS by at least 3 months, 3 (10%) were classified as improving safety, 13 (43%) reduced patient safety, 5 (17%) were associated with mixed evidence; the remaining 9 (30%) did not demonstrate any difference in safety over alternative treatments.

Across the entire sample, 42 of the 53 new cancer drugs (79%) licensed in the US and the EU between 2003 and 2013, and evaluated by Australian, English, or French HTA agencies through May 2015, demonstrated at least some evidence of an OS, QoL, or safety benefit. These results were supported by the feedback that was received from 2 anonymous medical experts from the FDA, both of whom generally agreed with the results that were obtained. One—an oncologist—stated that the results summarized in Table 5 were "in line with [his personal] perceptions" of the added clinical benefits of the new cancer medicines evaluated in this study.

Discussion

All new cancer medicines licensed between 2003-2013 by the FDA and EMA extended OS by an average (SEM) of 3.43 (0.63) months (0.29 [0.05] years) over 2003 treatment standards. This figure is based on regulatory assessments, and is consistent with two similar studies.(73,153)

While perhaps modest, this improvement in OS represents an important step forward for patients and society, as even minor improvements in survival can have a large aggregate effect on mortality at the population-level.(154) It is therefore promising to find that a majority of newly approved cancer drugs were associated with some known (55%) or unknown (70%) benefit in OS, with the largest share (43%) extending life by ≥3 months, an amount that English and Australian authorities consider to be clinically significant.(121,147)

This analysis is the first to use a recently published conceptual framework on the value of new anticancer treatments (12) to characterize the OS, QoL, and safety benefits associated with new cancer medicines. It finds that most newly approved cancer medicines (79%) increased OS by some known or unknown magnitude, or demonstrated at least some evidence of improved QoL or safety over alternative treatments. Most new cancer medicines are therefore bringing at least some benefit to cancer patients.

However, there was evidence to suggest that these benefits are concentrated within particular classes of therapeutics. Ten immunologic drugs were present in this sample, most of which function by antigenic targeting of cancer cells. Ipilimumab was the only drug of a novel class of immunomodulating agents, the immune checkpoint modulators. With the exception of bevacizumab—which elicits an antiangiogenic response—immunologic drugs were, on average, better at extending OS compared to non-immunologic drugs (5.02 vs 2.30 months). However, this was not true of all immunologic drugs—catumaxomab and ofatumumab, for instance, produced no discernible improvement in OS compared to paracentesis and chlorambucil, respectively, while

brentuximab and cetuximab were associated with an increase in OS, albeit one that was unquantifiable. Therefore, while cancer drug innovation is in general benefitting patients, the magnitude of those benefits appears to differ across medicines and therapeutic classes.

Though perhaps promising, findings from this study should be interpreted with caution. To validly draw inference on the impact from new immunologic drugs and other cancer therapeutics, this analysis should be repeated as the number of available molecules grows. Across the entire sample, regulatory evidence is sometimes based on modeled data, non-validated inputs, or comparisons against non-targeted or older active treatments (e.g. BSC, chlorambucil), though these may reflect clinical best practices. Interagency agreement on drug-related OS benefits also decreases as the level of benefit increases, indicating that there may be greater uncertainty about the value from new cancer drugs that claim to bring the greatest health benefit. And, as shown with frequently contrasting English and Australian assessments, the regulatory milieu seems to shape the interpretation of clinical evidence supporting the use of new medicines. For example, while both English and Australian regulators accepted that sunitinib extended life by 7.8 months relative to BSC for gastrointestinal stromal tumors, Australia's HTA agency expressed some unease with this claim, noting that this survival benefit "may be an overestimate" given limitations in the supporting evidence.

These findings raise important questions about how clinical benefits are measured and used to inform evidence-based policy, and they give reason to adapt treatment guidelines to the unique circumstances and preferences of the patient.

Regulators often have the authority to require submission of all applicable clinical data that is "necessary to address the remit and scope of the technology appraisal."(151) To estimate the clinical value of new medicines in the absence of real-world, observational data, the approach used in this study may therefore be preferable to secondary of the published scientific literature.

Still, technological assessments may not always reflect the full extent of clinical risks and benefits that are observed in practice. For instance, as is the case for KRAS expression in colon cancer, particular genomic profiles are now known to predict OS benefits. In part for this reason, gene expression profiling is increasingly recommended as a tool to help guide chemotherapy decisions.(155,156) Since many new anticancer drugs target proteins that are downstream of genes with driver somatic mutations,(155) any misapprehension about the genetic mediators of disease may prevent regulators from fully appreciating their clinical value. Indeed, validated biomarkers often do not exist to guide the selection of patients in clinical trials who most likely benefit from treatment.(92) Clinical practice may instead incorporate new evidence on the genetic predictors of respons,e as and when it develops,(155) enabling personalized and cost-efficient care that optimizes patient outcomes. To better reveal the real-world benefits from new cancer medicines, future studies should therefore periodically repeat this analysis with post-marketing,(150) observational or pragmatic clinical trial evidence. The National Cancer Institute's upcoming National Cancer Knowledge System may provide crucial insights in this regard.

As it stands, 1 in 3 (30%) of all newly approved cancer medicines were not associated with any OS benefit, while 1 in 5 (20%) neither extend life nor improve QoL or safety.

While perhaps reflective of non-active comparisons, the approval of new medicines for orphan indications with no alternative treatment, or the growing use of surrogate efficacy endpoints during regulatory evaluations,(64) these findings indicate that expenditures for up to 1 out of every 5 cancer drugs may be spent without any OS, QoL, or safety benefit to the patient.

In the short term, these findings help to inform clinical decision-making by patients and clinicians who, in personalizing treatment, may have to consider the economic implications of drug prescriptions alongside individual preferences for treatment-related risks and benefits. This may be true for US cancer patients, who typically shoulder high amounts of cost-sharing, but also if public health systems (e.g. England's NHS) do not publicly reimburse for new cancer medicines. Over the longer term, efforts should build on ASCO's Value Framework for cancer treatment options by developing evidence on mechanisms to weight clinical outcome measures according to their value to patients, and aligning these developments with drug review processes.(157) Future studies may start on this endeavour by evaluating whether measures of the expected clinical impact from new cancer medicines are reflected in HTA agency listing recommendations.

These findings raise a number of important questions about value-for-money in oncology. This analysis finds that there is in fact a wide distribution in the therapeutic benefits associated with recent cancer drug innovations, suggesting a similarly wide variation in the value that they bring to society. Some medications (e.g. pertuzumab) have significantly extended life, perhaps justifying large and growing expenditures. Others, however, appear to bring little to no tangible benefit to health, raising questions about the justification for additional expense over alternative treatments. Though

further research is needed, this analysis may indicate that spending on new cancer drugs is not always commensurate with their clinical benefits. This may give reason for patients and clinicians to take pause when considering new treatments, particularly if related expenditures are of concern.

Therefore, cancer drug innovation over the past decade has brought notable improvements in OS and QoL. These gains however are unevenly distributed across newly licensed cancer medicines, they often come at the cost of safety, and there are reasons to believe they may not always translate to real-world clinical practice. As calls for value-based healthcare grow, this analysis raises questions about how clinical benefits are measured by regulators, and how regulatory evidence is used to inform clinical decision-making. It also casts doubt on the assumption that at a societal level the cost of a given cancer medicine is associated with its beneficial impact for patients. Subsequent chapters take different approaches to explore this issue.

Key Learnings and Implications

- All newly licensed cancer medicines have extended OS by an average (SEM) of 3.43 (0.63 months) over 2003 treatment standards.
- Most newly approved cancer drugs were associated with some known (55%) or unknown (70%) benefit in OS, with the largest share (43%) extending life by ≥3 months.
- English HTA agencies were most likely to determine that new cancer medicines improved overall survival, QoL, and reduced patient safety.

- 1 in 3 of all newly approved cancer medicines were not associated with any OS benefit, while 1 in 5 neither extend life nor improve QoL or safety.

3

Generating Evidence on the Use and Cost of Cancer Medicines

Introduction

Recent rates of growth in prescription drug prices and long-running increases in health needs have left health systems around the world grappling with rapidly growing expenditures. As policymakers attempt to control growing costs, while also protecting patient health, interest has grown in value-based healthcare models that couple expenditure with clinical outcomes.

This is reflected in the literature. Within the field of cancer, for instance, several recent studies have sought to determine whether growing expenditures on cancer care are "worth it." Comparing cancer survival differences to the relative costs from treatment in the US and European countries, Philipson and colleagues (2012) for instance find that high-cost US cancer care generated $598 billion of additional value to US patients who were diagnosed between 1983 and 1999.(8) Soneji and Yang make a similar claim,(9) but also find that net economic returns vary by cancer indication and is often less than that achieved in Western European countries. To date, however, the literature has for the

most part been unable to assess the value of different cancer tools and treatments, including medicines.(8)

Several streams of evidence are needed to systematically do so. ASCO recently published Value Framework, for instance, identifies the clinical outcome parameters that can be used to measure the value of cancer therapeutics. Chapter 2 used it as a framework to systematically assess the clinical risks and benefits of new cancer medicines. However, how and to what extent these clinical risks and benefits are reflected in real-world clinical populations depends on their utilization by patients. Moreover, as ASCO points out, there is also the assumption that the "cost of a given intervention should bear a relationship to the beneficial impact" of cancer therapies. Therefore, in addition to evidence on their utilization, evidence on costs is also needed to assess the value associated with new cancer medicines.

Yet, even as interest grows in value-based healthcare, there is a dearth of reliable, comparative evidence on cancer drug utilization (74,75,(b)) and costs (159) that would otherwise support international research into the value from cancer drug spending.

Drug Utilization

There is as of yet no single dataset that provides comparable evidence on the utilization of cancer medicines at a patient-level.(74,75,(b)) Several nation-wide initiatives have made progress towards this end, yet each also faces its own set of challenges. The UK, for instance, created the SACT dataset in 2014, a national mandatory system collecting systemic anti-cancer therapy activity from all NHS England chemotherapy

providers.(160) SACT nevertheless continues to face questions regarding data quality, completeness, and access. The scope of SACT is also limited to cancer drug use in the UK, making it difficult to examine the value from cancer drug use and cost within a comparative framework.

There are a similar set of challenges in the US. The SEER program of the US NCI provides information on cancer incidence and survival. The SEER-Medicare linked dataset links clinical, demographic, and cause of death data from SEER with claims data for Medicare beneficiaries, including Medicare reimbursements and physician-administered drugs. The SEER-Medicare linked dataset nevertheless has limitations that are worth noting. The SEER registry covers only 28% of the US population,(161,162) and there are reasons to believe that the SEER-Medicare linked dataset captures an even smaller fraction of eligible cancer patients: Medicare data does not include claims for Health Management Organization enrollees; care provided in other settings, such as the Veterans Administration; care for patients where Medicare is the secondary payer; reimbursement for covered services not captured by Medicare data, such as out of pocket expenditures; or coverage provided by Medigap policies.(163) Sample bias in the SEER-Medicare linked dataset may therefore be of concern, raising questions about how well it reflects the use of cancer medicines throughout the US. Indeed, prior empirical studies have found that the SEER cancer program tends to underrepresent US cancer site-specific mortality rates of certain demographic groups, that underrepresentation is observed across most SEER registries, and that underrepresentation varies across US states.(164) The possibility of sample bias and non-representativeness complicates potential comparisons with data from other international settings, such as that of the SACT dataset in the UK. A brief overview of US cancer datasets is provided in Box 3.

Box 3. Overview of Available Cancer Registries in the US

In the US, the SEER program, and the SEER-Medicare Linked Database, collects and reports data on cancer incidence, prevalence, and survival, as well as treatment and costs. Private registries, including the NCDB, also exist, though they may not be designed for researchers to thoroughly evaluate patient-level cancer drug use and outcomes on a national scale. More information on the NCDB is provided below. The AHRQ sponsors the HCUP and its digital query system and portal (HCUPnet) to provide health statistics pertaining to inpatient admissions and emergency department utilization. This data source does not provide information on services or healthcare products prescribed or delivered within ambulatory care settings, or in-hospital or retail pharmacy settings, limiting its usefulness in this study.

The NCDB is a nationwide oncology outcomes database capturing 70 percent of all newly diagnosed cases in the US, and is jointly administered by the CoC of the ACoS and the ACS.(363) The NDCB maintains a number of useful online data applications to "evaluate and compare the cancer care delivered to patients diagnosed and/or treated at their facility with that provided at the state, regional, and national levels."(364) Key reporting applications include the: HCBR, NCDB Survival Reports (Survival), CP3R, RQRS, and the CQIP. These resources allow CoC-accredited cancer programs to evaluate and compare patient survival (Survival), facility level compliance (CP3R), short- and long-term quality and outcome data (CQIP), and perform real-time assessments of hospital-level adherence with NQF-endorsed quality of care measures for selected cancers (RQRS).(364) They do not however provide data on the patient-level drug care that is delivered to patients. By also focusing on the care that is prescribed or delivered within CoC-accredited cancer programs, these resources are also unable to capture the filling of scripts that may occur outside of hospital settings, e.g. through retail pharmacies.

In summary, even in the US, the resources that are available to collect evidence on cancer drug use and cost are, in many ways, limited. There and elsewhere, these gaps in evidence makes it difficult to reliably assess the value from cancer drug expenditures, and it therefore presents a challenge for value-based decision-making in healthcare.

Drug Costs

Similarly, a number of factors may make it difficult to carry out systematic and large-scale analyses of cancer drug costs using existing data sources.(165) As Onakpoya and colleagues (2015) highlight, treatment costs for orphan drugs—many of which are indicated for use in cancer (159,166)—may vary according to the "individual patients' needs including body size, disease progression, or complications of disease."(159) In the absence of publicly available, patient-level cancer drug registries that also provide real-world information on how these dose-determining factors contribute to heterogeneity in per patient costs, studies have often relied on questionable methods and costing data. Evidence has all the while been sourced from different time periods or places,(159,166) potentially biasing cost comparisons within and between countries. The issues that arise

from a lack of evidence, and their implications for rigorous and transparent research, are discussed in more detail below.

In the absence of a single, reliable data source for drug treatment costs in the UK, Onakpoya and colleagues (2015) performed a secondary search of the UK Medicines Information, the National Electronic Library for Medicines, North East Treatment Advisory Group, Scottish Medicines Consortium, and All Wales Medicines Strategy Group databases "for the most recent evidence." Where these sources of information were deemed to be inadequate to compute annual drug costs, Onakpoya and colleagues (2015) also searched the websites of The Pharma Letter, PharmaTimes, and Google Scholar. A similar issue exists in the US, where cost inputs may have to be obtained from "administrative databases and the published literature."(166) The expansiveness of these secondary searches reflect the lack of a single source of evidence on the cost of cancer medicines. It also raises questions on how reliably data from each of these sources can be compared and used in country-level studies. Indeed, Onakpoya and colleagues (2015) report finding "inconsistencies" in their estimates of drug costs and therefore call for a "more detailed and transparent analysis" of the costs of orphan medicines.

These issues have been highlighted in the field of cancer. In their review of economic studies in colorectal cancer, Yabroff and colleagues (2013) report that there is (167):

> "significant heterogeneity across populations examined, healthcare delivery settings, methods for identifying incidence and prevalent patients, types of medical services included, and analyses."

As a consequence, the authors argue that (167):

> "findings from studies with seemingly the same objective (e.g. [identifying] costs of chemotherapy in year following CRC diagnosis) are difficult to compare. Across countries, aggregate and patient-level estimates vary in so many respects that they are almost impossible to compare."

Moreover, as for utilization, there is often a significant amount of uncertainty in the total cost that will be incurred from treatment with cancer medicines. This owes in part to an unpredictable DoT, which is defined by patient progression-free survival, as well as incidence of unacceptable toxicities, and death.[e.g. (69–71)] Unlike in other disease areas, response to cancer treatment is often highly variable, and associated with a wide distribution in length of treatment. To bypass this issue, cancer drug costs may be annualized,(159) or evaluated as monthly DAC or the ETP,(12,73) both of which refer to the monthly cost for acquisition of cancer medicines based on list prices. However, besides being non-systematic, this approach does not adjust for potential differences in treatment duration across cancer medicines, and may therefore bias comparisons of drug costs. As a result, it may be difficult for researchers to test the hypothesis that drug clinical benefits are associated with their cost for treatment.

These challenges have made it difficult to develop comparable costing data to examine the value associated from cancer drug spending in any one context. Even in the UK—which provides universal healthcare coverage to all normal residents through the NHS

(168)—there is a lack of reliable, nationally-representative data on the cost of cancer care.(165) Hall and colleagues (2015) comment on this (169):

> "[In the UK,] detailed claims databases do not exist, either fail to capture local variation and full data granularity or require a heavy data collection burden; accurate and easily reproducible estimates of the true cost of care therefore remain elusive."

PLICS are being adopted to improve the accuracy and standardization of methods to calculate tariff-based payments for defined, hospital-based episodes of care.(170) Their adoption is however still underway, with only 64% of trusts indicating that their organizations were using PLICS as of 2013.(171) Trusts may also regard PLICS data as commercially sensitive and so may not share it, even with commissioners,(172) raising questions of bias if and when it is to be used in secondary research. And, even with workarounds,(173) PLICS only provide data on hospital-based care, and may therefore exclude the use of cancer medicines outside of this setting.

Recent efforts have attempted to link patients in the NCDR with data on hospital activity and NHS costs (NSRC).(165,174) While this approach utilizes well-regarded data sources to evaluate cancer treatment costs, it does have several limitations that are worth considering: while the NSRC dataset is said to provide the "most detailed picture available on the cost of the health services delivered by NHS organisations",(175) the NSRC is not designed to provide reference costs for treatment with individual medicines. At the same time, the NCDR only provides merged, patient-level data for 1990-2010,(176) making it difficult to examine cancer drug costs over recent years.

Available Data

Patient-level data linking drug exposure with costs and outcomes is rarely available for researchers to conduct independent clinical and economic evaluations.(177) This may owe in part to the organizational challenges that exist in systematically collecting this data. Anticancer medicines are generally prescribed within secondary care. Those medicines can however be dispensed from a number of settings, including hospital outpatient departments or retail pharmacies. To be representative, patient-level cancer drug registries must therefore be designed to collect data from various points of sale, and across multiple time periods. The creation of national registries on the use and cost of cancer therapeutics therefore demands scaled electronic data systems that collect information on drug prescriptions or dispensation.

Alternatively, privately-held datasets, such as QuintilesIMS's MIDAS, may collect representative data on cancer drug sales and pricing from a number of countries by combining data from local market audits. Previous studies have used cancer drug utilization through a volume proxy.(74,75) However, because cancer drug use is highly individualized and may occur over wide dosage ranges,(178) it may be difficult to compare drug utilization through volume measures. A similar argument applies to cancer drug pricing data, which requires some method of standardizing for the interval over which prices are incurred.(12,73,159) If and when PLICS data become available for secondary research in the UK, reference costs for expensive medicines may for example be calculated using the currency of patient months on treatment.(173) Without any information on treatment dosing and duration distributions for a population, it is difficult to evaluate and interpret volume-based utilization and drug pricing measures.

This evidence could be particularly useful for payers and policymakers, who may need to consider both the location and spread of costing distributions during value-based decision-making.

These issues apply both to the US and to Europe. Past initiatives—including EURO-MED-STAT (179) and the European Surveillance of Antimicrobial Consumption (ESAC-Net) (180)—have attempted to gather data on drug pricing, expenditure, and utilization. However, these have failed to generate comparable or robust pharmaceutical pricing and use data from hospital or ambulatory care settings for a number of disease categories, including cancer, and for any length of time.(74)

Context and Empirical Gaps

In the absence of comparable, patient-level data, studies have attempted to measure international variations in cancer drug utilization by examining differences in drug sales volumes.(74,75) This has been described as the preferred approach in the field of cancer,(74) where there is as of yet no widely accepted method for standardizing the usage of treatments. Indeed, unlike for other disease areas, the WHO does not publish data on DDDs—an average measure of the maintenance dose associated with individual treatments—for cancer medicines due to their "highly individualized use and wide dosage ranges."[e.g. (178)] However, because they may fail to account for drug dosage and treatment duration, it is difficult to rely on volume-based utilization measures in comparative analyses of the value from cancer drug spending.

There is also a dearth of reliable costing data that can be used in comparative analyses of the value associated with cancer medicines.(165) This owes in part to a lack of publicly available, patient-level data on cancer drug utilization, and on the factors that influence total prescribable drug dosage, including anthropometrics and DoT. In its absence, relevant studies have used costing estimates that may not adequately reflect the full cost from treatment with cancer medicines, potentially biasing comparative analyses. Cheng and colleagues (2012) find an overall dearth of cost-effectiveness studies for orphan medicines, and in oncology as a whole, and argue that this may reflect "evidence limitations or publication bias."(166) For orphan medicines, smaller patient populations may make it particularly costly and challenging to develop evidence.(166) Alternative approaches must be used to account for these issues.(78)

From a methodological perspective, patient-level data linking drug exposure with costs and outcomes is rarely available for researchers to conduct independent clinical and economic evaluations.(177) Although the US FDA in 2013 discussed making de-identified and masked clinical trial data available,(181) there have been no further developments since. The EMA also announced that it would publish patient-level data from 2014 onwards, but this has since been delayed.(181) Stand-alone clinical trial data is also often inaccessible for secondary research.(182) (b) (4)

To conduct comparative analyses of the cost and clinical impact of new cancer medicines, these challenges must first be addressed.

Summary of Research

This chapter generates comparative evidence on the expected course, use, and costs from treatment with recently launched cancer medicines in Australia, France, the UK, and the US. For this, (b) (4), using recent methodological advances (78,79) (b) (4) is used to account for gaps in the existing data. The evidence that is generated is then used in subsequent chapters to examine the value from spending on new cancer medicines.

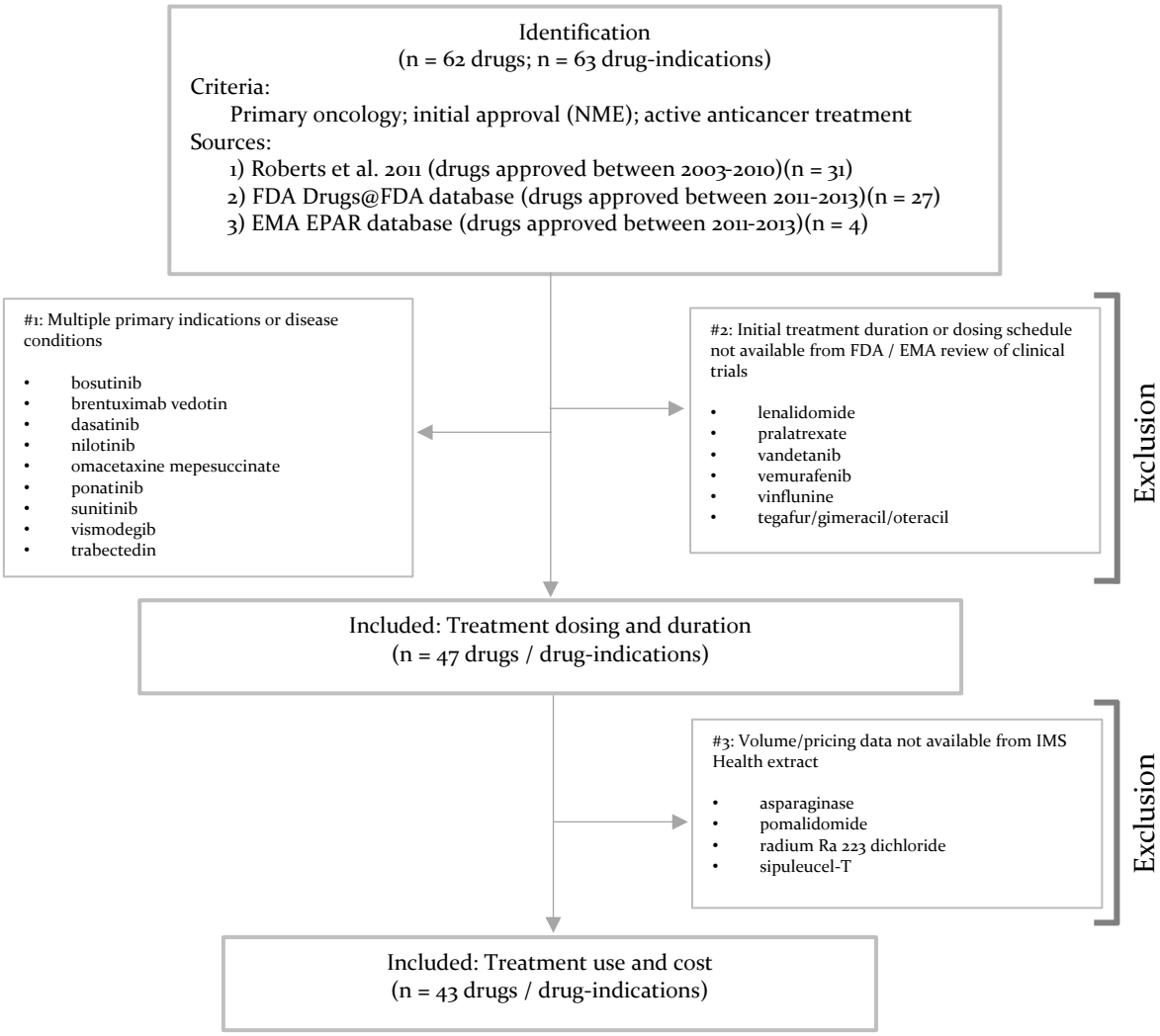
Methods

Sample Selection

All medicines that were included in Chapter 2 were eligible for inclusion in this study. As in Chapter 2, the methods from Roberts and colleagues (125) were used to identify all initial cancer drug approvals by the US FDA and EU EMA occurring between 2003-2013. All NMEs approved by the FDA or EMA over this period with a primary indication for oncology were eligible for inclusion. Any molecule that did not receive licensure by either the FDA or EMA between 2003-2013, and which did not have an initial, primary anticancer indication was therefore excluded. Supplemental applications to the US FDA or EU EMA, new non-active treatments, licensing supplements, labeling revisions, and new or modified indications were not considered.

This chapter conducted two sequential stages of analysis to model the a) treatment dosing and duration, and b) treatment utilization and cost associated with each drug. It focused exclusively on anticancer medicines approved with single, primary indications. Medicines were excluded from the first and second stage of analysis if they had been approved with multiple primary FDA indications, for multiple disease conditions—as data from QuintilesIMS did not provide drug indication—or if the treatment duration or dosing schedule was not available from regulatory sources. Medicines were excluded from the second stage of analysis if price or volume data were not available from QuintilesIMS. The drug selection process is depicted in Figure 7.

Figure 7. Drug Sample Inclusion/Exclusion Criteria



Source:

Authors' analysis of data, as described in Methods section.

Data Sources

Cancer drug pricing and volume data was obtained from QuintilesIMS MIDAS. The extract that was used in this analysis provided pricing and volume sales data captured at the point-of-sale for all cancer drug molecules marketed at any point between 2004 and 2015 in Australia, France, the UK, and the US. The extract aggregated pricing and volume data across both hospital and retail pharmacy settings for each year in the study period. Unit-level data on drug sales volume was given both in terms of standard dose units (e.g. capsule, tablet) and kilograms. Anticancer medicines were defined by QuintilesIMS as any molecule with an L01 or L02 ATC classification. Adjunctive therapies and products with other ATC codes were excluded from this dataset. Due to licensing restrictions, this thesis does not publish any raw volume or pricing data from QuintilesIMS.

For all drugs that met inclusion criteria, (b) (4)

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This study focused exclusively on the clinical trials that were considered to be pivotal by the FDA, as these are designed to provide statistically significant evidence of safety and efficacy for marketing approvals.(191,192)

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This approach was designed to reflect regulatory recommendations on when to stop treatment: if end-of-therapy is based on symptom assessment rather than a pre-defined treatment duration, the FDA for instance often explicitly recommends that treatment continue until clinical benefits cease, progressive disease occurs, or unacceptable toxicity develops.[e.g. (69–71)] Similar recommendations are made by other regulators: in its product labeling for cancer medicines, the EMA often recommends that treatment be continued until end-of-therapy, unacceptable toxicity, or "until progression of the underlying disease".[e.g. (219)] As is evidenced by the phase III study for vinflunine (VFL 302),(220) clinical trials are themselves often designed for ethical reasons to discontinue treatment or allow for patient cross-over once symptoms deteriorate, toxicity develops, or progression occurs.(221,222) Oncologists may also re-assess the use of treatments if disease progression occurs, functional status worsens, or side-effects arise.(223,224)

(b) (4)

Disease condition and rarity may impact the total use or price paid for cancer medicines.(50,227–229) US and EU orphan drug status and ATC classifications for FDA-approved indications were therefore obtained from orpha.net and the WHO's ATC/DDD index,(230,231) while Australian orphan drug status was obtained from the TGA's orphan drug registry.(232) Unlike recent studies,(78) latest available anthropometric reference data were obtained for the different countries in this analysis, and were also stratified by age and sex to account for age- (adult/pediatric) and sex-specific drug indications. (b) (4)

Theoretical Framework

(b) (4)

used to model expected treatment dosing and duration, and treatment utilization and cost. The theoretical framework that is described

here builds on the available literature, as well as existing health economic modeling procedures.[4]

Dosing and Treatment Duration

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Data Generation

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[5] (b) (4) [redacted]

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(b) (4)

Dosing and Treatment Duration

(b) (4)

Treatment Cost and Utilization

In the absence of any international registry capturing drug usage by patients, previous studies have recommended that volume be taken as a proxy measure of consumption, as sales data may be affected by exchange rate fluctuations and differing price levels.(74,75) To account for variations in drug potency, volume should be expressed in terms of DDDs—a measure of the average maintenance daily dose for the primary indication in adults—"wherever possible."(74) In oncology, however, this approach is complicated by the fact that DDDs are not published for cancer drugs by the WHO due to their "highly individualized use and wide dosage ranges."[e.g. (178)]. Without this standardized unit, it may be difficult to reliably compare cancer drug use within and across different countries. (b) (4)

Secondary Analysis

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First, England's NICE may publish Costing Statements as part of its evaluation of new health technologies to provide guidance on their expected impact on resource use in the NHS.[e.g. (248)] Costing Statements typically provide forecasts of the total number of patients who would be expected to use or be eligible for treatment in the UK. However, Costing Statements are often not published by NICE for new technologies;[e.g. cabozantinib, carfilzomib (249,250)] even if they are, the methods underlying these forecasts often lack transparency; they do not always provide forecasts on the number of patients who will be treated with new medicines;[e.g. (251)] they do not provide comparable estimates on drug utilization and costs for countries outside of the UK; and they only provide forecasts, rather than real-world figures. While they therefore cannot be systematically used as a resource for evidence on the real-world use and cost of cancer medicines, they do provide a benchmark for these parameters. (b) (4)

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Limitations

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Several points should however be considered: regulators use the single pivotal trials that typically follow feasibility stages as “primary clinical support” of marketing applications,(b) and health systems may refer to them to support decision-making on drug coverage, pricing, and reimbursement. Pivotal clinical trials may be expected to include medicines as they are likely to be used in the clinic, (b) (4) This reflects their objective, which is to provide meaningful evidence on the clinical impact from the intended use of new medicines.(191,192,261) (b) (4)

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With greater understanding of the biological mediators of clinical response, future studies may be able to use individual data, including genomic evidence, to personalize estimates of the use and cost associated with new medicines.

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While this limitation is acknowledged, it is important to consider several points. First, the country, age (adult/pediatric), and sex (male/female) stratifications that are used in this study are already an advance over the recently published literature. In their comparative study of drug costs and benefits of medical treatments in (b) (4) (b) (4) assume a standard weight (b) (4) and BSA (b) for a hypothetical patient.(78) The study makes no attempt to adjust these figures by country or disease indication, suggesting that this approach may bias estimates of standard posology. (b) (4)

Unfortunately, this approach may also be used by England's own HTA agency, NICE, when assessing new health technologies. For example, in its TA 216 for bendamustine,(263) NICE takes the mean cost of bendamustine per person from the manufacturer's submission (£4741.54). This figure, however, was estimated by assuming a fixed BSA (1.72 m^2) and an average treatment course of 4.9 cycles. Notably, anthropometric assumptions may not be used consistently across all TAs: in TA135, for example, NICE provides an expected cost for treatment with pemetrexed by assuming five treatment cycles, and a BSA of 1.8 m^2.(264) The basis for these figures is also often not given. These issues raise concerns over transparency and evidence-based decision-making by NICE and other regulatory bodies. They also highlight the need to develop a

systematic process that can estimate these parameters, while also accounting for uncertainty.

(b) (4)

Results

62 anticancer molecules were approved by the US (FDA) and EU (EMA) between 2003-2013 with a primary indication for oncology, and were therefore eligible for inclusion. Of those, treatment duration and recommended dosing information was not available for 6 medicines, while another 9 were approved for multiple primary indications or disease conditions, a level that could not be reconciled with the pricing and volume data that was available in this study. Treatment dosing and duration were therefore estimated for the remaining 47 medicines. Of these, volume and pricing data was not available from the QuintilesIMS pricing and volume data extract for 4 medicines, leaving 43 drugs that were included in treatment use and costing analyses (Figure 7).

The drug sample was well-distributed in terms of the cancer indications that were represented (*Table 8*). One of the 47 drugs that were included in this analysis was indicated for malignant ascites, five for breast cancer, five for GI cancer, five for lung cancer, six for prostate cancer, five for renal cancer, three for skin cancer, and one for thyroid cancer; the remaining 16 were indicated as hematologicals. 24 medicines had an active or withdrawn orphan status in the US or EU. Of these, one was indicated for malignant ascites (catumaxomab), one for lung cancer (pemetrexed), and one for thyroid cancer (cabazantinib); all medicines that were approved for renal (n = 5) or hematological (n = 16) neoplasms were also associated with an orphan status.

Chapter 2 describes the clinical benefits associated with each of the medicines that were included in this study, as well as the methods that were used to obtain this information. A brief overview is also provided here. There was a wide distribution in the OS benefits associated with each of the medicines included in this study (Table 8). Ranked by indication, all treatments that were newly licensed for breast cancer by the US FDA and EU EMA between 2003-2013 extended survival by the largest average amount between 2003-2013 (8.48 months). This was followed by medicines that were indicated for renal cancer (6.27 months), skin cancers (4.65 months), prostate cancers (3.17 months), GI cancers (2.90 months), hematological cancers (2.61 months), lung cancers (2.09 months), malignant ascites (0 months), and thyroid cancers (0 months). The largest share of these medicines improved (42%) QoL, but reduced (45%) patient safety. For more information on the clinical risks and benefits of new cancer medicines, including how they were assessed, please refer to Chapter 2.

Of the 47 drugs that were included in this study, 22 were associated with an explicit recommendation to treat patients until clinical benefits end, progressive disease occurs, or unacceptable toxicity develops. Although the FDA did not explicitly recommend that treatment stop at time of disease progression or upon the occurrence of unacceptable toxicity for 15 medicines, its medical reviews explicitly indicated that the pivotal clinical trials for most of these (n = 12) were designed to do so.

Table 8. Drug Sample Eligible for Study Inclusion, Therapeutic Characteristics, First FDA-Approved Change to Indicated Treatment, and Maximum OS Benefit Relative to Clinical Comparator, as Measured Across English, French, and Australian HTA Agencies

Drug	FDA Indication (1°)	ATC	Target	Orphan Status1	Initial Approval[2]	1st Change to Indicated Treatment[3]	OS Benefit (months)	Clinical Comparator
abiraterone acetate	Indicated for use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel.	L02BX03	Prostate	-	US: Apr-11 EU: Jul-11 AU: Mar-12	US: - EU: - AU: -	3.9-4.6	BSC (prednisolone)
afatinib	First-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.	L01XE13	Lung	AU	US: Jul-13 EU: Jul-13 AU: Nov-13	US: - EU: - AU: -	0	erlotinib / gefitinib
asparaginase E. chrysanthemi	An asparagine specific enzyme indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to E. coli-derived asparaginase.	L01XX02	Hematological	EU	US: Apr-11 EU: Nov-15 AU: -	US: - EU: - AU: -	n/a	n/a
axitinib	Treatment of advanced renal cell carcinoma after failure of one prior systemic therapy.	L01XE17	Renal	AU / EU (w)	US: Jan-12 EU: May-12 AU: Jul-12	US: - EU: - AU: -	≥ 3 months (Magnitude uncertain)	BSC
azacitidine	Treatment of patients with the following myelodysplastic syndrome subtypes: refractory anemia or refractory anemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia.	L01BC07	Hematological	AU / EU / US	US: May-04 EU: Oct-08 AU: Nov-09	US: - EU: - AU: -	9.4-9.6	conventional care
bendamustine	Treatment of patients with chronic lymphocytic leukemia (CLL).	L01AA09	Hematological	US	US: Oct-08 EU: Jul-10 AU: Jun-14	US: 2009 EU: - AU: 2014	0	chlorambucil
bevacizumab	In combination with intravenous 5-fluorouracil–based chemotherapy, indicated for first- line treatment of patients with metastatic carcinoma of the colon or rectum.	L01XC07	GI	-	US: Feb-04 EU: Oct-04 AU: Feb-05	US: 2006 EU: - AU: -	3.0-4.7	IFL / 5-FU/LV
bortezomib	Treatment of multiple myeloma patients who have received at least two prior therapies and have	L01XX32	Hematological	AU / US	US: May-03 EU: Jan-04 AU: Feb-06	US: - EU: - AU: -	6.1-11.5	high-dose dexamethasone

	demonstrated disease progression on the last therapy.							
cabazitaxel	Indicated in combination with prednisone for treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen.	L01CD04	Prostate	-	US: Jun-10 EU: Jan-11 AU: Dec-11	US: - EU: - AU: -	2.4-4.2	mitoxantrone
cabozantinib	A kinase inhibitor indicated for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC).	L01XE26	Thyroid	US	US: Nov-12 EU: Dec-13 AU: -	US: - EU: - AU: -	0	placebo
carfilzomib	Treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy.	L01XX45	Hematological	EU / US	US: Jul-12 EU: Sept-15 AU: -	US: - EU: - AU: -	n/a	n/a
catumaxomab	(EMA) Indicated for the intraperitoneal treatment of malignant ascites in adults with EpCAM-positive carcinomas where standard therapy is not available or no longer feasible.	L01XC09	Ascites	EU / US	US: - EU: Apr-09 AU: -	US: - EU: - AU: -	0	paracentesis
cetuximab	Used in combination with irinotecan, indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy.	L01XC06	GI	-	US: Feb-04 EU: Jun-04 AU: Jan-05	US: 2006 EU: 2006 AU: 2007	Increase (Magnitude uncertain)	BSC
clofarabine	Treatment of pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens.	L01BB06	Hematological	AU / EU / US	US: Dec-04 EU: May-07 AU: Sep-09	US: - EU: - AU: -	0	non-comparative
crizotinib	Treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.	L01XE16	Lung	AU	US: Aug-11 EU: Jul-12 AU: Sep-13	US: - EU: - AU: -	3.1-3.5	pemetrexed
dabrafenib	Treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.	L01XE23	Skin	AU	US: May-13 EU: Jun-13 AU: Aug-13	US: - EU: - AU: -	Increase (Magnitude uncertain)	dacarbazine / vemurafenib (safety)
decitabine	Treatment of patients with myelodysplastic syndromes (MDS) including previously treated and untreated, de novo and secondary MDS of all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia) and	L01BC08	Hematological	EU / US	US: May-06 EU: Jul-12 AU: -	US: - EU: - AU: -	n/a	n/a

	intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.							
degarelix	Treatment of patients with advanced prostate cancer.	L02BX02	Prostate	-	US: Dec-08 EU: Dec-08 AU: Feb-10	US: - EU: - AU: -	0	leuproprelin + LHRH agonists
enzalutamide	Treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel.	L02BB04	Prostate	-	US: Aug-12 EU: Apr-13 AU: Jul-14	US: - EU: - AU: -	4.5-4.8	placebo
eribulin	Treatment of patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting.	L01XX41	Breast	-	US: Nov-10 EU: Jan-11 AU: Aug-12	US: - EU: - AU: -	2.5-2.7	TPC
erlotinib	Treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen.	L01XE03	Lung	AU	US: Nov-04 EU: Jun-05 AU: Jan-06	US: - EU: 2007 AU: -	2	placebo / BSC
everolimus	Treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.	L01XE10	Renal	AU / EU (w)	US: Mar-09 EU: May-09 AU: Jul-09	US: 2010 EU: 2011 AU: 2005	5.2	BSC
gefitinib	Indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutation of EGFR-TK.	L01XE02	Lung	-	US: May-03 EU: Apr-09 AU: Apr-03	US: - EU: - AU: -	0	paclitaxel + carboplatin
ibrutinib	Treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.	L01XE27	Hematological	EU / US	US: Nov-13 EU: Jul-14 AU: Apr-15	US: 2014 EU: 2015 AU: -	n/a	n/a
ipilimumab	A human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody indicated for the treatment of unresectable or metastatic melanoma.	L01XC11	Skin	-	US: Mar-11 EU: May-11 AU: Jun-11	US: - EU: - AU: -	5.7	dacarbazine
ixabepilone	In combination with capecitabine, indicated for the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline and a taxane. // Ixabepilone as monotherapy is indicated for the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline, a taxane, and capecitabine.	L01DC04	Breast	-	US: Oct-07 EU: - AU: -	US: - EU: - AU: -	n/a	n/a
lapatinib	In combination with capecitabine, indicated for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.	L01XE07	Breast	-	US: Mar-07 EU: Jun-08 AU: Jun-07	US: - EU: - AU: -	0.3-2.4	capecitabine monotherapy

nelarabine	Treatment of patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens.	L01BB07	Hematological	EU / US	US: Oct-05 EU: Jun-05 AU: -	US: - EU: - AU: -	0	non-comparative
obinutuzumab	Indicated in combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia.	L01XC15	Hematological	EU / US	US: Nov-13 EU: May-14 AU: May-14	US: - EU: 2016 AU: -	Increase (Magnitude uncertain)	chlorambucil
ofatumumab	Treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab.	L01XC10	Hematological	EU / US	US: Oct-09 EU: Jan-10 AU: Dec-10	US: - EU: - AU: -	0	chlorambucil
panitumumab	Treatment of EGFR-expressing, metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.	L01XC08	GI	-	US: Sep-06 EU: Sep-07 AU: Jun-08	US: - EU: - AU: -	2.7-3.2	BSC / cetuximab (safety)
pazopanib	Treatment of patients with advanced renal cell carcinoma.	L01XE11	Renal	AU / EU (w)	US: Oct-09 EU: Apr-10 AU: Jun-10	US: - EU: 2012 AU: 2012	≥ 3 months (Magnitude uncertain)	BSC / interferon-alfa
pemetrexed	In combination with cisplatin, indicated for the treatment of patients with malignant pleural mesothelioma whose disease is either unresectable or who are otherwise not candidates for curative surgery.	L01BA04	Lung	EU (w) / US	US: Feb-04 EU: Jun-04 AU: Jun-04	US: 2004 EU: 2004 AU: 2004	2.8-3.3	cisplatin
pertuzumab	Indicated in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.	L01XC13	Breast	AU	US: Jun-12 EU: Dec-12 AU: May-13	US: - EU: - AU: -	15.7	trastuzumab + docetaxel
pomalidomide	A thalidomide analogue indicated for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate.	L04AX06	Hematological	AU/ EU / US	US: Feb-13 EU: May-13 AU: Jul-14	US: - EU: - AU: -	≥ 3 months (Magnitude uncertain)	standard care / high-dose dexamethasone (safety)
radium Ra 223 dichloride	An alpha particle-emitting radioactive therapeutic agent indicated for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease.	V10XX03	Prostate	-	US: May-13 EU: Sep-13 AU: May-14	US: - EU: - AU: -	2.8	placebo
regorafenib	Treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based	L01XE21	GI	-	US: Sep-12 EU: Jun-13 AU: Nov-13	US: 2013 EU: 2014 AU: 2015	1.4	placebo

	chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.							
romidepsin	Treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy.	L01XX39	Hematological	AU/ EU / US	US: Nov-09 EU: - AU: Aug-13	US: - EU: - AU: -	n/a	n/a
ruxolitinib	Treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.	L01XE18	Hematological	AU / EU (w) / US	US: Nov-11 EU: Apr-12 AU: Jun-13	US: - EU: - AU: -	Increase (Magnitude uncertain)	BSC
sipuleucel-t	An autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.	L03AX17	Prostate	-	US: Apr-10 EU: Jun-13 AU: -	US: - EU: - AU: -	4.0	BSC
sorafenib	Treatment of patients with advanced renal cell carcinoma.	L01XE05	Renal	EU / US	US: Dec-05 EU: Apr-06 AU: Sep-06	US: 2007 EU: 2007 AU: 2008	≥ 3 months (Magnitude uncertain)	BSC
temsirolimus	A kinase inhibitor indicated for the treatment of advanced renal cell carcinoma.	L01XE09	Renal	EU / US	US: May-07 EU: Sep-07 AU: Jun-08	US: - EU: 2009 AU: -	3.6	interferon-alpha
tositumomab	Treatment of patients with CD20 positive, follicular, non-Hodgkin's lymphoma, with and without transformation, whose disease is refractory to Rituximab and has relapsed following chemotherapy.	V10XA53	Hematological	EU (w) / US	US: Jun-03 EU: Feb-03 AU: May-04	US: - EU: - AU: -	n/a	n/a
trametinib	Treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.	L01XE25	Skin	AU	US: May-13 EU: Apr-14 AU: Feb-14	US: - EU: - AU: -	Increase (Magnitude uncertain)	dabrafenib
trastuzumab emtansine	Indicated as a single agent for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: a) Received prior therapy for metastatic disease, or b) Developed disease recurrence during or within six months of completing adjuvant therapy.	L01XC14	Breast	AU	US: Feb-13 EU: Sep-13 AU: Sep-13	US: - EU: - AU: -	5.8	lapatinib + capecitabine
vorinostat	Treatment of cutaneous manifestations in patients with cutaneous T- cell lymphoma (CTCL) who have progressive, persistent or recurrent disease on or following two systemic therapies.	L01XX38	Hematological	AU / US	US: Oct-06 EU: - AU: Dec-09	US: - EU: - AU: -	0	BSC
ziv-aflibercept	Indicated in combination with 5-fluorouracil, leucovorin, irinotecan- (FOLFIRI) for patients with metastatic colorectal cancer (mCRC) that is	L01XX44	GI	-	US: Aug-12 EU: Nov-12 AU: Apr-13	US: - EU: - AU: -	1.4	placebo

	resistant to or has progressed following an oxaliplatin-containing regimen.

Source:

Drug sample selection, as described in Methods section.

Notes:

[1] Orphan status obtained from orpha.net for the US and EU, and from the TGA's Orphan Drug registry for Australia.

[2] Initial approval for 1º FDA indication.

[3] New/Modified Indication (target), New Dosage Regimen, or Alteration to Patient Population by the FDA, or EMA, occurring within three years of initial approval (Y + 2), through 1 Jan 2016. For Australia, a search of ARTG registrations, AusPARs, Orphan Drugs, PBS, PI sheets from the TGA, and the TGA website was conducted. Adis Insight drug profiles were also searched if these data sources were insufficient.

Dosing and Treatment Duration

(b) (4)

(b) (4)

[redacted]

Treatment Cost and Utilization

(b) (4)

[redacted]

(b) (4)

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(b) (4)

[redacted]

Secondary Analysis

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Discussion

Several streams of evidence are needed to assess the value of cancer tools and treatments. As ASCO's recently published Value Framework highlights, a systematic approach is needed to assess the clinical risks and benefits of new cancer medicines. Chapter 2 of this thesis adapted ASCO's Value Framework to gather this evidence for all new anti-cancer medicines that were approved by the US FDA or EU EMA between 2003 and 2013. However, the extent to which drug-related clinical risks and benefits manifest in real-world settings depends on the use of new drugs by patients. ASCO's Value Framework also assumes that rigorous costing data would be available to determine whether drug health benefits are commensurate with their cost.

There is nevertheless a dearth of reliable, comparative evidence on cancer drug utilization (74,75,(b)) and costs (159) that would otherwise support international research into the value from cancer drug spending.

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[redacted]

Dosing and Treatment Duration

There is a wide variation in the total dose that would be expected from a full course of treatment with new cancer medicines. (b) (4)

[redacted]

(b) (4)

[redacted]

Treatment Cost

(b) (4)

These findings are consistent with the notion in the health economics literature that payers may pay premium prices for drugs that treat rare diseases,(227) as well as a body of empirical evidence.(166) Yet, it also appears to contradict Onakpoya and colleagues (2015),(159) who find no significant relationship in scatterplots of disease prevalence against annual cancer drug costs. This apparent contradiction may however be explained by methodological differences in the costing of cancer medicines: unlike Onakpoya and colleagues (2015), who evaluate annualized drug costs, this analysis uses (b) (4) as a standardizing currency. (b) (4)

(b) (4)

(b) (4)

Values for the expected total cost per patient per (b) (4) treatment typically, but not always, increased after initial market entry. These results corresponded with a compound annual growth rate of +10.7% in the total average cost per patient per (b) (4) treatment in France between the first and third year of marketing. The US and the UK experienced a similar, albeit moderated, increase in the compounded annual growth rate in this parameter (+5.3%, +1.7%, respectively). On a volume-weighted basis, where total expected drug costs were weighted by their expected utilization, the compound annual growth rate in the average per patient cost of treatment with new cancer medicines was highest in the US (+33%), followed by Australia (+24.3%), France (+23.7%), and the UK (-12.7%), over the first three years of marketing. Chapter 5 examines whether total expected costs for (b) (4) therapy upon market entry, or

in subsequent years, are associated with the added clinical benefits of new cancer medicines, as is assumed by ASCO's Value Framework.

Treatment Utilization

(b) (4)

Cancer drug utilization varied across treatment indications. Lung cancer medicines were associated with the largest average number of expected patients (b) (4) In contrast, hematological medicines were associated with the least number of patients (b) (4) These findings are consistent with cancer incidence in the US, where it was highest in 2000, 2005, 2010, and 2015, for skin, prostate, breast, tracheal, bronchus, and lung cancers.(266) These results were also consistent with orphan designations: most of the medicines (85%) with orphan status designations in the US were indicated for either hematological or renal cancers. Both indications were, on average, also associated with the least, expected number of patients (b) (4)

(b) (4)

[redacted]

[redacted]

Additional studies are needed to examine the implications for value-based spending. Although initial uptake of new medicines is faster in the US and France than in Australia or the UK, this gap diminishes in subsequent years. Delayed uptake of new medicines may reflect the existence of domestic policies and processes—including HTA—that exist

to signal the value to patients and payers from new medicines. If this is the case, and if domestic policies and processes are successful in signaling value, one would expect there to be a closer relationship between cancer drug utilization and the scale of their clinical benefits. As for cost, this issue is examined in Chapter 5.

Key Learnings and Implications

- There is a wide variation in the total dose and total duration of treatment that would be expected (b) (4)
- Mean estimates of the total expected cost from treatment varied widely across all newly licensed cancer drugs, were highest for hematologicals, increased over time, and varied across countries, with mean total drug costs consistently highest in the US.
- Cancer drug utilization also varied over time and across medicines, and were highest for lung cancer indications and non-orphan medicines.

4

Net Value from Cancer Drug Spending

Introduction

With annualized cancer drug costs now often exceeding US$100,000,(44) US policymakers and academics have increasingly raised questions over the justification for high drug prices.(32,269) Building off the notion that "price must reflect worth,"(32) Kantarjian and colleagues (2013) argue that newer drugs should only be endorsed when "clinical benefits truly reflect incremental value worth the differential price."(32) Despite growing calls for value-based healthcare, there is relatively little empirical evidence comparing spending on cancer medicines against measures of their clinical impact.(22,32–35)

To date, the literature has focused on value from the perspective of cancer care, aggregating medical treatment with drug therapeutics. Using conventional approaches to valuing statistical lives, studies have reported that high-cost cancer care in the US provides net positive value to society, and that higher spending correlates with gains in life expectancy.(8) Others have added nuance, finding that US cancer care provides net

positive value for most cancer indications, though at considerably lower return than in Western Europe.(9)

Context and Empirical Gaps

These studies nevertheless have several limitations that are worth considering. First, international differences in clinical standards, resources, and practices make it difficult to reliably compare value obtained from medical care. This is arguably less of a concern for drug therapeutics, which can be licensed for use in a number of countries. By focusing on total cancer care, the literature is also unable to disentangle the value from different tools and treatments,(8) such as cancer medicines. Prescription drugs are a mainstay in cancer care: they are instrumental in preventing metastases, slowing disease progression, curing cancer, and prolonging survival. A different approach to measuring value in oncology is therefore needed, particularly as drug innovations in therapeutic targeting, multi-agent therapy, and cancer immunotherapy transform patient care.

Considered alongside notable price increases,(44) it remains unclear how much value growing cancer drug expenditures bring to society. This owes in part to a dearth of reliable comparative data on cancer drug development, utilization, and expenditure, three key factors in the extraction of benefit from care.(270) Some have suggested, for instance, that the certainty of positive returns on investment incentivizes drug innovation in the US,(271) in turn expanding choice and value to the patient. Dedicated funding programs—such as England's CDF—may have helped in this regard by promoting access to the newest, but least cost-efficient, cancer medicines, though these today face funding shortfalls, cutbacks, and questions regarding value.(89,272)

Expenditures on cheaper, older generics could instead expand access to life-saving treatment and minimize the social burden from disease, particularly if cost-associated noncompliance is of concern (273) or if new medicines provide marginal survival benefits.

Summary of Research

The literature has generally adopted two approaches to determine whether spending on new tools or treatments provide value-for-money. The first approach assesses whether spending on new treatments results in net positive economic returns to patients and society.(22,33,35,80–82) This chapter adopts a cost-benefit approach to analyze whether the monetized value of survival gains attributable to cancer drug innovation, and based on patients' willingness to pay for a diminished risk of mortality, exceeds growth in drug spending, both at a societal- and drug-level. Chapter 5 adopts the second approach and assesses whether and to what extent spending on treatments is associated with measures of their clinical benefit.(73,85,274–277)

This chapter uses a proprietary dataset from QuintilesIMS to first describe real-world cancer drug development, utilization, and expenditure observed in Australia, France, the UK, and the US between 2004 and 2014. It then takes two different approaches to examine the net long-term value generated from spending on cancer medicines. First, using country-level, longitudinal data on neoplasm-related YPLLs, as well as aggregate spending data from QuintilesIMS, this chapter adapts the methods used by Eggleston and colleagues (2009)(82) to quantify the net long-term value generated at both a neoplasm- and country-level from cancer drug spending in Australia, France, the UK,

and the US. This assessment is based on patients' willingness to pay for a diminished risk of mortality owing to cancer drug treatment. Second, the methods by Eggleston and colleagues (2009)(82) are adapted into a simulation-based analysis that incorporates data from previous chapters—including evidence on expected drug use, cost and survival benefits—to calculate plausible estimates of the net value to patients and society from spending on each new cancer medicine.

Methods

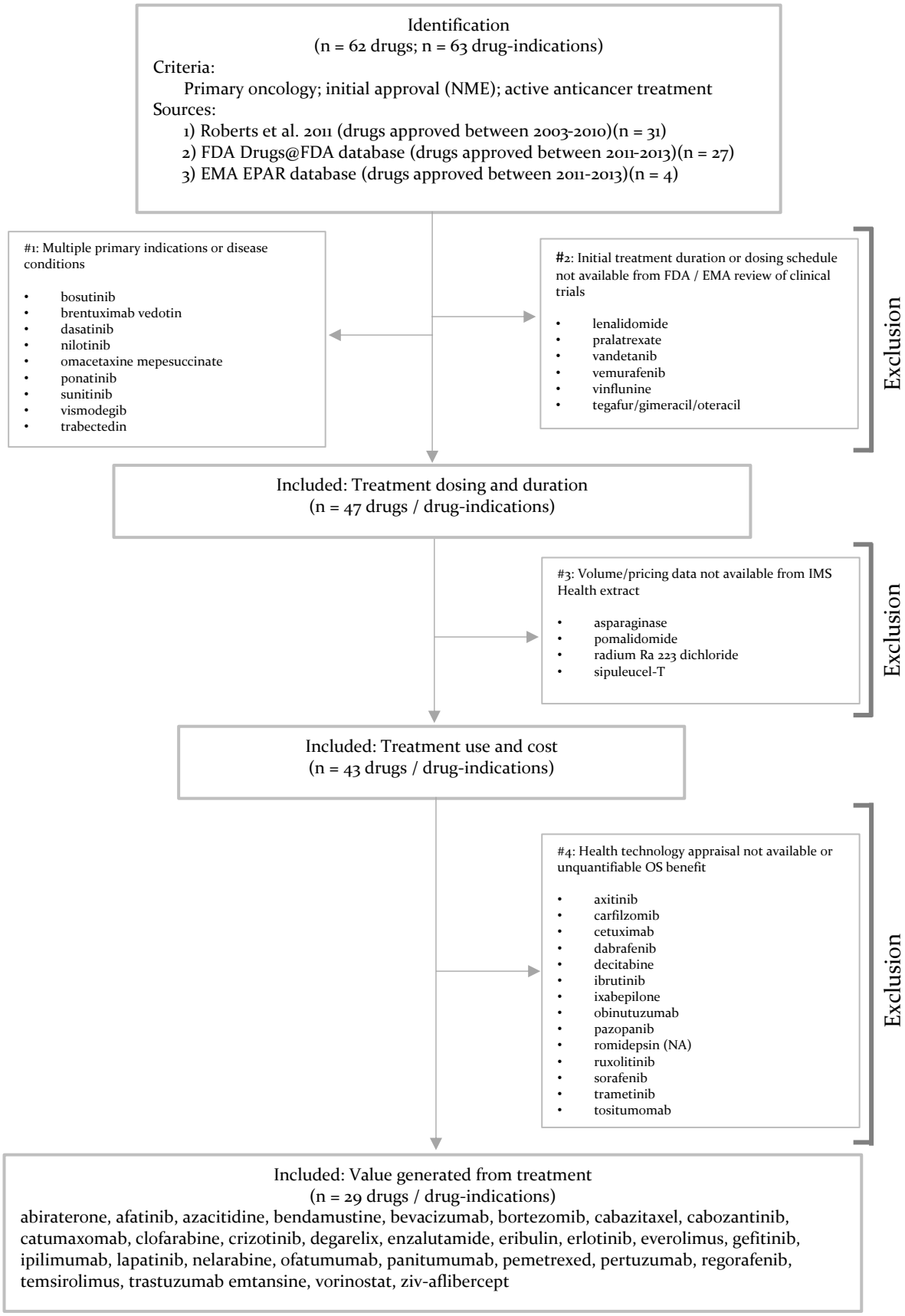
Sample Selection

Since they build on prior chapters, country-level analyses were limited to Australia, France, the UK, and the US. To assess the clinical impact from all new cancer medicines approved in the US or EU between 2003-2013, Chapter 2 took a systematic approach to evaluate HTA appraisals from English (NICE), French (HAS), and Australian (PBAC) HTA agencies published through May 2015. As was described there, these organizations are required to evaluate the clinical risks and benefits of new medicines in relation to existing clinical standards that are used for the same indication,(121–123) and their assessments are often used in value-based decision-making on issues including coverage, pricing, and reimbursement. Chapter 3 then (b) (4) .

All medicines that were included in Chapters 2 and 3 were eligible for inclusion in drug-level analyses of the value from spending on cancer medicines. As in Chapters 2 and 3,

the methods from Roberts and colleagues (33) were used to identify all initial cancer drug approvals by the US FDA and EU EMA occurring between 2003-2013. All NMEs approved by the FDA or EMA over this period with a primary indication for oncology were eligible for inclusion. Any molecule that did not receive licensure by either the FDA or EMA between 2003-2013, and which did not have an initial, primary anticancer indication was therefore excluded. Supplemental applications to the US FDA or EU EMA, new non-active treatments, licensing supplements, labeling revisions, and new or modified indications were not considered. Medicines were excluded from drug-level analyses if Chapter 2 was unable to quantify the OS benefits of new cancer medicines, either because HTA appraisals were not available from English, French, or Australian HTA agencies through May 2015, or because HTA agencies were not able to quantify OS benefits. For more information, please refer to Chapter 2. The drug selection process is depicted in (Figure 8).

Figure 8. Drug Sample Inclusion/Exclusion Criteria



Source:

Authors' analysis of data, as described in Methods section.

Data sources

Unit-level pricing and volume data was obtained from QuintilesIMS's proprietary MIDAS database. This data package provided yearly cross-sectional public pricing, sales volume, and molecule descriptors—manufacturer, product name, international product name, molecule, ATC code, and patent status—for all new and existing cancer medicines marketed between 2004-2014 across retail and hospital settings in Australia, France, the UK, and the US. Public price data in euros was captured at the point of sale to consumers, while sales volume was given both in terms of single standard dose units irrespective of presentation (e.g. capsule, tablet, ampoule) and kilograms. As in previous studies,(74,75) sales volume was used as a proxy measure of utilization. Cancer drugs were defined by QuintilesIMS as all molecules with an L1 or L2 ATC classification. Adjuvant therapies were excluded from this dataset.

Yearly incidence of malignant neoplasms was obtained from the OECD's OECD.stat registry (278) and the US CDC's USCS registry,(279) while one- and five-year average cancer prevalence data was obtained from the WHO's GLOBOCAN registry (280) for 2012, the only year for which data was available. YPLLs from all neoplasms were used as a population-based mortality indicator. This metric has previously been used in length-of-life applications to measure cancer burden on society,(281–284) impact of treatment exposure on survival,(285–287) and to compare health burdens across disease areas, years, and countries.(284,288) Unlike other related metrics of health burden, such as DALYs and YLDs, YPLLs do not subjectively value the state of health. Rather, they measure health burdens as the number of additional years that the patient could have potentially lived in the absence of disease. This metric is also used by health regulators and policy stakeholders—including, England's NICE and the HSCIC—to measure the

impact from efforts to avert premature death from causes that are considered to be amenable to healthcare, including neoplasms.(286,287)

Total neoplasm-related years of potential life lost (YPLL) per 100,000 population (age-standardized, both sexes) were obtained from the IHME GBD 2013 registry, which provides rigorous and comparable measures of epidemiological levels and trends worldwide.(289,290) For reference, these YPLL data were not adjusted for cancer incidence, but for total population. An overview to the IHME's methods for calculating comparative and cause-specific YPLLs is provided in Appendix 4.1.

To account for time discontinuities in these two data sources, a simple linear regression was used to extrapolate neoplasm-related YPLLs per 100,000 population and total yearly neoplasm incidence for each country in this analysis.

To do so, the following model was used over the entire panel for which YPLL data was available from the IHME between years 2000 and 2013 (latest available year)(2000, 2005, 2010, 2013):

$$\frac{YPLL}{100{,}000\ population}_{ct} = cons + Year_{ct} + \varepsilon_{ct} \qquad (6)$$

The dependent variable in *Eq. (6)* reflects the neoplasm-related YPLLs per 100,000 population in country c and year t. The results from this regression are provided in Table 1.

Table 11. Simple Regression with Panel Data, Neoplasm-Related YPLL / 100,000 Population (IHME)

	Model Summary					Parameter Estimates	
	R^2	F	df_1	df_2	Sig.	Constant	Year
Australia	**0.8451**	**10.91**	**1**	**2**	**0.0807**	**57760.310**	**-27.364280**
France	**0.9908**	**215.89**	**1**	**2**	**0.0046**	**84516.246**	**-40.359178**
UK	**0.9701**	**64.88**	**1**	**2**	**0.0151**	**91142.443**	**-43.788774**
US	**0.9754**	**79.26**	**1**	**2**	**0.0124**	**62509.710**	**-29.616311**

Source:

Authors' analysis of data, as described in Methods section.

A simple linear regression was also used to account for time discontinuities in the total neoplasm incidence data that was available. This analysis first obtained total yearly number of new cases of malignant neoplasms for Australia, France, the UK and the US from the OECD's OECD.stat registry for the entire panel of available years between 2000 and 2012 (latest available year).(278) For most countries in this sample, the OECD provided data for four years within this period, 2000, 2002, 2008 and 2012. For Australia, yearly neoplasm incidence data was only available for 2002, 2008 and 2012. Incidence was available from the OECD for the US. However, while the simple linear model shown above closely fit the data for most countries—R^2 values for country-level regressions ranging between 0.95 and 0.99—its fit with US data was unusually poor ($R^2 = 0.67$), perhaps pointing to reliability issues in the US data that is published by the OECD for this parameter. To correct for this, US OECD total malignant neoplasm incidence data was replaced by total malignant neoplasm incidence data from the US CDC USCS registry for 2000, 2002, 2008 and 2012.(279) This parameter was then used as the dependent variable in the following model to examine the relationship between total malignant neoplasm incidence and year:

$$NeoInc_{ct} = cons + Year_{ct} + \varepsilon_{ct} \qquad (7)$$

The dependent variable in *Eq. (7)* reflects total neoplasm incidence in country c and year t. The model incorporating OECD data for Australia, France, the UK, as well as US CDC data for the US, performed well, resulting in an R^2 value of between 0.95 and 0.99 for Australia, France, and the UK, and now resulting in an acceptable R^2 value of 0.88 for the US. The results from this regression are provided in Table 12.

Table 12. Simple Regression with Panel Data, Total Neoplasm Incidence (OECD, US CDC)

	Model Summary					Parameter Estimates	
	R^2	F	df_1	df_2	Sig.	Constant	Year
Australia	**0.9991**	**1143.67**	**1**	**1**	**0.0188**	**-7013069.60**	**3546.092100**
France	**0.9747**	**77.2**	**1**	**2**	**0.0127**	**-16186658.00**	**8221.719800**
UK	**0.9563**	**43.73**	**1**	**2**	**0.0221**	**-12444331.00**	**6350.076900**
US	**0.8821**	**14.97**	**1**	**2**	**0.0608**	**-47024263.00**	**24154.247000**

Source:

Authors' analysis of data, as described in Methods section.

Neoplasm-related YPLL data was incidence-adjusted to account for international differences in risk of illness and need for treatment.(291) Finally, annual population size estimates were obtained from the World Bank,(292) as were consumer price inflation indices.(293) Euro-US dollar conversion rates were also obtained from OANDA.(294)

Analysis

Country-Level

Drug Development

To shed light on drug development as a marker for patient choice, four parameters were calculated within each country-year cross-section: total unique cancer drug molecules available; percent of total US cancer molecules available; manufacturers per available cancer molecule; and percent of total unique molecules available exclusively in branded form. Drug availability was calculated in terms of unique molecules marketed in each country, and was defined by yearly sales volume ≥1 standard unit.

Utilization and Expenditure

Cancer drug utilization is difficult to compare internationally. In part because drug dosages can vary, previous studies have recommended that volume be used to compare utilization across settings, and that volume be expressed in terms of DDDs "wherever possible."(74) Cancer drugs, however, are unique in that they are not typically assigned DDDs by the WHO due to their "highly individualized use and wide dosage ranges."[e.g. (178)] In the absence of other utilization measures—including number of patients treated with individual medicines—previous studies have suggested that comparative

analyses of cancer drug utilization use grams of active molecule as a standard measuring unit.(74,75) This is echoed by the WHO, which also recommends that the utilization of antineoplastic agents be measured in grams, given the lack of other publicly-available volume measures.[e.g. (178)] In line with published studies,(74,75) country-level analyses of cancer drug utilization in this chapter were based on gram units.

Total drug spending was derived through the following process: nominal euro public pricing per standard unit was first converted to constant 2014 terms by using consumer price inflation indices from the World Bank. Euro pricing was converted to US dollar equivalents using period average euro-USD exchange rates for Q4 2014, the delivery quarter of the QuintilesIMS dataset. Unit-level public drug prices were then multiplied by standard unit sales for each marketed molecule to derive annual unit-level expenditures. Finally, annual unit-level expenditures and utilization volumes were summed by drug patent status, ATC group, and country.

Crude comparisons of cancer drug use and spending may be misleading if associated populations are of unequal size or have unequal epidemiological risks of disease.(291) Spending on anticancer medicines is not meant to prevent disease, but to actively mitigate its impact on health once disease has occurred. From the perspective of this study, countries with an unusually high number of incident cancer cases could therefore be expected to have higher rates of cancer drug use, expenditure, and YPLLs, *ceteris paribus*, while the opposite claim could also apply for countries with an unusually low incidence of cancer. Different epidemiological risks of disease may reflect prevention-related factors (e.g. environmental risks) that are not the focus of this study. While prevention is certainly an important dimension to drug spending, and is therefore

deserving of attention, this study instead focused on the remedial value of spending on active treatment once disease has occurred. To therefore adjust for potential differences in the total population across countries, and in relative risks associated with developing cancer, this study adjusts country-level drug sales volume, expenditure, and YPLLs per 100,000 population by yearly incidence of malignant neoplasms. This methodology has been advocated in the literature as a means of reliably comparing cancer drug utilization across country settings.(74,75)

In line with established methods,(74,75) base-case analyses therefore adjusted drug utilization and expenditure by the total annual incidence of malignant neoplasms between 2004-2014. Total annual incidence of malignant neoplasms was derived for each country through a simple linear regression using country-level panel data from the OECD and US CDC, as described above. Incidence-adjusted cancer drug spending and utilization was then calculated by dividing country-level spending and utilization figures by yearly estimates of total new cases of malignant neoplasm. To test for robustness, sensitivity analyses also adjusted cancer drug utilization and expenditure by the total population in each country-year, and the one- and five-year cancer prevalence in each country for 2012 (data only available for one year). For reference, one-year cancer prevalence figures correspond to the initial stage treatment, while five-year cancer prevalence figures instead typically correspond to the cured stage.(295) These methods are adapted from previous studies comparing international prescription drug usage.(74,75) The reasons for preferring this approach are also described below.

First, in line with previous reports,(74,75) base case analyses adjusted total yearly cancer drug utilization and expenditure by total cancer incidence observed in each country-year

between 2004-2014. Sensitivity analyses also adjusted cancer drug utilization and expenditure by one- and five-year cancer prevalence, which was only available from the WHO GLOBOCAN registry for 2012. As is discussed later in this chapter, the overall trends from this analysis were consistent with incidence-adjusted results. Besides providing a measure of validation for base-case analyses, this finding also suggests that cancer incidence is similarly proportional to cancer prevalence across the sample of countries that are included in this study. A similar outcome was observed when analyses were adjusted by total population in each country-year.

Second, as there is no comparable, patient-level registry on actual cancer drug use,(75) this approach was used to adjust for the number of patients expected to be on active anticancer treatment. As it applies to cancer, prevalence can be defined as the number of living patients who have ever been diagnosed with cancer, including those who were treated for cancer in the past and who may be receiving adjuvant therapy. One-year cancer prevalence is in fact defined by the GLOBOCAN registry as the number of cancer patients still alive one year after diagnosis; a similar definition exists for five-year cancer prevalence.(295) Since antineoplastic agents are only indicated for use in patients with active malignancies, it would be inappropriate to adjust current utilization of, and expenditure on, active chemotherapeutic agents by prevalence figures that include patients with non-active disease. Furthermore, the methods used in Chapter 3 could in theory be used to adjust for the total number of patients on active, anticancer therapy in each country-year. Country-level analyses in this study however evaluated aggregate sales volumes, and therefore were not adjusted using estimates of the number of patients on treatment from Chapter 3, which only focused on new medicines.

Third, adjusting cancer drug utilization and expenditure by incidence rather than prevalence arguably provides a more accurate estimate of the total value obtained from expenditure on cancer drugs. Yearly cancer incidence captures all new cancer cases occurring within that year, while cancer prevalence is defined as the total number of patients who are still alive within some period after diagnosis.(295) Total yearly incidence can therefore be thought of as an upper limit to the one-year prevalence of cancer, and both parameters would, in theory, equal one another were no deaths to occur. Given the often-lethal nature of cancer, however, estimates of total yearly cancer incidence are expected to be higher than one-year cancer prevalence in most settings. Country-level estimates of yearly cancer incidence from the GLOBOCAN registry are in fact often greater than those observed for one-year cancer prevalence. A similar argument applies to total incidence of malignant neoplasms over a five-year period, and the corresponding five-year prevalence value.

As with incidence, adjusting for cancer prevalence helps to overcome potential biases from international differences in the risk of illness onset, and therefore helps to compare drug usage internationally.(74,75) However, adjusting for prevalence—as defined by GLOBOCAN—fails to account for patients who die within one year of diagnosis but who nevertheless would be expected to receive at least some treatment for active malignancies. In the absence of observational data that is internationally comparable,(75) total incidence of malignant neoplasms is therefore taken as the most representative estimate of the number of patients with active malignancies who would be expected to receive treatment. It is therefore used to adjust country-level estimates of cancer drug utilization, expenditure, and net value from drug spending.

Net Value

On an aggregate level, cancer drug spending is generally meant to prolong life once disease has occurred. YPLLs due to all neoplasms is therefore taken over time as a country-level indicator of the impact on health from cancer drug spending. The incremental change in total, incidence-adjusted drug expenditures and neoplasm-related YPLLs were calculated for each country-year in this analysis relative to their base values in 2004. Both parameters were then used to derive incremental cost-effectiveness ratios corresponding to the incremental change in expense and the incremental change in health between 2004 and year t. Long-term estimates of net value were calculated by subtracting incidence-adjusted excess treatment costs (ΔC) from the monetized value of survival gains (ΔV) observed in each country c between 2004 and year t (*Eq. (8)*), based on patients' willingness to pay for a diminished risk of death from drug treatment.(82) This approach was adapted from Eggleston and colleagues (2009),(82) who used it to estimate the net value of health care for patients with type 2 diabetes. The recent literature has also adopted this approach to examine the value from long-term changes in healthcare spending and cancer survival in cancer populations.(22,33,35,80) For reasons explained in Chapter 3, its use of US SEER data nevertheless makes it difficult to conduct this analysis across country settings.

$$NV_{ct} = \Delta V_{ct} - \Delta C_{ct} \qquad (8)$$

Country-level analyses used US$100,000 to conservatively value a statistical life year in the absence of disease ($VSLY$). Given its centrality to this study, a brief overview to the value of a statistical life year is provided in Box 4.

Box 4. Overview of the VSL and the VSLY

The concept of the VSL and $VSLY$ is explained in detail elsewhere.(365) An overview to this concept is nevertheless provided here. The VSL is a monetary figure representing the amount of wealth (W) that an individual would be willing to forgo in return for a reduction in the probability of death (P). The $VSLY$ specifically relates to the monetary sum that an individual would be willing to forgo in return for some probabilistic increase in extending life by one year. This is represented through the following (299,365):

$$VSLY = \frac{r * \left(\frac{\Delta W}{\Delta P}\right)}{1 - (1 + r)^{-L}}$$

Where L is defined as life expectancy, and r is the discount rate, which is assumed to be 3%.(299)

The value that is assigned to life does not need to be constant, and can vary across individuals due to a number of different factors, including personal wealth and preferences, and is frequently calculated through stated preferences.(365) Disease type and severity can also impact the value that is assigned to life, with the literature suggesting that a premium applies to cancer. Nevertheless, since modern health systems generally involve a tradeoff between health and wealth, the concepts of VSL and $VSLY$ can be used to represent the transactions that are incurred by payers in return for treatment that is believed to be associated with some probabilistic extension to life. The literature has provided many estimates for the $VSLY$, though most generally range between $100,000–$300,000.(33,80,297–300,366–371) New treatments for use in cancer at the end of life may be valued at the higher end of this range, or ~$300,000 per life year.(304) Alternative methods for measuring patients' willingness to pay for improve survival may try to calculate a patient's WTP for longevity gains using lifetime income data, while accounting for discrete increases in survival probabilities.(303) Studies that have adopted this approach in cancer estimate that the annual value placed on CML treatment, based on the average lifetime income of patients, is ~$110,000 per life year gained.(35) Within this backdrop, this chapter takes $100,000 per life year gained from treatment as a conservative VSLY estimate.

To then estimate the long-term net value generated by each country from cancer drug spending, yearly, incidence-adjusted estimates of the net value generated from survival gains were multiplied by country-level estimates of the total yearly number of incident cases of neoplasm.

To examine the net value from spending on cancer medicines, in particular, it was necessary to assume that some percentage of survival improvements were attributable to pharmaceutical innovation (a). *Eq.(8)* was modified to account for this:

$$NV_{ct} = [(a_{ct} * |\Delta YPLL_{ct}|) * VSLY] - \Delta C_{ct} \quad (9)$$

Base-case levels of attribution were calculated for each country as the percentage between country-specific improvements in neoplasm-related YPLLs and the average, total improvement in OS of 3.43 (SEM, 0.63) months between 2003-2013 from all new anticancer medicines approved by the US FDA or EU EMA over this period, a finding from Chapter 2 of this thesis. This figure represented 19%, 14%, 17%, and 26% of the total improvement in neoplasm-related YPLLs observed in Australia, France, the UK, and the US, respectively, between 2004-2014 (Table 13). These values were consistent with a recent study reporting that all 58 cancer drugs newly marketed over the 18-year period 1995-2013 increased cancer life expectancy by an average of 0.46 years in the US.(73) They are however somewhat more conservative than those reported by Jönsson & Wilking (2007), in which 44% of the increase in the cancer survival rate observed in the US over the seven-year period 1992-1999 was attributed to increased utilization of post-1990 drugs.(296)

Table 13. Attribution of Long-Term Improvement in Cancer Patient Survival to Cancer Drug Innovation

Country	$\Delta OS_{drugs,\ 03\text{-}13}$ (years)[1]			$\Delta YPLL_{country,\ 04\text{-}14}$ (years)[2]	Attribution (%)[3]		
	Mean	-SEM	+SEM		a_{Mean}	a_{-SEM}	a_{+SEM}
Australia	**0.29**	**0.23**	**0.34**	**1.472**	**19%**	**16%**	**23%**
France	**0.29**	**0.23**	**0.34**	**2.053**	**14%**	**11%**	**16%**
UK	**0.29**	**0.23**	**0.34**	**1.641**	**17%**	**14%**	**21%**
US	**0.29**	**0.23**	**0.34**	**1.109**	**26%**	**21%**	**31%**

Source:

Authors' analysis of data, as described in Methods section.

Notes:

[1] From chapter 2, average (SEM) OS benefits between 2003-2013 associated with all anticancer medicines newly licensed by the US FDA and EU EMA over this period.

[2] Total, country-level, incidence-adjusted, neoplasm-related YPLLs. For convenience, values for the change in YPLL between 2004-2014 are multiplied by -1.

[3] Percentage of the improvement in total, country-level, incidence-adjusted, neoplasm-related years of potential that can be attributed to cancer drug innovation. Calculated as $[(\Delta OS_{drugs,\ 03\text{-}13,\ years}) / (\Delta YPLL_{country,\ 04\text{-}14,\ years})] * 100$.

A multivariate linear regression was used to examine the country-level determinants of value from cancer drug spending. In particular, previous studies have explored the relationship between country-level expenditures on total cancer care and cancer outcomes,(8) but have not accounted for patterns of cancer drug utilization. To begin to explore the relationship between country-level patterns of cancer drug use and patient outcomes, this study examined the association between incidence-adjusted, country-level years of potential-life lost, total cancer drug utilization, and generic drug penetration.

Drug-Level

Net Value

The methods outlined by Eggleston and colleagues (2009) were also used within a simulation-based analysis to estimate the long-term net value from spending on new anticancer medicines. This approach was designed to help account for parameter uncertainty, and to estimate the range of plausible outcomes pertaining to the net economic value from drug-related extensions to life.

In this section, health gains were defined in terms of the expected OS benefit to patients from treatment with new medicines (OS_i). Estimates of the total OS benefit from new cancer drugs over best alternative therapies were extracted from Australian, English, and French health technology appraisals, as explained in Chapter 2. A triangular distribution was used to model any variability in the magnitude of drug-specific OS benefits accepted by English, French, and Australian HTA agencies. Survival benefits were monetized using a triangular distribution of published estimates for values of a statistical life year

($VSLY$), which typically range between US$100,000-US$300,000 per life year.(80,297–300) A peak probabilistic weight was assigned to the midpoint of any range in these measures. This approach builds on the methods used elsewhere: Lakdawalla and colleagues (2009, 2015) take a fixed estimate of $200,000 to assign monetary value to gains in life-years, while assessing the impact from uncertainty in this parameter with the use of sensitivity analyses.(80,301)

In the absence of patient-level registries to describe the total cost of treatment associated with comparator therapies, excess treatment costs per patient i in each country c and year t following market entry (eTC_{ict}) were estimated by assuming that they equaled 10%, 50%, or 90% of the full, expected cost for treatment with the new intervention. Data on the expected drug costs for treatment with new cancer medicines was obtained from Chapter 3. Base-case analyses considered a conservative excess treatment cost estimate equal to 10% of total cost per (b) (4) treatment with each new medicine, and assumed that treatment duration (b) (4) For more information on how these estimates were derived, please refer to Chapter 3.

This approach is consistent with recent articles describing growth in cancer drug pricing. Kantarjian and colleagues (2013) suggest that cancer drug pricing is often not based on evidence, but rather set to reflect what the market can bear, arguing (32):

> "pharmaceutical companies seem to analyse the market response to the most similar previous agent and to set the price of the new one somewhat higher."

Rockoff (2015) similarly describes an "arcane" drug pricing process for Pfizer's Ibrance that considered two benchmarks, Herceptin—a widely used medicine for breast cancer that looked "about as good" as Ibrance, according to clinical experts—and Afinitor—Ibrance's most direct and recently developed competitor. On a monthly basis, Herceptin was priced ~50% ($4,775 in late 2013) below the agreed-upon price for Ibrance ($9,850). Meanwhile, the monthly price for Afintor was initially "slightly [below]" that of Ibrance.

The deterministic model of the net value generated per patient i from treatment with each new medicine in each country c and year t following market entry (NV_{ict}) is represented by *Eq. (10)*.

$$NV_{ict} = (VSLY_i * OS_i) - (eTC_{ict}) \qquad (10)$$

The total, expected net economic value generated at a societal level from extensions to life from individual cancer medicines was then estimated. For this, per patient estimates of net value generated from drug spending in each country-year (NV_{ict}) were multiplied by the total expected number of patients receiving treatment in each year following market entry (TP_{ct}), with the latter variable populated using data from Chapter 3. For more information on the methods used to estimate TP_{ct}, please refer to Chapter 3.

$$NV_{ct} = NV_{ict} * TP_{ct} \qquad (11)$$

A series of 2,000 Monte Carlo simulations were used to generate a range of plausible estimates of the net economic value per patient and to society from spending on individual cancer medicines. Since new or modified indications can be approved over the active life cycle of new medicines, this analysis was limited to the first three years of marketing after initial licensing (Y0, Y1, and Y2). Yearly observations were also censored once new or modified indications (target conditions), dosing regimens, or modifications to the approved patient population were approved for new medicines. For more information, please refer to Chapter 3. (b) (4)

Sensitivity Analysis

Failure to adjust for population and epidemiological factors can confound country-level comparisons of cancer drug utilization and expenditure.(74,75) In the absence of international registries providing long-term data on patient care and outcomes,(75) this study adjusted country-level analyses of cancer drug utilization and expenditure by total yearly incidence of neoplasms, drawing on data that was available over the entire 2004-2014 period. Yearly cancer incidence captures all new cancer cases occurring within that year. In contrast, one- and five-year cancer prevalence is defined by the GLOBOCAN registry as the number of cancer patients still alive one- or five-years after first receiving their diagnosis.(295) This approach is preferred as antineoplastic agents are, by definition, typically given to patients with active malignancies. Adjusting for prevalence—as it is defined by GLOBOCAN—fails to capture the full population of patients who die within one year of diagnosis but who nevertheless may be expected to receive at least some treatment during the stage of active malignancy. To nevertheless

test for robustness, sensitivity analyses adjusted country-level estimates of cancer drug utilization and expenditure by total population and cancer prevalence.

Base case values of the percentage of long-term survival gains that could be attributed to pharmaceutical innovation were calculated on the basis of findings from Chapter 2. Chapter 2 found that all anticancer medicines newly licensed by the US FDA and EU EMA extended OS by a total average of 3.43 (SEM, 0.63) months between 2003-2013, which represented 19%, 14%, 17%, and 26% of the total improvement in neoplasm-related YPLLs observed in Australia, France, the UK, and the US, respectively, between 2004-2014 (Table 13). Under the assumption that new medicines were integrated into Australian, French, UK, and US markets after receiving licensure by regulatory authorities, these figures were taken as base case estimates of the percentage of long-term, country-specific survival gains that could be attributed to drug development. To account for uncertainty in these parameters, two sensitivity analyses were performed. The first re-calculated attributable health gains using ± 1 SE (0.63 months) of the mean, total long-term OS benefit (3.43 months). The second assumed that 10%, 25%, 50%, 75%, or 90% of the survival gains that were observed in this study owed to the development of new medicines.

Country-level analyses assumes that the total yearly incident population represents the total number of cancer patients receiving cancer drug treatment. Given that patients may survive from earlier periods and require systemic, anticancer treatments over a multi-year period, the actual patient population in any year may be larger than the total number of new cancer cases. If the treatment population is indeed larger than the population with incident disease, this approach would likely overestimate per-patient

costs and utilization of treatment. There are several reasons to nevertheless believe that this is not a major concern in this study: even if one were to assume that some number of actively treated patients (x) carry-over from the previous year ($y-1$), a similar number of patients ($\sim x$) are also likely to carry over to the following year ($y+1$). In the absence of an international registry providing comparable data on cancer drug use, this chapter also conducted a sensitivity analysis to model the potential impact from such a scenario by assuming that the total population receiving treatment was 50% larger than the total number of incident cancer cases.

Moreover, differences in value obtained from spending on cancer medicines are likely to partially reflect differences in the mode and intensity of treatment. To shed light on how these factors could account for differences in the value obtained from the cancer drug expenditures that were observed in this study, main analyses were stratified by dosage form (oral, injectable) and years since market launch (0-5 years, 6-10 years, >10 years).

Limitations

QuintilesIMS drug pricing data reflects the list price rather than transaction price; discounts and rebates are not built in. Given the potentially guarded nature of drug procurement, it is impossible for this study to systematically adjust for pricing discounts. Regardless, any level of discount would mean that this analysis overestimates drug expenditures and underestimates value. It is however unclear whether this limitation has any practical impact on this study: this issue applies to costing estimates for all drugs and all four countries, and medicines in the same therapeutic category often receive comparable levels of discount.(302) The interpretation of this analysis nevertheless

remains valid with respect to costs that are based on list prices. Future studies should however explore this issue.

Yet, QuintilesIMS data also does not incorporate costs associated with drug dispensing, administration, or supportive care, suggesting that this analysis underestimates the social cost associated with cancer treatment. This issue may be particularly important in oncology, where drug treatments are often dispensed in dissolvable preparations for intravenous, intramuscular, or subcutaneous administration in inpatient or outpatient settings.

This chapter conducts a cost-benefit analysis, and uses the VSLY to monetize life years gained. This approach is adopted from previous studies examining the value of new healthcare interventions,(82) including for cancer.(22,35,80) Alternative methods for health economic evaluation exist, including cost-effectiveness and cost-utility analyses. Cost-utility analyses, for instance, can adjust clinical outcomes by measures of quality of life, but require that quality weights be derived through standardized procedures. Cost-benefit analysis is designed to address the question of whether the benefits of an intervention exceed its costs, and is therefore used in this chapter. This approach was also adopted to assess all new cancer drug treatments, rather than focus on specific agents.(22)

One challenge to cost-benefit analysis is in the assignment of monetary values to health benefits. This study was designed to assess the value generated from drug-related survival benefits based on the VSLY, which measures patients' willingness to pay for

improved survival. Alternative approaches include using classic WTP thresholds, or calculating a patient's WTP for longevity gains using lifetime income data, while accounting for discrete increases in survival probabilities.(303) Yin and colleagues describe the use of this approach in CML (35):

> "the annual value of TKI-related survival gains is equivalent to the increase in annual income necessary to make a CML patient indifferent to the pre- and post-treatment survival curves, which is also equivalent to the patient's willingness to pay for treatment."

Using this approach, Yin and colleagues (2012) estimate that the annual value placed on treatment with first-line imatinib, based on the average lifetime income of patients, is ~$110,000 per life year gained.(35) This value is similar to, yet still higher, than the VSLY used in this chapter. It is also unclear whether patients may in fact be willing to "pay nearly their entire end-of-life wealth for as little as a few extra weeks of life."(33)

Unlike other approaches, the VSLY elicits stated preferences, and may therefore provides a more objective measure of the value from probabilistic extensions to life. This may be particularly important in cancer, where premiums may apply to end-of-life valuations.(304) Even where alternative approaches have been used to monetize life gains, the VSLY-based approach is accepted as a viable "method for estimating the value of cancer survival improvements."(33) The more recent literature has also relied on this approach.(22,80) It is nevertheless important to interpret results with caution: while this chapter adopts established methods, and uses a conservative VSLY estimate, standardized VSLY estimates may not apply consistently to all patients and contexts.

Future studies may build on this analysis by deriving VSLY estimates that are specific to drug-indication settings.

In the absence of RWD on the clinical impact from entry and uptake of new cancer medicines, base-case calculations of net value attributed 19%, 14%, 17%, and 26% of the total, long-term improvement in neoplasm-related YPLLs in Australia, France, the UK, and the US, respectively, to cancer drug innovation. This approach was based on the finding from Chapter 2 that all anticancer medicines newly licensed by the US FDA and EU EMA between 2003-2013 increased OS by 3.43 (SEM, 0.63) months. The US figure was also consistent with those reported in US-based studies.(73,296) To nevertheless examine the impact from any uncertainty in attributing health gains to the development of new cancer medicines, a sensitivity analysis was performed by assuming that anywhere between 10% and 90% of long-term health gains could be attributed to pharmaceutical innovation. Since recent pharmacological breakthroughs exist alongside innovations in medical care,(305) and evolving public health systems, it is unreasonable to presume that drug development accounts for none (0%) or all (100%) of the long-term improvement in cancer survival observed in any country.

Since internationally comparable data on actual drug use is not yet available for all marketed cancer medicines,(75) country-level analyses used sales volume as a proxy.(74,75) In theory, there may be some disparity between sales volume and drug utilization. This however is unlikely to be a major concern in cancer, where drug adherence is likely to be high: cancer treatment is often dispensed at time of prescription or in professional healthcare settings, and even if it is not, cancer patients would be expected to follow prescribed treatment regimens closely.

Cancer drugs were excluded from drug-level analyses if HTA agencies were unable to quantify their impact on OS, as this evidence is necessary to monetize drug-related gains in life-years. While there is no reason to believe that this restriction introduces bias, future studies should attempt to validate this approach by incorporating more recent and definitive evidence of the impact on survival from new cancer medicines.

The MIDAS extract from QuintilesIMS only included pricing and volume data for cancer medicines that were licensed between 2003-2013. Without the means for estimating the costs for all therapeutic comparators, uncertainty in excess treatment costs was addressed through sensitivity analysis: this parameter was set to equal 10%, 50%, and 90% of the total cost (b) (4) of treatment with each new medicine (Chapter 3), with base-case analyses based on the first, and most conservative, scenario. There is a dearth of systematic, publicly available evidence describing how treatment costs evolve over time. The approach used here was nevertheless consistent with a recent article describing the "arcane" drug pricing process for Pfizer's Ibrance (306): around the time of market entry, the monthly price of a widely-used breast cancer medicine that clinical experts suggested was clinically comparable was ~50% less than that of Ibrance. Ibrance's price was, at the same time, "slightly above" that of its most direct and recently developed comparator, Novartis AG's Afinitor. To nevertheless reduce the uncertainty in excess treatment cost estimates, future studies should extend this analysis by licensing an unrestricted pricing and volume dataset and by using RWD, as it becomes available.

In line with previous studies,(82) this analysis monetizes survival exclusively, and does not consider other dimensions of clinical impact from treatment. Chapter 2 found that

while the largest share of new cancer medicines is associated with QoL benefits, a similarly large share reduces patient safety. Improvements in QoL would be expected to increase the value that patients give to health, which would likely skew the monetized value of survival gains upward; reductions in safety would do the opposite. That cancer patients may exhibit negative time discounting (307)—perhaps explaining "cancer premiums" that apply to VSLYs (298)—could suggest that temporary reductions in safety have a relatively low impact on the net value derived from treatment if it means longer overall life. This is in fact reflected in ASCO's Value Framework for cancer treatment options, where survival benefits are given the most weight when estimating NHB scores for new medicines.(12) The degree to which this is true may however vary by cancer staging, severity, and personal preferences.

In the absence of patient-level data to monetize changing health states across all new cancer medicines, this chapter does not attempt to model the economic value from drug-related changes in QoL and safety. To address this gap, future studies could attempt to bridge the methodology used here with the valuing health literature, as well as recent empirical advances quantifying the willingness-to-pay for QoL benefits.(308)

Finally, the lack of a comparable, international cancer drug registry also prevents this study from exploring how personal and demographic factors, as well as local preferences for treatment across cancer stages, that may impact the association between spending and clinical outcomes. Although these analyses would help inform the interpretation of results, their absence does not bias this study. Future investigations may nevertheless wish to explore these issues as internationally comparable, patient-level data becomes available.

Results

Country-Level Analysis

Drug Development

All countries witnessed an increase in the total number of available cancer drug molecules between 2004-2014, though rates of entry vary (Table 14). Availability of cancer drug molecules today is highest in the US, with the UK and France close behind. With the exception of Australia, global cancer drug availability has moved towards parity with the US (Table 14), suggesting comparable levels of value to patients from drug development.

There has been a decline in the branded drug share of oncology drug markets, with countervailing growth in the number of generic medicines. A majority of cancer molecules nevertheless remain available exclusively in branded form (Table 14). Among the four countries, France has led the decline in branded market share, though the country continues to have the highest proportion of cancer drugs available exclusively in branded form. Unlike other countries included in this analysis, Australia witnessed a modest increase in branded market share between 2004-2014 (Table 14), perhaps owing to delays in drug entry.(309)

Table 14. Description of Cancer Drug Markets, Sales Volume, and Expenditures, 2004-2014

	Australia		France		UK		US	
	2004	**2014**	**2004**	**2014**	**2004**	**2014**	**2004**	**2014**
Market								
Total molecules available	75	97	87	126	81	127	86	131
Percent of US molecules	87%	74%	101%	96%	94%	97%	100%	100%
Manufacturers / drug	1.8	2.8	1.6	2.8	2.2	2.6	2.3	2.7
Percent total molecules, branded[1]	48%	54%	79%	71%	63%	63%	66%	65%
Sales Volume								
Total[2]	4039	6897	17567	25131	13552	23103	69527	87786
Incidence-adjusted[3]	43291	53565	60645	67577	48189	67019	50351	54109
Incidence-adjusted, branded[3]	35542	44346	49508	52478	36587	21307	17953	15597
Incidence-adjusted, generic[3]	7749	9219	11137	15099	11603	45712	32397	38512
Expenditures								
Total[4]	$1.6	$3.4	$7.4	$13.7	$4.3	$11.2	$53.3	$119.9
Incidence-adjusted[5]	$17,515	$26,498	$25,601	$36,830	$15,461	$32,615	$38,571	$73,920
Incidence-adjusted, branded[5]	$15,121	$23,919	$24,091	$32,304	$13,600	$25,826	$35,701	$66,088
Incidence-adjusted, generic[5]	$2,393	$2,579	$1,511	$4,527	$1,861	$6,789	$2,870	$7,831

Source:

Authors' analysis of data, as described Methods section.

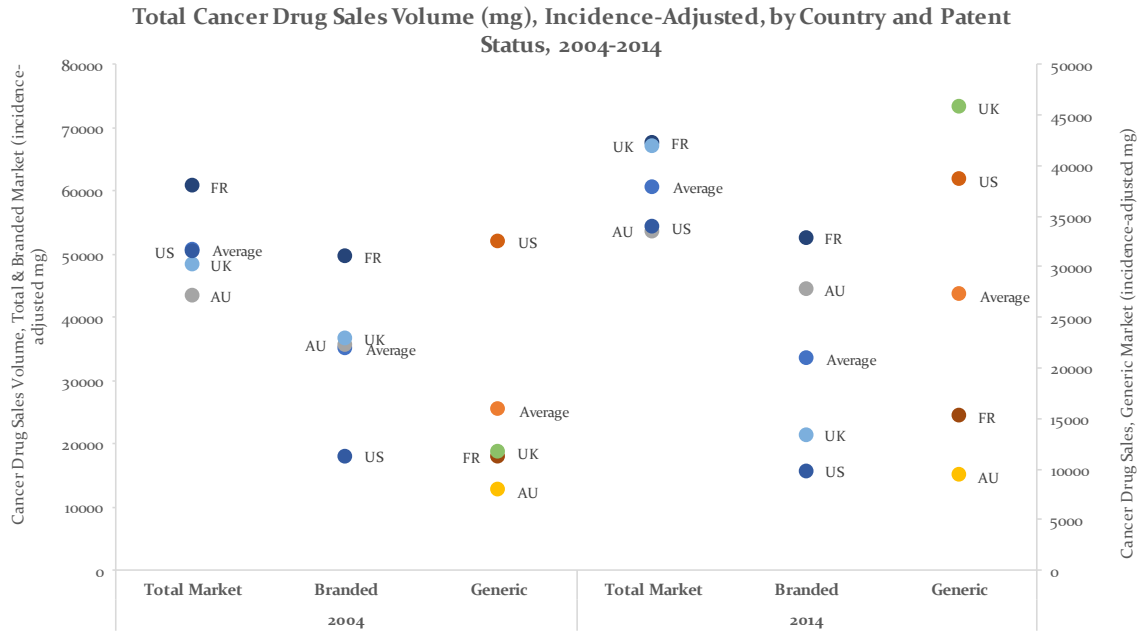
Notes:

[1] Percentage of total available molecules sold exclusively in branded form.
[2] Volume sales given in terms of kilograms (million milligrams).
[3] Volume sales given in terms of incidence-adjusted milligrams.
[4] Expenditures given in terms of billion constant 2014 US dollars.
[5] Expenditures given in terms of incidence-adjusted, constant 2014 US dollars.

Utilization

There were wide variations in incidence-adjusted cancer drug use across the four countries. Relative to other countries, Australia consistently used a low volume, while France used a high volume, of cancer medicines. Total, incidence-adjusted volumes of utilization are now significantly greater than the global average in France and the UK, and significantly less than the global average in Australia and the US (Figure 9).

Figure 9. Total Cancer Drug Sales Volume (mg), Incidence-Adjusted, by Country and Patent Status, 2004-2014

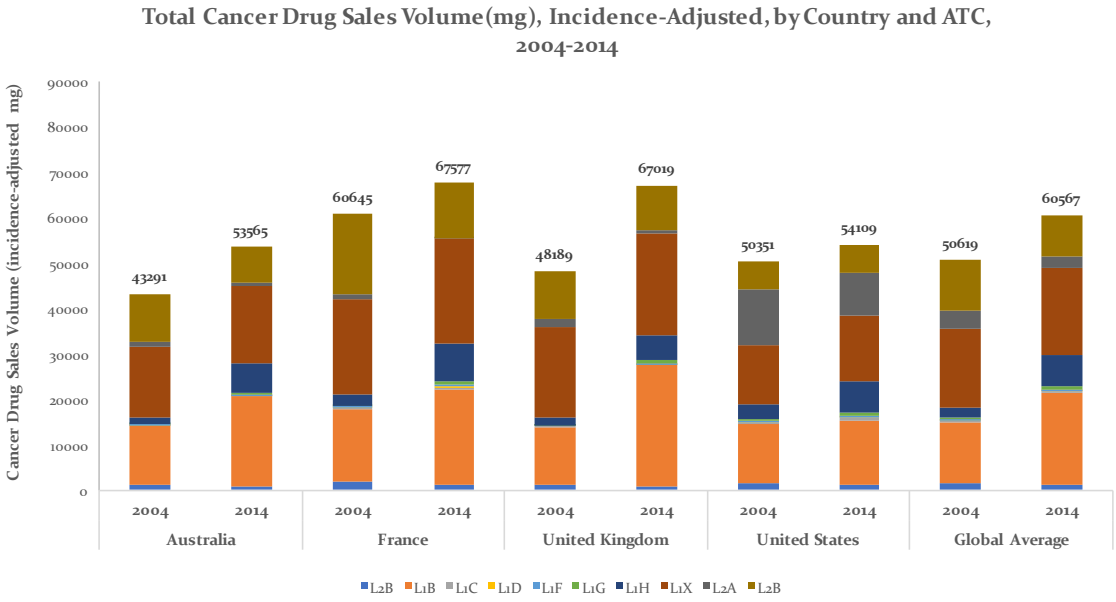


Source:

Authors' analysis of data, as described in Methods section.

Patterns of drug utilization however varied by patent status, over time (Figure 9), and across cancer drug classes (Figure 10). The US, for instance, was associated with a consistently high volume of use of generics, but a low volume of use of branded medicines, relative to the other countries in this analysis. In 2014, the US fell above the 95% confidence interval for the global average sales volume of antimetabolites (L1B) proportional to country-specific, incidence-adjusted sales volumes of all cancer medicines. The same was also true for all other antineoplastics (L1X), and cytostatic hormone antagonists (L2B), suggesting comparatively high levels of utilization of these molecules. The US however fell below the global 95% confidence interval for sales volume of platinum antineoplastics (L1F), monoclonal antibody antineoplastics (L1G), and cytostatic hormones (L2A)(Figure 10).

Figure 10. Total Cancer Drug Sales Volume (mg), Incidence-Adjusted, by Country and ATC, 2004-2014



Source:

Authors' analysis of data, as described in Methods section.

Expenditure

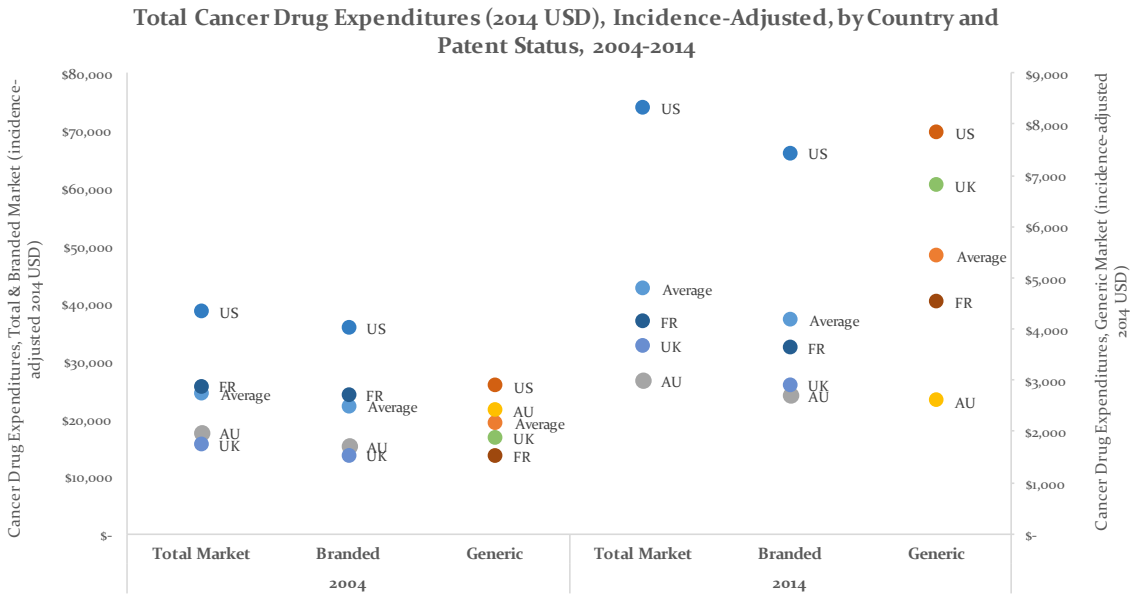
Global expenditures on cancer drugs have risen sharply between 2004-2014, in total and across both branded and generic drug markets. Compound annual growth rates in total, incidence-adjusted cancer drug expenditures varied widely, averaging 4% in France, 4% in Australia, 7% in the US, and 8% in the UK (Table 14).

Total expenditures on branded medicines accounted for a sizeable portion of the overall increase in expenditure on cancer drugs, with incidence-adjusted compound annual growth rates in expenditure on all branded drugs of 3% in France, 5% in Australia, 6% in the US, and 7% in the UK. Expenditures on branded medicines increased even as their market share declined, reflecting branded drug prices that rose at a compounded annual rate of 1% in France, 4% in the UK, 8% in the US, and 9% in Australia.

Incidence-adjusted expenditure on generic medicines nevertheless rose at a faster rate in most countries, rising at a compounded rate of 1% in Australia, 11% in the US, 12% in France, and 14% in the UK per annum (Table 14). Increases in generic drug expenditure reflected increased generic drug use, but also increases in generic drug price. At a country-level, these rose at a compounded rate of 0.3% in Australia, 4% in the US, 5% in the UK, and 9% in France.

Total expenditures on cancer medicines also varied widely, even after standardizing for cancer epidemiology (Figure 11). On an incidence-adjusted basis, the US has consistently outspent other countries across all classes of cancer therapeutics, as well as both branded and generic drug markets.

Figure 11. Total Cancer Drug Expenditures (2014 USD), Incidence-Adjusted, by Country and Patent Status, 2004-2014

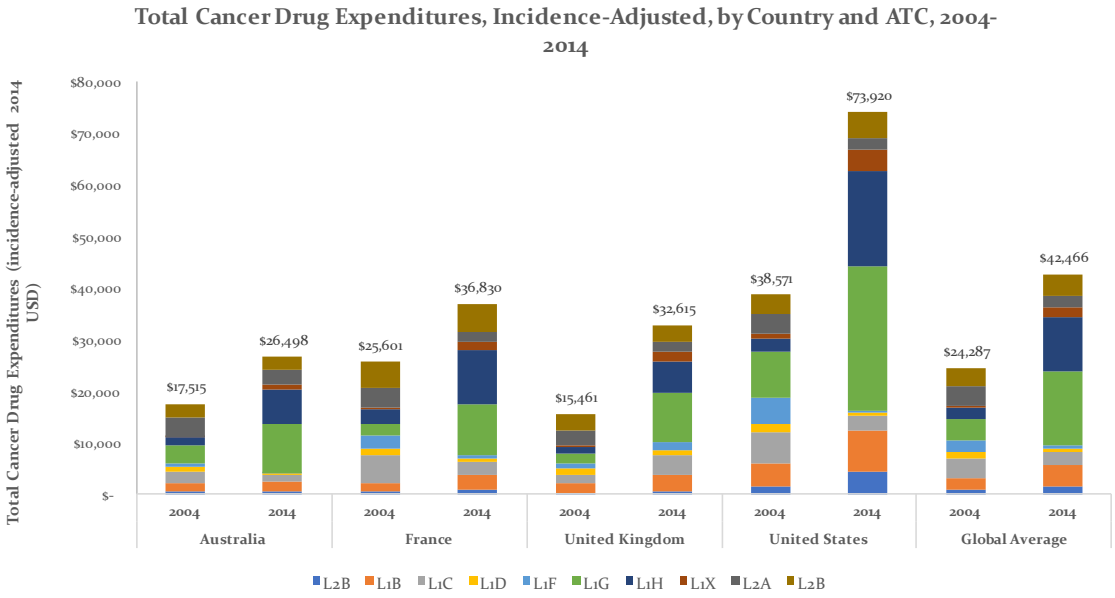


Source:

Authors' analysis of data, as described in Methods section.

Growth in total US drug spending appears to be associated with increased spending on monoclonal antibody antineoplastics (L1G) and protein kinase inhibitor antineoplastics (L1H)(Figure 12). The UK has risen from fourth to third in total, incidence-adjusted expenditures on cancer medicines relative to the other countries in this analysis, and, except for the US, it now outspends all other countries on generic medicines. Australia, in contrast, has consistently controlled its expenditures on cancer medicines, and now spends less than all other countries in this analysis on both branded and generic medicines (Figure 11).

Figure 12. Total Cancer Drug Expenditures, Incidence-Adjusted, by Country and ATC, 2004-2014



Source:

Authors' analysis of data, as described in Methods section.

Net Value

All countries witnessed an increase in incidence-adjusted total expenditure on cancer drugs between 2004-2014, as well as a decline in YPLLs from all neoplasms (Table 15).

Table 15. Incidence-Adjusted Cost, Effect and Incremental Cost-Effectiveness Ratio, 2004-2014

Country	Cost[1,2]			Effect[1,3]			ICER[1,2,4]
	t = 2004	t = 2014	Δ t	t = 2004	t = 2014	Δ t[4]	
France	$25,601.27	$36,830.44	$11,229.17	7.835	5.781	2.053	$5,468.52
Australia	$17,514.54	$26,498.12	$8,983.58	6.304	4.832	1.472	$6,102.50
UK	$15,460.92	$32,614.71	$17,153.79	7.193	5.553	1.641	$10,456.35
US	$38,571.21	$73,919.51	$35,348.30	6.720	5.610	1.109	$31,861.53

Source:

Authors' analysis of data, as described in Methods section.

Notes:

[1] Adjusted to reflect incidence-adjusted expenditure (cost, C) or YPLLs (effect, E).

[2] Figures given in terms of constant 2014 US dollars.

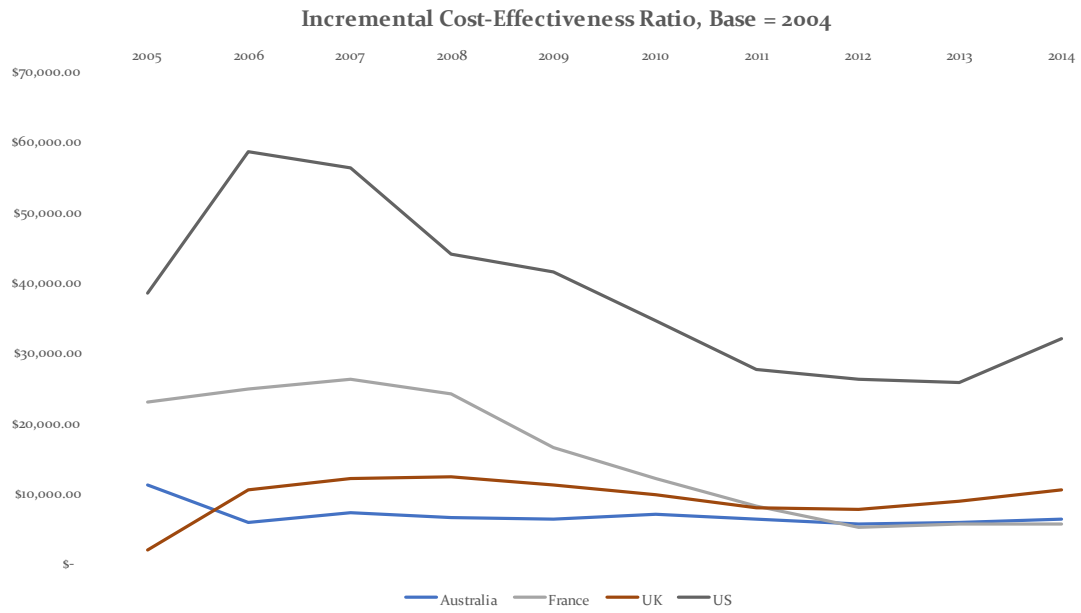
[3] Effect is given in terms of YPLL.

[4] For convenience, values for the change in YPLL between 2004-2014 are multiplied by -1.

[5] Values may not sum due to rounding errors.

For all countries in this analysis, the incremental cost-effectiveness ratio corresponding to the long-term change in cost per year of potential life lost averted between 2004 and 2014 fell within the north-east quadrant of the cost-effectiveness plane (Table 15), as have those for intervening years (Figure 13). These findings suggest that while cancer drugs have grown more expensive since 2004, they have also become more effective.

Figure 13. Incremental Cost-Effectiveness Ratio, Base = 2004



Source:

Authors' analysis of data, as described in Methods section.

However, there is significant heterogeneity in this measure of health economic value over time and across countries. ICERs have generally improved over the last decade for most countries in this analysis. The UK however is a major outlier in this measure: relative to 2004, it spent $8,678.01 more per year of potential life lost averted in 2014 than it did in 2005. This is indicative of increases in expenditure on cancer treatments that are proportionally larger than improvements in health outcomes, and may reflect governmental policies to modernize research and services, e.g. as stipulated in the 1999 White Paper Saving Lives: Our healthier nation and the 2000 NHS Cancer Plan.(310)

In general, although the past decade has witnessed an improvement in the incremental cost effectiveness ratio associated with cancer drug treatment—which reached their nadir in or around 2006—for most countries (particularly the US) there has been a recent reduction between 2013-2014 in the value obtained from long-term increases in cancer drug spending. The US is also consistently associated with the lowest improvements in health from cancer drug spending, spending more than three times as much as the next country (UK) per year of potential life lost averted in 2014 (Figure 13). At the extremes, France obtained close to six times as much return in health gains per dollar spent on cancer drugs as the US in 2014.

Estimates of net value were calculated by assuming that 19%, 14%, 17%, and 26% of the long-term improvement in YPLLs in Australia, France, the UK, and the US, respectively (a_{Mean}) owe to innovations in cancer medicines (Table 16). For all countries except the US, cancer drug care produced net positive value under all scenarios (Table 16). Although the US did not obtain net positive economic returns from long-term increases in cancer drug spending under base case assumptions, this analysis indicates that

positive returns from spending on cancer medicines would have been generated in 2014 if ≥32% of the long-term improvement in YPLLs had been attributable to drug development (Table 16).

Table 16. Net Value from Cancer Drug Spending, per Neoplasm and to Society, Country Mean ± Standard Error Level of Attribution (a), 2004-2014

Country	Net Value per Neoplasm[3,4]			Net Value to Society[5]		
	a_{-SEM}	a_{Mean}	a_{+SEM}	a_{-SEM}	a_{Mean}	a_{+SEM}
Australia	**$14,351.57**	**$19,601.97**	**$24,852.38**	**$1.85**	**$2.52**	**$3.20**
France	**$12,108.95**	**$17,360.03**	**$22,611.11**	**$4.50**	**$6.46**	**$8.41**
UK	**$6,172.63**	**$11,421.08**	**$16,669.52**	**$2.13**	**$3.94**	**$5.75**
US	**-$12,005.81**	**-$6,753.75**	**-$1,501.69**	**-$19.48**	**-$10.96**	**-$2.44**

Source:

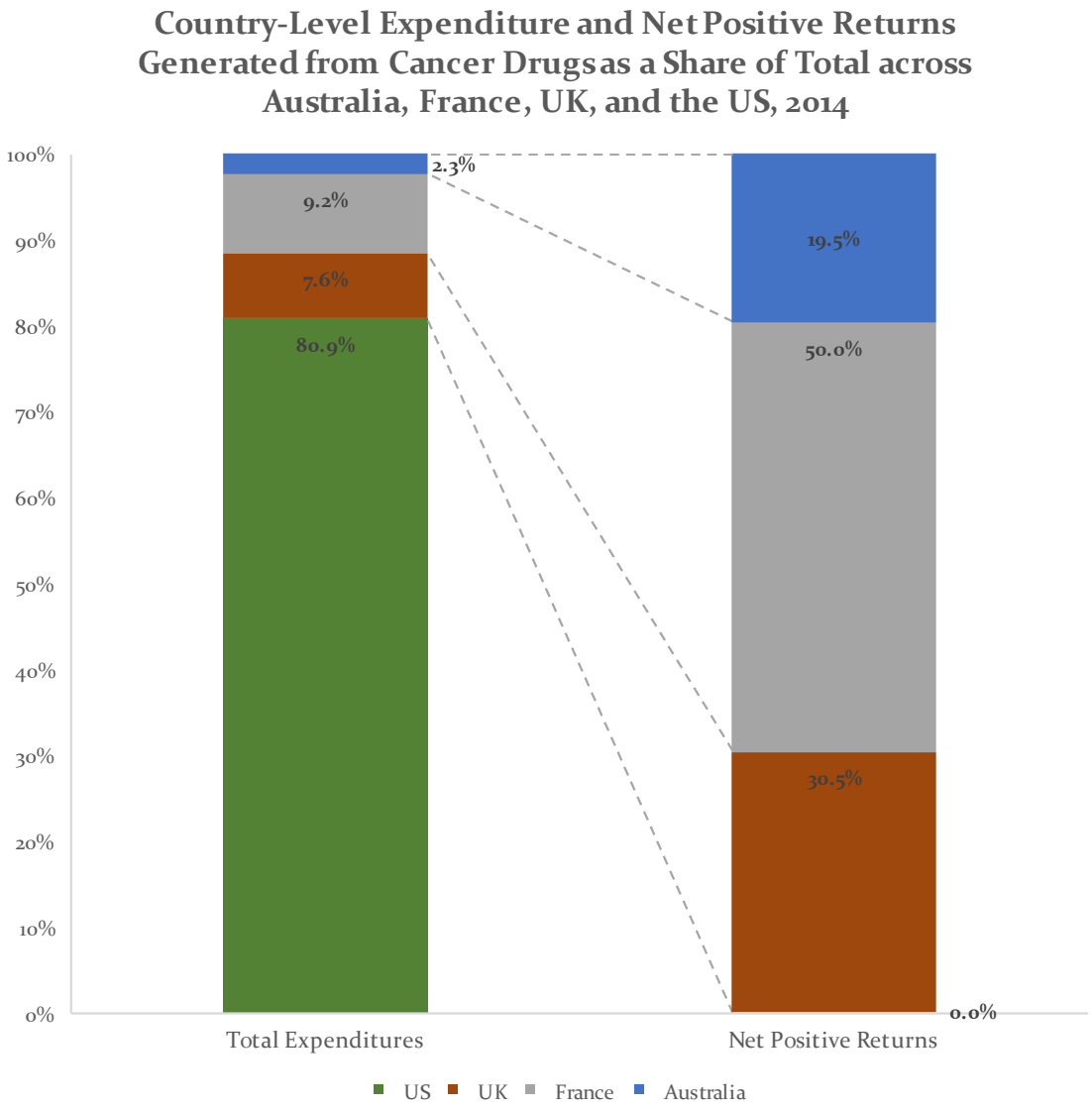
Authors' analysis of data, as described in Methods section.

Notes:

[1] Country records sorted by estimates of the net value generated per neoplasm when the percentage of long-term survival gains attributed to cancer drug innovation equals a_{Mean}. See ERGEFORMAT Table 13 for the values of attribution *a* that are used in this analysis (mean, SEM).

Across the four countries, total net positive economic returns from oncology drug care amounted to US$1.96 billion in 2014 under the base case assumption that cancer medicines contributed to 19%, 14%, 17%, and 26% of the long-term improvement in YPLLs in Australia, France, the UK, and the US, respectively (a_{Mean}) (Table 16). From the perspective of value, the US accounted for 80.9% of total expenditures on cancer drugs across the four countries evaluated in this study, yet it was the only country to obtain negative net economic returns (-$10.96 billion) in 2014 from oncology drug spending under base case assumptions (Figure 14).

Figure 14. Country-Level Expenditure and Net Positive Returns Generated from Cancer Drugs as a Share of Total across Australia, France, UK, and the US, 2014

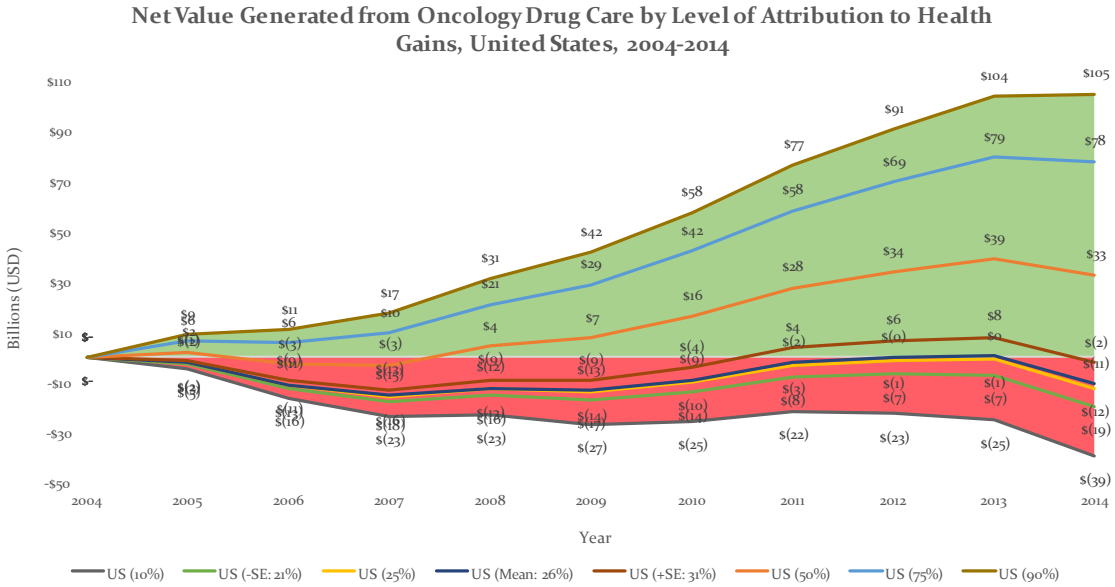


Source:

Authors' analysis of data, as described in Methods section.

Base-case, country-level analyses indicate that long-term increases in total US expenditures on cancer medicines resulted in a net negative return of -$10.96 billion in 2014 (Figure 15). A notable uptick in the net value derived from cancer drug spending was observed between 2007-2013, perhaps reflecting therapeutic developments. However, long-term estimates of the net value derived from cancer drug spending has more recently begun to trend downwards (Figure 15). The US lags behind Australia (Appendix 4.2), France (Appendix 4.3), and the UK (Appendix 4.4) in total net economic returns generated in 2014 from cancer drug spending.

Figure 15. Net Value Generated from Oncology Drug Care by Level of Attribution to Health Gains, United States, 2004-2014



Source:

Authors' analysis of data, as described in Methods section.

Multivariate linear regressions with longitudinal data were used to explore the association between country-level drug development, patterns of utilization, and improvements in cancer outcomes (Table 17). The analysis suggests that generic drug use may be weakly associated with reductions in neoplasm-related YPLLs. While the complexity of country-level associations requires that these results be interpreted with caution, results from this analysis suggest that it may be possible to optimize patient survival by making it easier to access oncology drug treatment.

Table 17. Country-Level Multivariate Linear Regression Analysis with Panel Data, Cancer Drug Use and Health Outcomes for Australia, France, the UK, and the US

Variable	Model[1]							
	(A)	(B)	(C)	(D)	(E)	(F)	(G)	(H)
Dep. Var.	YPLLi	YPLLi	YPLLi	YPLLi	YPLLi	YPLLi	YPLLi	YPLLi
Ind. Var[2]	1	1, 2	1, 3	1, 2, 3	1, 4	1, 2, 4	1, 2, 4, 5	1, 2, 3, 4, 5
log(kg_inc)	-4.770** (0.900)	-1.247 (1.567)	0.199 (1.147)	0.227 (1.016)	-0.673 (1.603)	-1.39 (0.644)	-1.329 (1.172)	-0.113 (0.866)
% kg generic		-0.0620**		-0.0137 (0.007)		-0.062* (0.026)	-0.035* (0.014)	-0.013 (0.010)
Year = 2005			-0.193** (0.0457)	-0.175* (0.060)				
Year = 2006			-0.383* (0.146)	-0.348 (0.149)				-0.152 (0.089)
Year = 2007			-0.575* (0.229)	-0.503 (0.219)				-0.314 (0.173)
Year = 2008			-0.735* (0.273)	-0.625* (0.255)				-0.437 (0.215)
Year = 2009			-0.886* (0.291)	-0.749* (0.277)				-0.554 (0.241)
Year = 2010			-1.043* (0.340)	-0.876* (0.317)				-0.658 (0.289)
Year = 2011			-1.185** (0.322)	-0.991** (0.292)				-0.783* (0.273)
Year = 2012			-1.328** (0.352)	-1.178** (0.333)				-0.935** (0.281)
Year = 2013			-1.467** (0.384)	-1.274** (0.348)				-1.055** (0.323)
Year = 2014			-1.605** (0.423)	-1.364** (0.388)				-1.125* (0.369)
1 lag: log(kg_inc)					-3.888 (1.669)	0.329 (1.736)	0.526 (0.758)	0.518 (0.468)
1 lag: % kg generic							-0.035*** (0.005)	-0.007* (0.002)
Constant	-7.506* (2.583)	5.155 (5.077)	7.609 (3.542)	8.135* (3.259)	-7.007* (2.758)	5.684 (7.294)	6.67 (5.581)	8.705* (3.134)
Country FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Observations	44	44	44	44	40	40	40	40
R^2	0.465	0.801	0.953	0.959	0.470	0.775	0.829	0.965
Adj R^2	0.452	0.791	0.937	0.943	0.442	0.756	0.810	0.947

Source:

Authors' analysis of data, as described in Methods section.

Notes:

[1] Table provides estimated coefficients (SEM) of country-level associations between total cancer drug sales volume (kg) per incident neoplasm, percentage of total cancer drugs sales volume (kg) associated with generics, year dummies, and 1-year lags on the mean number of neoplasm-related YPLLs per incident neoplasm (YPLLi) for Australia, France, the UK, and the US between 2004-2014.

[2] 1: kg_inc; 2: % kg generic; 3: year dummies; 4: 1 lag, kg_inc; 5: 1 lag, % kg generic.

[2] Reference categories: Year = 2004.

[3] Standard errors (SE) are provided in brackets. Variable descriptions are provided in text. ***: $p \leq 0.01$, **: $p \leq 0.05$, *: $p \leq 0.10$

Drug-Level Analysis

Net Value

The net value generated per patient from spending on the 43 new cancer medicines that were included in this analysis varied widely (Appendix 4.5), with base-case estimates for the US ranging between -$17,243.59 for clofarabine (SD: $8,613.28; p25: -$22,812.32; p50: -$15,358.18; p75: -$8,096.32) to $248,579.01 for pertuzumab (SD: $54,323.34; p25: $209,067.44; p50: $249,569.02; p75: $286,987.97) in the first year of marketing, Y0. On average, breast cancer medicines generated the greatest net value per patient in Y0 in the US (mean: $97,902.34; SD: $103,844.52; p25: $29,754.25; p50: $61,003.71; p75: $166,050.42). This was followed by medicines that were indicated for renal cancer (mean: $85,131.96), skin cancer (mean: $81,378.06), prostate cancer (mean: $44,982.75; SD: $31,990.41; p25: $22,421.62; p50: $55,565.09; p75: $67,543.87), hematological malignancies (mean: $35,779.39; SD: $76,495.91; p25: -$11,465.04; p50: -$5,696.81; p75: $143,898.71), GI cancer (mean: $34,507.83; SD: $19,877.37; p25: $18,074.36; p50: $31,444.72; p75: $50,941.30), and lung cancer (mean: $16,817.91; SD: $26,606.78; p25: -$5,421.28; p50: $15,782.75; p75: $39,057.10).

On average, orphan medicines were associated with larger estimates of net value per patient (in Y0, US, mean: $56,575.10; SD: $82,528.27; p25: -$6,239.54; p50: $32,081.61; p75: $85,131.96) than non-orphan medicines (in Y0, US, mean: $38,194.40; SD: $27,223.74; p25: $18,074.36; p50: $41,126.96; p75: $62,067.36).

For the medicines with data from all four countries, estimates of the net value generated from treatment were, on average, lowest in the US, where the mean value in Y0 equaled

$63,466.25 (SD: $73,565.29; p25: $19,121.10; p50: $44,900.46; p75: $83,521.84). It was followed by the UK (mean: $64,328.22; SD: $72,738.03; p25: $20,402.78; p50: $46,952.83; p75: $84,905.70), Australia (mean: $66,010.31; SD: $74,734.34; p25: $7,986.16; p50: $48,730.35; p75: $90,800.33), and France (mean: $66,370.62; SD: $73,322.31; p25: $21,119.12; p50: $48,107.37; p75: $89,577.93).

Average estimates of net value generated from treatment with new cancer medicines generally remained stable over time. In the US, the average net value generated from treatment across all available medicines equaled $47,752.36 in Y0 (SD: $61,911.10; p25: -$516.12; p50: $38,485.59; p75: $69,067.28), $49,632.04 in Y1 (SD: $64,183.89; p25: -$541.42; p50: $41,160.46; p75: $69,581.06), and $48,934.91 in Y2 (SD: $65,816.26; p25: -$569.36; p50: $38,381.60; p75: $68,466.99). Similar trends were observed in Australia, France, and the UK.

Estimates of the total, net value generated in each country-year from spending on new cancer medicines were obtained by incorporating evidence on the total, expected number of patients completing (b) (4) therapy (Chapter 3). As for per-patient estimates, these varied across the medicines that were included in this analysis (Appendix 4.6). In the US, for instance, they ranged between -$29,418,407.46 for gefitinib to $1,347,571,272.95 for bevacizumab (SD: $10,646,925,469.84; p25: $234,944,619.8; p50: $485,167,041.94; p75: $1,084,290,490.7) in the first year of marketing. Skin cancer medicines were associated with the largest, mean estimate of the total net value to society (in Y0, US, mean: $430,737,678.65). This was followed by medicines that were indicated for GI cancer (mean: $369,118,531.96; SD: $652,690,640.30; p25: $28,306,866.88; p50: $55,689,749.24; p75: $ 709,930,197.03), renal cancer (mean: $297,386,223.61), breast

cancer (mean: $259,771,283.99; SD: $204,679,388.61; p25: $124,710,255.54; p50: $265,614,620.88; p75: $394,832,312.44), prostate cancer (mean: $205,688,538.29; SD: $311,439,301.31; p25: $15,800,134.13; p50: $78,690,304.54; p75: $395,576,942.45), hematological malignancies (mean: $171,086,530.49; SD: $349,949,920.85; p25: $585,458.55; p50: -$281,151.49; p75: $280,327,191.87), and lung cancer (mean: $10,355,135.93; SD: $37,171,965.43; p25: -$15,059,216.68; p50: $5,548,619.32; p75: $35,769,488.54).

On average, orphan medicines generated less net economic value to society (in Y0, US, mean: $178,051,798.02; SD: $278,908,048.57; p25: -$301,814.16; p50: $11,797,264.53; p75: $280,327,191.87) than non-orphan medicines (in Y0, US, mean: $249,232,516.85; SD: $405,199,198.15; p25: $10,870,158.03; p50: $55,689,749.24; p75: $358,381,684.49).

For the medicines where data was available for all four countries, net economic returns to society from treatment were, on average, highest in the US, equaling $833,662,703.21 in the first full-year of marketing, Y1 (SD: $1,323,311,438.70; p25: $76,277,447.07; p50: $351,281,540.48; p75: $972,972,604.57). It was followed by France (mean: $145,663,116.87; SD: $160,736,281.77; p25: $19,921,205.64; p50: $113,410,323.10; p75: $175,896,680.35), the UK (mean: $31,894,554.48; SD: $42,745,035.32; p25: $1,496,828.38; p50: $16,551,287.97; p75: $31,742,701.25), and Australia (mean: $15,365,191.83; SD: $32,935,125.41; p25: $656,894.02; p50: $6,488,406.44; p75: $11,812,920.16).

Net value to society from treatment with new cancer medicines increased over time, and at a rate that exceeded that of the net value generated per patient, likely reflecting drug uptake. In the US, for instance, the average net economic return to society from

treatment with all new cancer medicines equaled $212,218,543.06 in Y0 (SD: $339,800,361.84; p25: -$281,151.49; p50: $39,090,377.37; p75: $286,025,690.33), $636,228,222.82 in Y1 (SD: $1,078,218,732.48; p25: -$770,489.23; p50: $222,401,594.82; p75: $796,987,759.35), and $598,576,135.72 in Y2 (SD: $865,388,893.90; p25: -$888,589.92; p50: $249,123,692.86; p75: $684,800,599.36). Estimates of the total net value to society from cancer drug spending also increased over time in France, the UK, and Australia.

Sensitivity Analysis

To examine the impact from uncertainty in the actual treatment population size on country-level analyses, a sensitivity analysis was performed using a modeled total patient population size that equaled 1.5x the total number of incident cases of neoplasm that were calculated for each year-country. This adjustment had a negligible impact on long-term ICERs (Appendix 4.7), and though it scaled down estimates of the net economic return from cancer drug expenditures, they remained positive under most circumstances (Appendix 4.8).

Sensitivity analyses were also conducted by assuming that between 10%-90% of the long-term, country-level improvements in survival could be attributed to cancer drug development (Appendix 4.9). This finding suggests that the US requires proportionally larger survival benefits from new cancer medicines for current levels of spending to provide net economic returns that mirror what is achieved elsewhere.

Adjusting cancer drug usage and expenditure by total population and cancer prevalence did not significantly alter the findings from country-level analyses. Cancer drug

utilization and expenditure trends were also largely consistent across oral and injectable cancer drug dosage forms, as well as cancer drug age groups. One exception to this was the group of drugs that were first marketed 6-10 years ago: countries tended to limit utilization of these medicines, instead making use of newer (0-5 years) or older (>10 years) alternatives.

Discussion

Global expenditures on cancer drug care rose between 2004-2014, but so too has cancer drug development contributed to improvements in patient survival. Internationally, however, there appears to be a significant amount of heterogeneity in the value obtained from expenditures on cancer medicines. At a country-level, France achieved close to six times as much return in total gains in neoplasm-related survival per dollar spent on cancer drugs as the US. This disparity is not only driven by economics: while the US consistently outspent other countries on cancer medicines between 2004-2014, it also witnessed one of the smallest improvements in cancer-related YPLLs.

Nevertheless, expenditures on cancer medicines appear to provide most countries with positive economic value. Using data from Chapter 2, base-case, country-level analyses suggest that Australia, France, and the UK obtained net positive returns of $2.52, $6.46, and $3.94 billion in 2014, respectively, from expenditures on cancer medicines. There has been a gradual increase in the value obtained over time, and sensitivity analyses also consistently found net positive returns under most scenarios.

The US however can do better. At a country-level, the US outspends all other countries on cancer medicines, despite having the highest level of generic penetration and comparable levels of cancer drug utilization. This finding persists even after adjusting for population and cancer epidemiology,(74,75) and is consistent across branded and generic markets, cancer drug classes, and over time. Country-level analyses suggest that growth in US cancer drug expenditures is not primarily driven by utilization—arguably key to improving patient outcomes (270)—but rather by high drug prices. From the perspective of value, the US was the only country of the four analyzed in this study to be associated with net negative economic returns from total, long-term increases in aggregate cancer drug spending—at a country-level, the monetized value of long-term improvements in cancer survival owing to new medicines, based on patients' willingness to pay for a diminished risk of death from drug treatment, was less than the long-term increase in cancer drug spending. The US accounted for 80.9% of total cancer drug expenditures in 2014 across the four countries evaluated in this study, yet it received 0% of the global total net positive economic returns generated that year from spending on cancer medicines (Figure 14).

These findings were consistent with drug-level analyses. Estimates of the net economic value generated from the use of new cancer medicines were highest in France, followed by Australia and the UK. They were however consistently greater than those observed in the US. Under the assumption that the monetized value of survival gains is consistent across the four countries, this analysis suggests that lower economic returns from cancer drug spending owe to relatively high drug prices in the US.

Even though aggregate cancer drug expenditures continue to result in net positive value in most places, there are reasons to take caution. Globally, while aggregate expenditures on branded cancer medicines have risen to new highs, even as volumes have fallen, expenditures on generic cancer drugs have often risen at a faster pace and are not fully accounted for by increases in utilization. On an incidence-adjusted basis, the UK now spends nearly as much as the US on generic cancer drugs, and France and the UK are today spending about as much as the US did ten years ago for all cancer medicines. At the same time, most of the countries evaluated in this chapter have witnessed a compound annual growth rate in total cancer drug expenditures that exceeds historical rates of general and medical inflation, and which are comparable to, if not greater than, cancer drug expenditure growth in the US. The UK has in fact witnessed the fastest rate of compounded growth per annum in cancer drug expenditures (8%), closely followed by the US (7%). While these findings suggest that these expenditures continue to provide net positive value in Australia, France, and the UK, it is unclear whether this is sustainable over the long-term.

Moreover, new cancer medicines have not necessarily resulted in net positive value. Over the past ten years, the monetized value of drug-related survival gains has greatly exceeded increases in cost for some indications, but not for others, represented at the extremes by breast and lung cancers. The unevenness in the magnitude of net economic returns is even more pronounced at a drug-level. Pharmaceutical innovations have, in some instances, brought large, positive economic returns from their impact on survival (e.g. pertuzumab). In other cases, the use of some new medicines is expected to have generated little, or indeed negative, net value. This appears to validate reporting from Bach & Pearson (2015), who state that currently "some drug prices do not seem to be

consistent with the drug's benefits, while some other prices do."(311) From this perspective, health systems should not necessarily regard growing cancer drug costs as an issue. Of greater importance is the development and preferential use of cancer medicines that provide the greatest therapeutic good to patients.

To conclude, country- and drug-level analyses both suggest that greater value will not be obtained by simply cutting expenditures on cancer medicines. Australia, for instance, witnessed the smallest rate of growth in cancer drug expenditures between 2004-2014. Yet, it also experienced one of the smallest, country-level improvements in patient survival. France, on the other hand, controlled overall growth in total cancer drug expenditures—and those for branded drugs in particular—while also achieving greater improvements in health outcomes. Net economic returns from use of new cancer medicines were higher in France than in the UK in the first full-year of drug marketing. This was despite the UK and France having comparable population sizes, and incidence-adjusted total drug expenditures were higher in France than in the UK throughout the entire period of analysis. Since net value also varies across new cancer medicines, indiscriminate cuts to drug expenditures are unlikely to be value-optimizing if they do not consider the clinical impact from treatment. Greater value therefore may not necessarily result from cost containment, but appears to more closely be associated with greater access to clinically meaningful medicines. Given an appropriate policy and clinical context, it seems possible to meet growing health needs while managing increases in cost. Instead of focusing exclusively on expenditure, a more constructive approach may be to coordinate across siloed objectives in policy and health with the aim of improving value to patients and society.

Key Learnings and Implications

- Base-case, country-level analyses found that Australia, France, and the UK obtained net positive economic returns of $2.52, $6.46, and $3.94 billion in 2014, respectively, from long-term increases in spending on cancer medicines.
- The US outspends other countries on cancer medicines, even after adjusting for population and cancer epidemiology, and was the only country of the four to be associated with a net negative economic return from total, long-term increases in aggregate cancer drug spending.
- At a drug level, the monetized value of drug-related survival gains has exceeded increases in cost for some new cancer medicines, but not for all.

5

Value-Based Spending on New Cancer Medicines

Introduction

Cancer medicines have driven new brand spending over recent years, with spending in oncology rising from $0.5bn in 2009 in the US to $2.1bn in 2013.(23) Spending has in fact risen faster for cancer medicines than for many other diseases, in part because of rapidly growing drug prices, as well as increased rates of use.(312)

Faced with rapidly growing drug costs, ASCO recently developed its Value Framework to compare the relative clinical benefits, toxicity, and costs from cancer treatments, providing physicians and patients with a standardized approach to assess the value of new medicines.(12) Their efforts are based on the assumption that, at a societal level (12):

> "the cost of a given intervention … bears a relationship to the beneficial impact it has for patients who receive that treatment."

This assumption underpins other value-based healthcare initiatives: in the US, for instance, the Institute for Clinical and Economic Review and the DrugAbacus both work on determining prices for medicines that are commensurate with their impact on health.(59) From this perspective, value-based spending on cancer medicines—a product of drug costs and utilization—should be associated with their therapeutic benefits to patients.

This position is increasingly adopted in the literature. Despite concerns over affordability and clinical adherence,(44,90) some have argued that high costs may be warranted if new cancer treatments also bring significant benefits to patients.(44,46) Fojo and colleagues (2014) argue that pharmaceutical companies in fact deserve to charge premium prices for therapies offering premium benefits, but that marginal benefits should not be rewarded.(313) This position may in part be justified if value-based drug spending incentivizes the development of medicines that offer meaningful therapeutic improvements to patients.(313)

As financial pressures mount, countries have taken different approaches to ensure value-for-money in drug spending. Direct or indirect mechanisms of regulating price and pharmaceutical access exist, and may be informed by assessments of the clinical risks and benefits of new medicines. On the supply side, countries may also allow for free pricing of medicines, with no policies or regulations to ensure that pharmaceutical expenditures are commensurate with value to patients and society. An overview of policies to ensure value-for-money in pharmaceutical spending in Australia, France, the UK, and the US is provided in Box 5.

Box 5. Overview of Approaches to Ensure Value-for-Money in Drug Spending

Countries may negotiate drug pricing directly with manufacturers on the basis of the comparative clinical effectiveness of new medicines. France, for instance, assesses the ATV of newly licensed medicines against existing comparators on a five-point Likert scale (ASMR), which ranges between major improvement (I) and no improvement (V). Along with other factors that include sales forecasts and size of the target population,(50) ATV is then used to inform price negotiations with manufacturers.(329) Medicines that provide no added clinical benefit to patients can only be listed if they cost less than their competitors.(372) In contrast, medicines that are rated with an ATV of I-IV have the possibility of higher pricing relative to competitors.(372) Those that are highly rated (ATV I-III) may not require price negotiations, a policy that may also expedite access to the most clinically meaningful medicines.(372) ATV is then re-assessed every five years, or sooner if independent scientific commissions believe it appropriate.(329)

At a high-level, Australia uses a similar system to control drug spending. Once medicines have been licensed for use by the national TGA, manufacturers must file an application with the PBAC to receive reimbursement through the country's PBS. The PBAC assesses the comparative clinical- and cost-effectiveness of new medicines to determine whether to recommend their listing on the PBS, along with other criteria that include budget impact, severity of the treatment condition, and availability of alternative therapies.(327) Most prescription drugs are however included on the PBS,(373) providing patients with subsidized access to medicines. Following a positive PBAC recommendation, the PBS's Pricing Section undertakes pharmaceutical price negotiations that may be based on prescription volumes, economies of scale, and various pricing methods, including the cost-plus method and reference pricing. To recommend pharmaceutical pricing to the minister, the Pricing Section may also consider PBAC advice on clinical and cost-effectiveness.(49) Unlike France, however, Australia does not provide a clear framework describing the process that is used to link drug prices to their clinical benefits. Once listed on the PBS, medicines may be sold at the price that is set by the PBS, and at a fixed copayment.(374)

Indirect methods of price regulation also exist. In the UK, pricing of all licensed, branded drugs is not directly regulated, but is often managed through the voluntary PPRS, which institutes mechanisms for price cuts, as well as profit controls that weigh price and volume. Reserve statutory powers to control pharmaceutical prices also exist for medicines that are not regulated through the PPRS.(56) While the latest version of the PPRS failed to incorporate VBP mechanisms linking national health technology assessments to price setting due to "technical problems and uncertainty,"(57) it may offer a platform to directly negotiate VBP of medicines in the future. In response to prior calls for value-based pricing, PPRS 2009 nevertheless implemented a flexible pricing arrangement that, among other stipulations, allowed companies to increase or decrease their original list price once by up to 30% in light of new evidence.(56) The UK's use of cost-effectiveness as a key criterion in decision-making on reimbursement can however indirectly pressure manufacturers to lower drug prices when cost-effectiveness is not realized.(375) Indeed, as of 2016, all new anti-cancer medicines are referred to NICE for evaluation, which issues recommendations on whether they should be made available for routine commissioning throughout the NHS.(43) This reflects the agency's core mission, which is to "assess and signal value on behalf of the entire NHS."(376) The UK may nevertheless use financially- or output-based patient access schemes that allow early access to medicines, and help manufacturers improve their clinical- or cost-effectiveness.(56) To allay concerns regarding accessibility, the UK utilizes a dedicated funding scheme for cancer medicines—the CDF—that provides access to medicines that are not routinely available through the NHS. The CDF was initially established in 2011 as a three-year stopgap measure to ensure access to cancer medicines while also acting as a bridge to a new system of VBP.(43) To ensure that spending on the CDF provides value-for-money, the UK recently reformed the program by: capping the program's yearly budget to £340m; re-designing the program as a Managed Access Scheme; where optimized draft recommendations exist, only providing interim funding to subgroups within the optimized recommendation; only providing interim funding from the NHS to manufacturers if they sign onto a non-negotiable funding contract that subjects them to, as required, expenditure control mechanisms; only providing access through the program to medicines that NICE considers to demonstrate a "plausible potential for [satisfying] the criteria for routine commissioning, but [which are associated with] significant remaining clinical uncertainty"; and only providing 2-year interim funding for medicines that sign onto a Managed Access Agreement, which stipulates the requirements for continued data collection and the level of reimbursement that brings plausible cost-effectiveness estimates to below acceptable thresholds.(43) The option for individual funding requests from public payers exists to fund treatment with non-recommended medicines, however it only applies to "clinically exceptional" cases.(43)

High-level policies or regulations to control pharmaceutical spending are not used in the US. By law, the social insurance programs Medicare and Medicaid are not allowed to directly negotiate pharmaceutical pricing,(59) may not consider costs within the drug reimbursement decision-making process, and yet may be required to cover new medicines.(60) Indeed, the MMA of 2003 issued guidance through contract provisions to Medicare PDPs to cover "all or substantially all" medications within six protected classes of medicines, including antineoplastics and immunosuppressants. The MIPPA of 2008 codified CMS guidance and established the Six Protected Classes of drugs under Medicare Part B, with the PPACA of 2010 providing additional protection.(61) CMS proposed limiting the protected drug classes to exclude antidepressants and immunosuppressants in 2015; this measure was not adopted due to opposition from patients, providers, and advocates.(61) Bach and Pearson (2015) argue that Medicare's ability to apply a VBP system is hindered by policies that require Part D private drug plans to cover all drugs of certain protected classes, while a flat co-insurance rate without an upper limit has put highly effective but expensive medicines out of reach for Medicare beneficiaries without supplemental health insurance.(59) Private insurers are required to provide coverage for most new medicines, and may be unable to obtain significant price concessions from manufacturers, especially for drugs offering clinical advantages or using novel mechanisms of action.(59) While insurers may negotiate lower prices for drugs that have therapeutic substitutes or questionable benefits by excluding them from formularies,(62) the extent to which this occurs in the US remains unclear.

Context and Empirical Gaps

To date, it remains unclear whether spending on new interventions is associated with measures of their beneficial impact to patients, and how that association may vary across health systems.

In the US, a key recent study reports a positive correlation between the ETP of new medicines—each drug's monthly cost to the Medicare program—and incremental survival benefits, finding that US prices for anticancer medicines increase by 120 percent for each additional life-year gained.(73) Several limitations however should be considered. First, the lack of an international comparison prevents researchers from judging the strength of any country correlation between drug spending and their clinical benefits.(314) Second, monthly ETPs, or similar concepts,(159) may not adequately reflect actual treatment costs, and may therefore bias drug cost comparisons. Howard and colleagues (2015) in fact admit that a "drug's treatment episode price is not a comprehensive measure of the impact of that drug on health care costs."(73) Third, survival is generally taken as the gold standard among oncology efficacy endpoints.(64,93,94) Focusing on survival exclusively however is inconsistent with ASCO's Value Framework, which argues that patients may also consider other clinical outcomes, including QoL and safety.(12) By not accounting for other potential clinical benefits, regression-based studies examining the relationship between drug costs and their clinical impact are likely to suffer from misspecification bias.

These limitations reflect the dearth of publicly-available evidence. As was explained in Chapter 3, there is as of yet no international dataset that provides reliable and

comparable evidence on the use or cost of cancer medicines. Its absence makes it difficult for researchers to examine whether spending on new cancer medicines is indeed related to their clinical impact, and to determine how and to what extent this relationship varies across country settings.

Summary of Research

The literature has generally adopted two methodological approaches to determine whether spending on new tools or treatments provide value-for-money. Chapter 4 made use of the first by adopting a cost-benefit approach to analyze whether the monetized value of survival gains attributable to cancer drug innovation, and based on patients' willingness to pay for a diminished risk of mortality, exceeds growth in drug spending, both at a societal- and drug-level.

The second approach assesses whether and to what extent spending on treatments is associated with measures of their clinical benefit.(73,85,274–277) Extending this approach, this chapter uses regression analysis to test the value-based hypothesis that spending on new cancer medicines is associated with their beneficial impact to patients, measured through drug-related effects on overall survival, quality of life, and safety. To do so, it incorporates data on the clinical risks and benefits associated with new cancer medicines from Chapter 2, as well as (b) (4) evidence on the use and cost of new cancer medicines from Chapter 3. To provide comparative insights on the extent to which this occurs, this analysis is carried out using data from Australia, France, the UK, and the US. This chapter finds that spending on new cancer medicines may only weakly be associated with their impact on OS, QoL, and safety. The strength of this relationship

however varies across countries, and is most prominent in the UK, suggesting that it may be mediated by policies that are meant to ensure value-for-money in cancer drug spending.

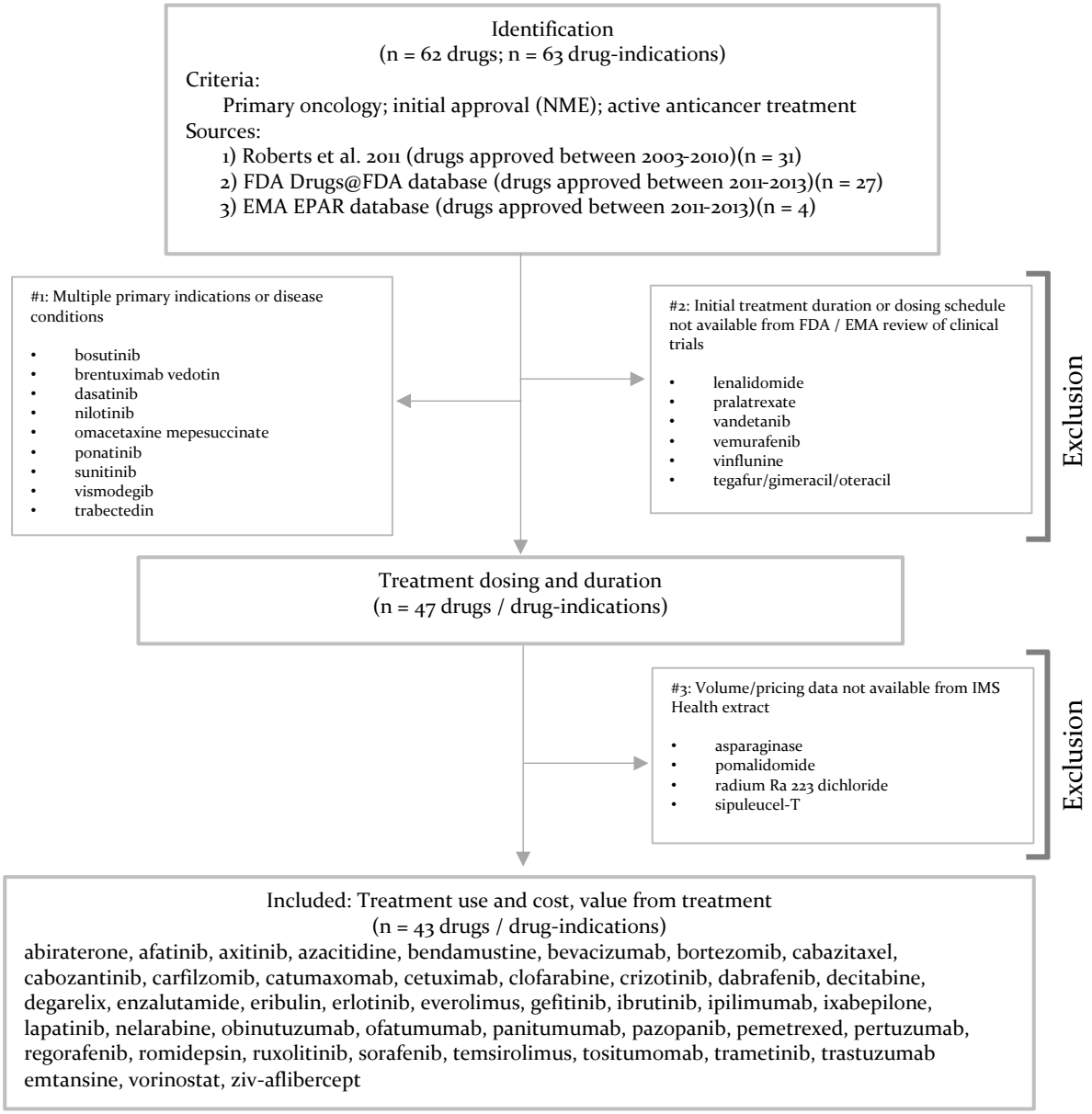
Methods

Sample Selection

All medicines that were included in Chapters 2, 3, and 4 were eligible for inclusion in this study. As in Chapters 2 and 3, the methods from Roberts and colleagues (2011) were used to identify all initial cancer drug approvals by the US FDA and EU EMA occurring between 2003-2013.(125) All NMEs approved by the FDA or EMA over this period with a primary indication for oncology were eligible for inclusion. Any molecule that did not receive licensure by either the FDA or EMA between 2003-2013, and which did not have an initial, primary anticancer indication was therefore excluded. Supplemental applications to the US FDA or EU EMA, new non-active treatments, licensing supplements, labeling revisions, and new or modified indications were not considered.

In this study, medicines were excluded if Chapter 3 had been unable to generate estimates on the total cost or use associated with each treatment. For more information, please refer to Chapter 3. The drug selection process is depicted in (Figure 16).

Figure 16. Drug Sample Inclusion/Exclusion Criteria



Source:

Authors' analysis of data, as described in Methods section.

Data Sources

Summary measures of the effect on OS, QoL, and safety from treatment with each new cancer medicine were obtained from Chapter 2. As was previously explained, information on recommended patient populations (treatment indications, usage restrictions), novel interventions [ATC code, therapeutic target], and therapeutic comparators were extracted from English, French, and Australian appraisals for each eligible drug-indication.

As was explained in Chapter 2, a narrative synthesis approach was used to classify summary HTA agency assessments of the drug-related impact on OS, QoL, and safety. These assessments are based on a comparison against main therapeutic comparators—defined as the therapy that would most likely be replaced by the new intervention (121–123)—which do not often differ across appraisals.(315) Where available, quantitative estimates of the impact on OS for the first approved indication of each newly licensed cancer medicine were extracted. In some instances, HTA agencies may have concluded that new medicines are associated with an unquantifiable increase in OS. OS was therefore also coded as a categorical variable: drugs could be associated with a known or unknown OS benefit of ≥3 months; <3 months; an increase in survival, but of unknown magnitude; and no demonstrated increase in OS. HTA agency summary assessments of the overall effect on QoL and safety were classified into four categories: an overall improvement or reduction in QoL or safety, mixed evidence, or no established difference relative to best alternative treatments. For more information on the methods used to derive these summary estimates, please refer to Chapter 2.

For each country, mean and median estimates of the total cost (b) (4) of treatment, and expected number of patients completing (b) (4) therapy, with each new medicine in the first (Y0), second (Y1), and third (Y2) year of marketing were obtained from Chapter 3. (b) (4)

For all drugs that met inclusion criteria, the FDA's Drugs@FDA database was used to obtain FDA prescription drug labels, as well as medical and statistical reviews, corresponding to the year initial licensure was received. Prescription drug labels were used to extract FDA approved primary indications, FDA approval type (biologic licensing application, new drug application), date of initial FDA approval, date of first FDA-approved new or modified indication (target), new dosing regimen, or modified patient population through 1 Jan 2016, recommended dose and treatment duration, if available, and approval for use in pediatric and adult populations. (b) (4)

Value-based policies that are meant to rationalize pharmaceutical spending may consider condition and its rarity.(50,227–229,322,323) US and EU orphan drug status and ATC classifications for FDA-approved indications were therefore obtained from orpha.net and the WHO's ATC/DDD index.(230,324) Australian orphan drug status was

obtained from the TGA's orphan drug registry.(232) A clinical expert also used FDA-approved primary indications to classify all new cancer medicines by their therapeutic target. Across the entire eligible sample, medicines were classified as being indicated for malignant ascites, thyroid cancers, GI cancers, lung cancers, hematological malignancies, prostate cancers, skin cancers, renal cancers, and breast cancers.

Annual population size estimates were obtained from the World Bank,(292) as were consumer price inflation indices.(293) Nominal pricing data was converted to constant 2015 terms by using consumer price inflation indices from the World Bank, as described in Chapter 2. Yearly incidence of malignant neoplasms was derived for Australia, France, the UK, and the US using data from the OECD's OECD.stat registry (278) and the US CDC's USCS registry.(279) For this, simple linear regressions were used to account for time discontinuities. For more information on these data sources or methods, please refer to Chapter 4.

Analysis

In line with Howard and colleagues (2015),(73) this analysis focused exclusively on initial FDA- or EMA-approved anticancer indications. New or modified indications can be approved over the active life cycle of new medicines. In the absence of data on indication for use from QuintilesIMS, analyses were limited to the first three years of marketing after initial licensing. Yearly observations were also censored once new or modified indications, dosing regimens, or modifications in approved patient populations were accepted for new medicines.

As is explained in previous chapters, crude comparisons of cancer drug use may be misleading if associated populations are of unequal size or have unequal epidemiological risks of disease.(291) Countries with an unusually high number of incident cancer cases would be expected to have higher rates of cancer drug use and expenditure, *ceteris paribus*. To therefore adjust for potential differences in the total population size across countries, and in the relative risks associated with developing cancer, base-case analyses adjust drug utilization measures—number of patients completing (b) (4) therapy in each country-year—using data from Chapter 4 on the total yearly incidence of malignant neoplasms. This methodology has previously been advocated as a means of comparing cancer drug utilization across different settings.(74,75)

If cancer drug spending provides patients and society with value-for-money, then measures of their beneficial impact to patients should in theory be positively associated with spending on those new treatments.(12) This hypothesis extends from the notion that clinical decision-making is likely to consider drug-related effects on efficacy, as well as QoL and safety.(12)

The extent to which this hypothesis holds true may vary across countries, depending on the effectiveness of local policies that are meant to ensure value-for-money in drug spending. At the same time, payers may be willing to accept a higher maximum cost per unit of outcome obtained from the use of new medicines if they are given a high social value.(228) Social valuations of new health technologies may be associated with lifetime health prospects and dependencies,(325) treatment intent,(322,326) unmet health needs, availability of alternative treatments, and rarity of the treated condition.(50,227,228,322,323,327) Indeed, Goldman and colleagues (2007) review the

evidence on the association between cost-sharing features of prescription drug benefits and prescription drug use, and find that consumer sensitivity to cost sharing depends on a drug's therapeutic class and importance.(328)

The following linear model was therefore used to examine whether the beneficial impact associated with new cancer medicines bears positively on spending, and whether the relationship is mediated by country setting:

$$Y_{ic} = \beta_0 + i.indication_i + orphan_{ic} + country_c + OS_i + \sum_{c=1}^{4}(OS_i * country_c) + QoL_i + \sum_{c=1}^{4}(QoL_i * country_c) + safety_i + \sum_{c=1}^{4}(safety_i * country_c) \quad (12)$$

On the left-hand side of this model, Y_{ic} is used to represent the two dependent variables of interest that are constituent to drug spending: total cost per patient per (b) (4) treatment and number of patients completing (b) (4) therapy with each new medicine i in country c. Data are also considered by year $(t = 0, 1, 2)$. On the right-hand side of this model, $i.indication_i$ accounted for the target condition of each new medicine i included in this chapter—ascites, breast, GI, haematological, lung, prostate, renal, skin, and thyroid malignancies—while binary variable $orphan_i$ represented the orphan status of each medicine i in country c. To examine the relationship between drug-specific measures of clinical benefit and use and cost of new

cancer medicines, main effects from OS (OS_i), QoL (QoL_i), and safety ($safety_i$) were included. The unit of observation is therefore cost and utilization measures (Y_{ic}) for each drug-indication, country, and year considered.

Any country-level difference in value-based policy may mean that the association between measures of clinical benefit and spending on new cancer medicines depends on setting. To test the hypothesis that the relationship between the focal independent variables measuring clinical benefits and cancer drug spending varies by setting, interaction effects with country as the mediator variable were also considered.

Multiple linear regression was used to test the value-based proposition that spending on new cancer medicines is associated with their beneficial impact to patients. Drug-related effects on OS, QoL, and safety were assumed to be time-invariant in relation to comparator treatments. This approach was consistent with regulatory mechanisms that may re-assess the added therapeutic value of new medicines every five years after initial licensure.(329) An annual cross-sectional study design with robust standard errors was therefore used to model the association between drug clinical benefits and spending, with data from the first year of marketing (Y0) used in base-case analyses. This approach is consistent with that used by Howard and colleagues (2015).(73)

To help ensure that the normality assumption was met, the Shapiro-Wilk test was used to determine whether to use a square root, log, or inverse transformation on the dependent variables of interest. Base-case analyses modelled OS as a continuous variable, used mean estimates of the total cost per patient per (b) (4)

treatment, and number of patients completing (b) (4) therapy, with each new cancer medicine, (b) (4) [redacted] For primary analyses, a p value of less than 0.05 was needed to reach statistical significance. t tests were used to test the null hypothesis that coefficients were equal to zero. All analyses were performed in Stata 14 (College Station, TX: StataCorp LP), and hypothesis testing was 2-sided.

Sensitivity Analysis

As explained in Chapter 2, HTA agencies may give quantitative or qualitative assessments of the impact on OS from treatment with new medicines. They may, for instance, accept a measurable improvement in OS relative to best alternative treatments, or conclude that a new medicine is associated with an unquantifiable increase in OS, with the latter likely suggesting less certainty about drug-related clinical benefits. Base-case analyses were therefore limited to the set of medicines with quantifiable changes in OS. To nevertheless gauge the impact from this approach, sensitivity analysis was used by coding drug-related effects on OS as a categorical variable.

An annual cross-sectional study design was used to reflect the time-invariance that was assumed for drug-related effects on OS, QoL, and safety, with base-case analyses using data from the first year of drug marketing (Y_0). To examine whether results persisted over time, sensitivity analyses also used data from the second (Y_1) and third (Y_2) year of marketing.

Failure to adjust for population and disease epidemiology can confound international comparisons of cancer drug utilization.(74,75) In the absence of international registries providing long-term data on patient care and outcomes,(75) this study adjusted measures of cancer drug utilization by total yearly neoplasm incidence. To test for robustness, and to also examine whether rates of cancer incidence are comparable throughout populations in Australia, France, the UK, and the US, sensitivity analyses adjusted measures of cancer drug utilization by the total population in the country-year that corresponded with drug sales.

Base-case analyses were based on mean rather than median estimates of the dependent variables of interest. (b) (4) From a societal perspective, decision-making that tries to efficiently allocate scarce resources must consider the cost and outcomes associated with treatment of all eligible patients. To nevertheless examine the impact on this study from this approach, sensitivity analyses used median estimates for the dependent variables of interest.

Without publicly-accessible, and internationally comparable, long-term data on patient care and outcomes,(75) (b) (4)

(b) (4)

Limitations

(b) (4)

QuintilesIMS drug pricing data reflects the list price rather than the transaction price; confidential discounts and rebates are not built in.(330) Price discounts may be increasingly common in high-income country community settings,(331) but information on how they are applied to patented pharmaceuticals remains scarce. Given the potentially guarded nature of drug procurement, it is impossible to systematically adjust for pricing discounts. Any discount would mean that this analysis is based on overestimates of drug costs, and any such measurement error in the dependent variable may bias cross-country comparisons. It is however unclear whether this limitation has any practical impact on this study: first, this issue applies to costing estimates for all drugs and all four countries. Second, medicines in the same therapeutic category often receive comparable levels of discount.(302) Based on the disclosed rebate offers by CMS, international studies may in fact assume a constant 23% price reduction for purchasers of specialty medicines, except in Brazil, India, Egypt, and Mongolia, where special pricing arrangements or generic licensing agreements apply.(b) Moreover, the average value of confidential discounts as a share of the official list price for specialty medicines also clusters around 10-30% for payers in high-income countries.(331) The interpretation of this analysis nevertheless

remains valid with respect to costs that are based on list prices. Future studies should however explore this issue.

Moreover, 43 medicines were eligible for inclusion in this study, with additional subsets of data available by country, year, (b) (4) and mean/median statistics. Although this sample encompasses all medicines that had been approved by either the FDA or EMA with a single, primary anti-cancer indication over the 10-year period 2003-2013, and which could be reconciled with the longest longitudinal dataset that is available from QuintilesIMS, this remains a relatively small sample. Future studies should build on this analysis by extending it to other countries, or by re-running it as additional anti-cancer medicines are approved.

This study focuses on drug-related effects on OS, QoL, and safety. This approach is designed to reflect ASCO's Value Framework, which argues that decision-making over treatment options considers drug-related effects on efficacy, QoL, safety, and cost. In contrast to previous studies that have focused exclusively on the correlation between drug pricing and efficacy,(73) this study therefore accounts for any concomitant impact from treatment on QoL and safety that may be value-optimizing.

However, this study did not consider surrogate measures of efficacy, including progression-free survival and response rates. If it is accepted that surrogate efficacy markers represent unique dimensions to the clinical benefits from treatment, then their absence would mean that regression analyses in this chapter may be prone to misspecification bias. However, as was previously argued, surrogacy implies that their

value to patient health is at least in part captured by the three clinical outcome measures that are considered in this analysis—OS, QoL, and safety. This study was also designed to reflect ASCO's Value Framework, which argues that efficacy should be measured using surrogate markers if data on OS is not available. For its part, the FDA states that while surrogate markers of efficacy may be predictive of clinical benefits, they are "not themselves a measure of clinical benefit".(108) And, there is evidence to suggest that any difference between OS and PFS is often negligible: in their sample of 20 drugs, Howard and colleagues (2015) found that the absolute difference between these two measures was less than one month for five drugs, and less than two months for 13 drugs.(73) Similarly, in the instances where OS data may not be available, DrugAbacus considers the margin of gain in PFS to be equivalent to the gain in OS.

Results

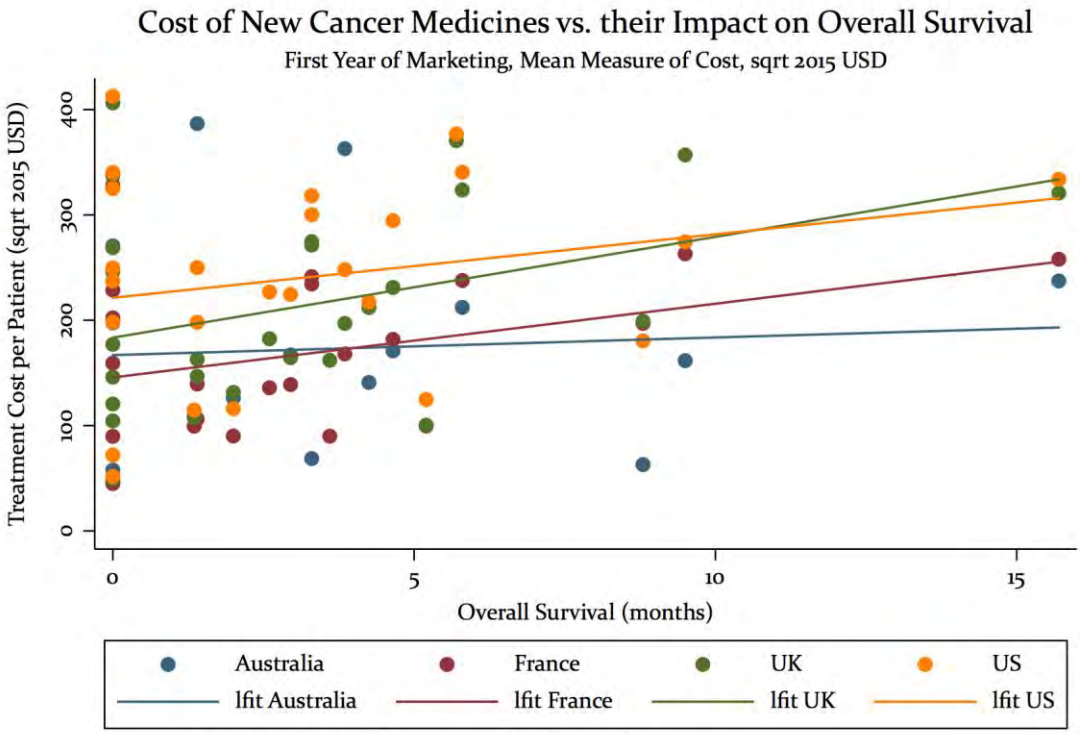
62 anticancer molecules were approved by the US (FDA) and EU (EMA) between 2003-2013 with a primary indication for oncology, and were therefore eligible for inclusion. Of those, treatment duration and recommended dosing information was not available for 6 medicines, while another 9 were approved for multiple primary indications or disease conditions, information that could not be reconciled with the level of specificity in the pricing and volume data that had been licensed for use in this study. Of those that remained, volume and pricing data was not available from the QuintilesIMS data extract for 4 medicines. Chapter 3 was therefore able to generate (b) (4) for the total cost per patient per (b) (4) treatment, and number of patients completing (b) (4) therapy, in each country-year for 43 new anticancer medicines. These 43 medicines were included in this chapter (Figure 16).

Cancer Drug Costs versus Clinical Benefits

(b) (4)

There was a positive correlation between OS and the total expected cost per patient per (b) (4) treatment in each of the countries examined in this analysis (Figure 17). The strength of correlation however varied across the countries that were considered, with a simple linear regression indicating that gains in OS predicted square root transformed total drug costs per patient per (b) (4) treatment in the UK ($b = 9.57$, $t(25) = 2.37$, $p = 0.026$) and France ($b = 7.00$, $t(20) = 2.28$, $p = 0.034$). While still positive, regression coefficients did not reach either the 0.05 or 0.10 significance level in either the US ($b = 6.02$, $t(23) = 1.46$, $p = 0.156$) or Australia ($b = 1.67$, $t(14) = 0.35$, $p = 0.734$). Drug costs tended to rise with improvements in QoL in France and the UK (Appendix 5.1), but did not increase with improvements in safety in any setting (Appendix 5.2).

Figure 17. Cost of New Cancer Medicines vs. their Impact on Overall Survival



Source: Authors' analysis of data, as described in Methods section

Multivariate linear regression analysis was used to determine whether clinical benefits from new medicines predicted the dependent variable of interest, the total cost per patient per (b) (4) treatment with new medicines (Table 18). In line with results from the Shapiro-Wilk test, a square root transformation was used in base-case analysis to correct for nonlinearity.

Models (H) and (E) resulted in the best goodness-of-fit. Compared with model (E), including QoL terms increased the amount of variance in total drug costs that could be explained [model (H)], suggesting that drug-related effects on QoL can help explain drug costs more than OS alone. However, in relation to base model (A), a majority of the model's explanatory power came from accounting for drug-related effects on OS [model (E)]. In contrast, including drug-related effects on safety—model (F)—decreased model explanatory power.

Accounting for treatment descriptors, OS, and QoL, cancer drug costs per patient per (b) (4) treatment were highest in the US under model (H), followed by the UK. Orphan status was found to have a significant effect on cancer drug treatment costs. Cancer drug costs were significantly higher for breast, GI, hematological, skin, and thyroid indications than for malignant ascites. There was also a positive, albeit insignificant, main effect from gains in OS. Although the coefficients for the interactions between country and OS on cancer drug costs were not significant, they were consistently positive and their magnitude varied widely between countries, led by the UK. Interaction terms between there being no drug-related effect on QoL and both the UK and France were significant and negative, pointing to country-moderated effects on cancer drug costs in these countries.

Table 18. Multivariate Linear Regression Analysis, Total Cost per Patient per (b) (4) Treatment with New Medicines and their Beneficial Impact to Health in the First Year of Drug Marketing in Australia, France, the UK, and the US

Variable	Model[1]									
	(A)	(B)	(C)	(D)	(E)	(F)	(G)	(H)	(I)	(J)
Dep. Var.	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp
Ind. Var[2]	1	2	3	4	1, 2	1, 3	1, 4	1, 2, 3	1, 2, 4	1, 2, 3, 4
orphan	-3.135 [22.09]				61.94* [28.13]	25.76 [21.27]	24.78 [18.56]	82.27** [29.32]	45.05 [26.65]	93.43* [35.32]
breast	68.72* [26.83]				84.13 [43.13]	98.92** [36.17]	122.5* [49.88]	97.00* [44.32]	122.8 [62.35]	160.2* [63.52]
gi	55.13 [28.51]				105.4** [38.80]	81.68** [30.69]	113.9* [47.78]	109.9* [42.15]	132.6* [60.50]	165.2* [64.68]
hematological	99.45*** [14.23]				79.23* [33.37]	105.3*** [29.51]	110.9* [42.84]	83.33* [39.70]	110.0* [52.63]	113.2* [55.35]
lung	21.49 [27.67]				64.93 [41.66]	57.67 [38.31]	78.75 [46.57]	88.8 [51.17]	106.2 [56.40]	130.7 [65.51]
prostate	27.08 [33.97]				72.36 [46.88]	61.47 [43.36]	93.89 [54.52]	92.27 [50.14]	123.1 [64.53]	163.1* [68.30]
renal	14.23 [12.89]				-54.08* [26.54]	23.07 [26.21]	53.89 [43.63]	-62.79 [37.85]	4.165 [54.29]	-17.52 [60.43]
skin	89.16** [30.79]				222.1*** [38.50]	144.1*** [42.32]	154.4** [50.30]	247.3*** [39.92]	265.3*** [60.57]	331.7*** [63.68]
thyroid	188.1*** [22.09]				253.2*** [28.13]	217.0*** [21.27]	245.4*** [51.27]	273.5*** [29.32]	313.9*** [59.88]	359.7*** [64.06]
OS		1.675 [4.732]			-1.765 [5.017]			4.595 [4.651]	-1.527 [5.447]	3.78 [6.144]
FR		-21.22 [44.18]	29.49 [25.01]	13.91 [50.48]	-14.45 [43.69]	47.83 [25.58]	14.65 [25.41]	83.94 [44.48]	16.91 [45.54]	41.95 [44.40]
UK		16.53 [45.23]	66.32* [26.64]	52.49 [42.54]	14.65 [44.57]	83.04** [27.17]	68.34* [27.54]	109.3* [42.63]	45.52 [40.86]	65.31 [33.95]
US		54.41 [46.85]	82.16** [28.27]	41.85 [53.37]	52.34 [45.81]	96.75** [30.38]	50.11 [39.90]	143.1* [57.10]	26.18 [53.93]	46.77 [50.77]
FR # OS		5.325 [5.639]			9.923 [5.418]			2.255 [4.979]	11.49 [5.923]	3.892 [6.611]
UK # OS		7.899 [6.245]			12.51* [5.701]			5.203 [5.084]	14.21* [6.295]	6.35 [6.746]
US # OS		4.349 [6.283]			8.104 [6.789]			1.111 [6.990]	9.032 [6.871]	-0.657 [7.519]
QoL_ME			9.484 [22.97]			-38.78 [25.60]				
QoL_reduce			35.62* [16.49]			-36.85 [36.65]		-30.18 [50.50]		-60 [59.88]
QoL_NE			57.31 [41.98]			75.2 [42.96]		131.1 [67.19]		139.2 [86.31]
QoL_ME # UK			17.99 [31.07]			15.86 [29.30]				
QoL_reduce # FR			-71.25 [45.95]			-44.44 [40.39]		-18.47 [63.79]		42.07 [89.80
QoL_reduce # UK			-68.77 [52.32]			-40.33 [46.35]		-13.11 [62.18]		43.58 [91.57]
QoL_reduce # US			-31.28 [30.76]			-13.59 [38.05]		0 [.]		0 [.]
QoL_NE # FR			-63.39 [49.98]			-89.77 [49.27]		-149.5* [69.27]		-179.9* [85.24]
QoL_NE # UK			-55.16 [52.94]			-87.67 [51.49]		-147.7* [68.82]		-185.4* [87.20]

QoL_NE # US			-35.64 [54.04]			-61.51 [53.66]		-144.6 [76.76]		-211.3* [92.70]
safety_ME				30.37 [39.36]			41.36 [38.02]		13.86 [52.67]	-33.39 [56.66]
safety_reduce				67.54 [47.77]			71.38 [42.39]		92.62 [73.55]	-17.98 [63.04]
safety_NE				38.24 [50.22]			22.42 [44.37]		37.68 [66.61]	-75.04 [72.90]
safety_ME # FR				5.82 [58.66]			17.47 [40.92]		-10.51 [68.38]	41.11 [80.71]
safety_ME # UK				8.447 [53.18]			-0.984 [44.84]		-8.889 [68.66]	49.36 [75.15]
safety_ME # US				39.88 [63.04]			36.65 [57.64]		41.44 [77.98]	103.7 [86.47]
safety_reduce # FR				-51.76 [64.06]			-47.71 [46.21]		-100.3 [80.12]	26.11 [71.50]
safety_reduce # UK				-35.98 [60.62]			-57.77 [49.77]		-102.7 [79.54]	31.95 [73.56]
safety_reduce # US				1.121 [68.20]			-5.198 [56.80]		-28.37 [89.52]	129.9 [91.78]
safety_NE # FR				39.98 [71.21]			52.37 [59.51]		23.48 [80.35]	147.8 [82.45]
safety_NE # UK				14.65 [66.83]			20.61 [62.02]		29.83 [83.31]	164.1 [84.70]
safety_NE # US				73.7 [74.15]			72.83 [67.61]		93.16 [86.56]	249.6* [95.60]
Constant	149.2*** [22.09]	166.9*** [37.74]	147.1*** [16.49]	127.1*** [32.23]	69.43 [61.01]	49.68 [42.16]	9.865 [52.39]	-28.87 [64.52]	-12.06 [66.93]	-55.56 [68.49]
Observation	131	90	119	119	90	119	119	90	90	90
R^2	0.161	0.174	0.147	0.188	0.388	0.308	0.306	0.452	0.482	0.54
Adj R^2	0.099	0.104	0.041	0.07	0.254	0.149	0.129	0.26	0.245	0.242

Source:

Authors' analysis of data, as described Methods section.

Notes:

[1] Base-case analysis with a sqrt transformation of the dependent variable, total cost per patient per (b) (4) treatment (TCp) in the first year of marketing (mean estimate (b) (4) from Chapter 3), assuming treatment duration (b) (4)

[2] 1: Treatment descriptors (treated condition, rarity); 2: OS; 3: QoL; 4: safety.

[3] Reference categories: ascites; AU; QoL: improve; safety: improve.

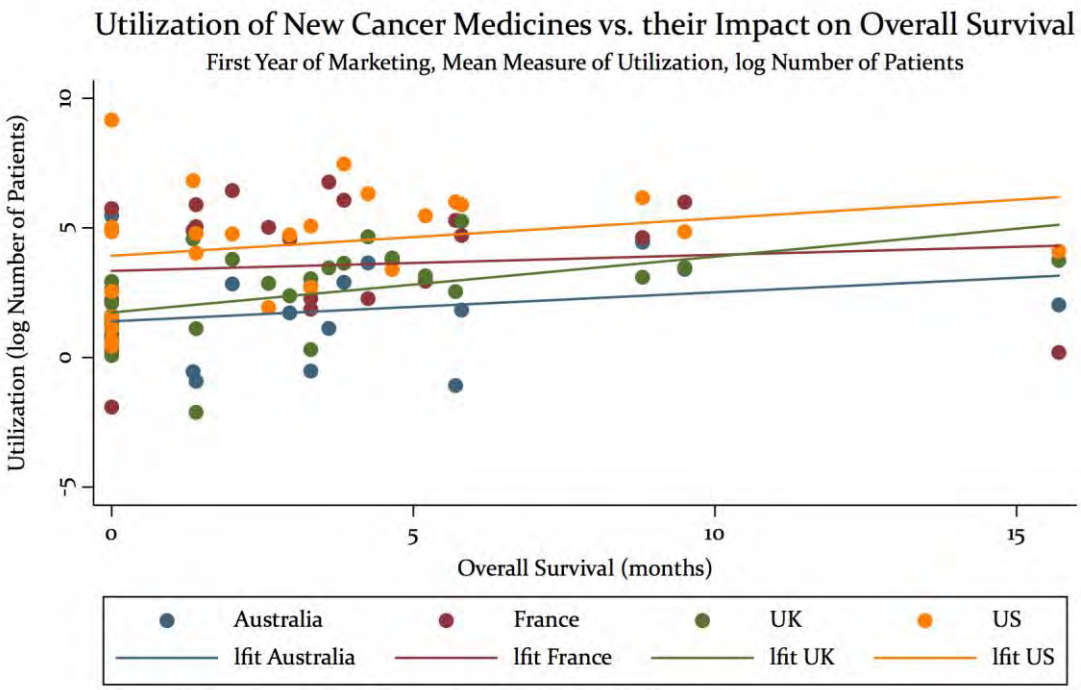
[4] Standard errors (SE) are provided in brackets. ***: $p \leq 0.01$, **: $p \leq 0.05$, *: $p \leq 0.10$

(b) (4)

There was a positive correlation between OS and the total, incidence-adjusted number of patients completing(b) (4) treatment with new cancer medicines across each of the countries examined in this analysis (Figure 18). However, the strength of this correlation varied across the study countries. A simple linear regression indicated

OS was a significant predictor of the natural log-transformed number of patients completing (b) (4) therapy in Yo in the UK (b = 0.215, t(25) = 3.17, p = 0.004). It was followed by the US (b = 0.144, t(23) = 1.22, p = 0.233), Australia (b = 0.112, t(17) = 1.13, p = 0.275) and France (b = 0.062, t(23) = 0.33, p = 0.743). In all four countries, drug utilization rose with improvements in QoL (Appendix 5.3) and safety (Appendix 5.4).

Figure 18. Utilization of New Cancer Medicines vs. their Impact on Overall Survival



Source: Authors' analysis of data, as described in Methods section
Note: Total number of patients completing (b) (4) treatment, per 100,000 incident cases of neoplasm

Multivariate linear regression analysis was used to examine the relationship between the dependent variable of interest, the total number of patients completing (b) (4) treatment per 100,000 cases of incident neoplasm with each new medicine, and drug clinical benefits. In line with results from the Shapiro-Wilk test, a natural log transformation was used in base-case analyses to correct for nonlinearity.

Compared with model (E), inclusion of both QoL [model (F)] and safety [model (G)] terms improved adjusted R^2 estimates (Table 19), suggesting that drug-related effects on both QoL and safety can help better explain variance in rates of incidence-adjusted cancer drug use than OS alone. Compared to base model (A), drug-related effects on QoL [model (G)] accounted for the most variance in cancer drug use. This was followed by drug-related effects on safety [model (G)] and OS [model (E)]. Full model (J) was associated with the highest adjusted R^2 value.

Controlling for treatment descriptors, OS, QoL, and safety, cancer drug utilization per 100,000 cases of incident neoplasm was significantly higher in the US than in Australia under Model (J). Although there was no main effect from the UK on incidence-adjusted cancer drug use, it was the only country in which there was a trend towards significance in the interaction between country identifier and drug-related OS benefits ($p = 0.123$). Clinical decision-makers in the UK therefore appear to be most likely to adopt new treatments when they provide the greatest survival benefit to patients. Interaction terms between there being a drug-related reduction in QoL and France, as well as no effect on safety and the US, were significant and negative. These results point to country-mediated relationships between cancer drug use and measures of clinical benefit.

Table 19. Multivariate Linear Regression Analysis, Total Number of Patients Completing (b) (4) Therapy with New Medicines per 100,000 Incident Cases of Neoplasm and their Beneficial Impact to Health in the First Year of Drug Marketing in Australia, France, the UK, and the US

Variable	Model[1]									
	(A)	(B)	(C)	(D)	(E)	(F)	(G)	(H)	(I)	(J)
Dep. Var.	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi
Ind. Var[2]	1	2	3	4	1, 2	1, 3	1, 4	1, 2, 3	1, 2, 4	1, 2, 3, 4
orphan	-0.17 [0.624]				0.14 [0.724]	-0.516 [0.621]	0.487 [0.633]	-0.732 [0.827]	1.215 [0.873]	0.19 [0.945]
breast	1.973** [0.726]				0.409 [0.990]	0.748 [0.750]	0.0682 [0.958]	-0.285 [0.951]	0.196 [1.056]	-0.708 [0.956]
gi	2.039* [0.849]				0.909 [1.103]	1.244 [0.785]	0.551 [0.971]	0.265 [1.055]	1.234 [1.165]	0.38 [0.957]
hematological	0.42 [0.366]				-0.562 [0.561]	-0.329 [0.476]	-1.628** [0.556]	-0.699 [0.507]	-1.028*** [0.291]	-0.940** [0.310]
lung	1.527* [0.727]				0.803 [0.831]	0.00962 [0.857]	-0.384 [0.821]	-0.802 [1.044]	0.0766 [0.818]	-0.159 [1.160]
prostate	1.844* [0.773]				0.922 [0.957]	0.748 [0.753]	-0.159 [0.954]	-0.107 [0.938]	0.249 [1.042]	-0.62 [0.996]
renal	0.909 [0.591]				1.029 [0.793]	0.0258 [0.541]	-1.545 [0.861]	0.25 [0.964]	-0.255 [0.988]	0.0986 [1.182]
skin	0.476 [0.937]				0.293 [1.304]	-0.405 [0.963]	-1.38 [1.025]	0.087 [1.258]	0.619 [1.289]	-0.665 [1.165]
thyroid	-0.138 [0.624]				0.173 [0.724]	-0.483 [0.621]	-1.376 [0.954]	-0.7 [0.827]	-0.00765 [1.213]	-0.951 [1.147]
OS		0.112 [0.0983]			0.158 [0.128]			-0.0194	0.124 [0.096	0.0949 [0.109]
FR		1.947 [1.015]	1.367 [0.755]	-0.492 [1.518]	2.227* [1.007]	1.104 [0.906]	-0.492 [1.603]	0.397 [1.468]	-0.305 [2.181]	-0.0317 [2.429]
UK		0.342 [0.753]	0.0493 [0.765]	-1.215 [1.674]	0.67 [0.853]	-0.185 [0.870]	-1.215 [1.458]	-1.542 [1.351]	-0.19 [1.443]	-0.303 [1.608]
US		2.529** [0.941]	1.818* [0.833]	2.999 [1.623]	2.896** [0.967]	1.549 [0.941]	2.895* [1.384]	1.095 [1.639]	4.268* [2.004]	4.349* [2.053]
FR # OS		-0.0504 [0.211]			-0.0861 [0.239]			0.000546 [0.230]	-0.152 [0.210]	-0.126 [0.193]
UK # OS		0.103 [0.120]			0.0611 [0.147]			0.206 [0.143]	0.0205 [0.117]	0.194 [0.124]
US # OS		0.0321 [0.154]			-0.0121 [0.175]			0.101 [0.192]	-0.00971 [0.144]	0.0874 [0.166]
QoL_ME			-3.120*** [0.670]			-2.218** [0.834]				
QoL_reduce			0.911 [0.495]			1.621 [0.936]		1.236 [1.346]		1.726 [1.325]
QoL_NE			-2.187** [0.697]			-2.852*** [0.758]		-3.402** [1.206]		-1.434 [1.552]
QoL_ME # UK			-2.109* [0.888]			-2.143* [0.920]				
QoL_reduce # FR			-4.484** [1.707]			-4.775* [1.875]		-6.797*** [1.904]		-6.715** [2.069]
QoL_reduce # UK			-3.181 [2.050]			-3.5 [2.137]		-0.296 [1.840]		1.599 [2.208]
QoL_reduce # US			-0.822 [0.950]			-0.849 [1.128]		0 [.]		0 [.]
QoL_NE # FR			2.310* [1.039]			2.738* [1.069]		3.312* [1.409]		2.584 [1.611]
QoL_NE # UK			1.920* [0.962]			2.418* [0.995]		3.135* [1.326]		3.564* [1.532]

QoL_NE # US			1.922 [1.148]			2.362* [1.123]		2.504 [1.594]		2.181 [1.777]
safety_ME				-1.819 [1.366]			-2.105 [1.308]		-1.292 [1.541]	-0.216 [1.514]
safety_reduce				-2.739** [0.958]			-3.223*** [0.812]		-3.616* [1.400]	-1.771 [1.782]
safety_NE				-1.587 [0.918]			-1.987* [0.813]		-2.508 [1.436]	-0.801 [1.842]
safety_ME # FR				3.109 [1.956]			3.352 [2.017]		3.707 [2.386]	2.527 [2.426]
safety_ME # UK				2.176 [2.219]			2.482 [2.073]		1.77 [1.776]	0.192 [1.742]
safety_ME # US				-0.969 [2.094]			-0.451 [1.946]		-2.434 [2.328]	-3.58 [2.264]
safety_reduce # FR				3.747* [1.711]			3.841* [1.768]		4.322 [2.189]	2.425 [2.653]
safety_reduce # UK				2.985 [1.783]			3.139 [1.614]		2.189 [1.648]	-1.055 [2.050]
safety_reduce # US				0.586 [1.798]			0.784 [1.578]		0.179 [2.106]	-2.098 [2.521]
safety_NE # FR				0.824 [1.690]			1.13 [1.706]		1.524 [2.229]	-0.919 [2.607]
safety_NE # UK				-0.24 [1.823]			0.00782 [1.611]		-0.174 [1.503]	-3.199 [1.927]
safety_NE # US				-2.309 [1.801]			-1.778 [1.552]		-3.127 [2.109]	-5.144* [2.440]
Constant	1.579* [0.624]	1.393* [0.645]	2.333*** [0.495]	3.371*** [0.828]	0.599 [1.251]	2.544* [1.119]	4.116*** [1.140]	3.949* [1.640]	3.066 [1.538]	3.392 [1.908]
Observation	137	96	125	125	96	125	125	96	96	96
R^2	0.101	0.25	0.33	0.325	0.311	0.418	0.409	0.443	0.531	0.633
Adj R^2	0.037	0.19	0.251	0.232	0.172	0.292	0.268	0.265	0.335	0.419

Source:

Authors' analysis of data, as described in Methods section.

Notes:

[1] Base-case analysis with a natural log transformation of the dependent variable, total number of patients completing [redacted] therapy in the first year of marketing per 100,000 incident cases of neoplasm (TPi)(mean estimate [redacted] from Chapter 3), assuming treatment duration [redacted]

[2] 1: Treatment descriptors (treated condition, rarity); 2: OS; 3: QoL; 4: safety.

[3] Reference categories: ascites; AU; QoL: improve; safety: improve.

[4] Standard errors (SE) are provided in brackets. ***: p ≤ 0.01, **: p ≤ 0.05, *: p ≤ 0.10

Sensitivity Analysis

Sensitivity analyses were used to examine the impact from: re-coding OS benefits as a categorical variable (Appendix 5.5; Appendix 5.6), using data from the second and third year of drug marketing (Appendix 5.7; Appendix 5.8; Appendix 5.9; Appendix 5.10), using population-adjusted cancer drug utilization measures (Appendix 5.11), using median rather than mean estimates from generated distributions of the dependent variables of interest (Appendix 5.12; Appendix 5.13), (b) (4) . Results were often consistent with main analyses, particularly in the direction of significant regression coefficients.

Sensitivity analysis re-coded the drug-related impact on OS as a categorical variable. Model (E) explained the highest proportion of variance in cancer drug costs (Appendix 5.5), while Model (J) continued to explained the largest amount of variance in incidence-adjusted use (Appendix 5.6). Although the direction of parameter estimates was largely stable, this approach often reduced their significance.

To examine whether results were consistent over time, regression equations were run using data from the second and third year of marketing. Compared to main analyses, there was little change in the amount of variance in drug costs per patient per (b) (4) treatment that was accounted for by models in either the second (Appendix 5.7) or third (Appendix 5.9) year of drug marketing. As in base-case analyses, model (J) accounted for the most variance in incidence-adjusted cancer drug use in the third year of drug marketing (Appendix 5.10). In contrast, model (G), which only

considered characteristics of disease and the drug-related impact on safety, provided the best fit of cancer drug use data in the second year of drug marketing (Appendix 5.8).

Adjusting the total number of expected patients completing (b) (4) therapy by country-year population size rather than by neoplasm incidence produced highly similar results to base-case analyses (Appendix 5.11). This finding suggests that rates of incidence of neoplasm are comparable throughout populations in Australia, France, the UK, and the US.

Using median rather than mean estimates for total drug costs per patient per (b) (4) treatment (Appendix 5.12) resulted in model (I) explaining the most variance in the dependent variable, followed by model (J). There was however little difference in the parameter estimates that resulted. Using median rather than mean estimates did not change which model best explained variance in number of patients completing (b) (4) treatment (Appendix 5.13), and had little impact on parameter estimates.

(b) (4) resulted in model (E) best able to account for variance in total drug costs per patient per (b) (4) treatment. Parameter estimates were however largely consistent, irrespective of (b) (4) that was assumed for treatment duration. Assuming that DoT (b) (4) did not affect which model accounted for the

most variance in number of patients completing (b) (4) treatment, and had little impact on the parameter estimates that resulted.

Discussion

Against the backdrop of growing cancer drug expenditures, ASCO recently published its Value Framework to compare the relative clinical impact and cost associated with new cancer treatments. The framework gives clinical decision-makers a means of systematically assessing the value of new cancer therapies to patients and society. ASCO's efforts are based on the assumption that, at a societal level (12):

> "the cost of a given intervention … bears a relationship to the beneficial impact it has for patients who receive that treatment."

This study used evidence from earlier chapters to test the proposition that spending on new cancer medicines—defined by both their cost and use—is predicted by their beneficial impact to patients.

Within the sample of new and eligible anticancer medicines that were licensed between 2003-2013, this chapter finds that drug-related improvements in OS, QoL, or safety may only weakly be predictive of cancer drug costs or utilization.

This study finds that per patient cancer drug costs are generally highest in the US and the UK, followed by France and Australia. Incidence-adjusted cancer drug use is also highest in the US, followed by France, the UK, and Australia. These findings are broadly consistent with the existing literature: In their sample of 31 cancer medicines, Vogler and colleagues (2015) find that cancer drug list prices are on average highest in France, followed by the UK and Australia.(77) Their findings are consistent with Goldstein and colleagues (2016), who also report that median monthly prices for cancer medicines are far higher in the US than in the UK and Australia.(265) On a per capita basis, Richards (2010) and O'Neill & Sussex (2013) report that cancer drug use is generally highest in France and the US, and lowest in the UK and Australia.(74,75)

This study finds that cancer drug costs and utilization may be positively correlated with their impact on OS (Figure 17), QoL (Appendix 5.1), and safety (Appendix 5.2) in Australia, France, the UK, and the US. At least with respect to drug-related effects on OS, these findings are also consistent with Howard and colleagues (2015) who—despite methodological limitations[6]—report a positive correlation between treatment episode prices and incremental survival benefits in the US.(73)

However, that is not to say that cancer drug spending is necessarily worth the cost to patients or health systems. This chapter finds positive interactions between drug-related

[6] These have previously been described. Briefly, however, they include: the lack of an international comparison to provide a benchmark for evaluation of US figures; potentially biased monthly pricing estimates that may not adequately reflect the full expected cost from treatment with each new medicine; the failure to account for disease-specific factors that may impact on pricing, as well as other clinical outcome measures, such as quality of life and toxicity. This reflects an inconsistency with ASCO's Value Framework over how to measure clinical impact from new medicines, and may therefore indicate the use of mis-specified models.

improvements in OS and cancer drug costs, particularly in the UK and France. Interaction terms between there being no drug-related effect on QoL and cancer drug costs in both the UK and France were also significant and negative. A positive, albeit non-significant, interaction between drug-related improvements in OS and incidence-adjusted utilization of new anticancer medicines was also found in the UK and the US, with parameter estimates for the former nearing significance at the 0.10 level. Interaction terms between there being a drug-related reduction in QoL and France, as well as no effect on safety and the US, were also significant and negative. These findings suggest that countries are, to some degree, able to mediate the relationship between spending and measures of clinical benefit from new cancer medicines. The extent to which they do, however, differs.

To conclude, ASCO's proposition that "the cost of a given intervention [in oncology] … bears a relationship to the beneficial impact it has for patients who receive that treatment" does not necessarily play out in the real-world. While there often appears to be a positive association between spending on new cancer medicines and measures of their clinical benefit to patients, the strength of this association varies widely across countries, and is not significantly different from zero in some settings. The UK and France, for instance, appear to be particularly successful in ensuring that the costs for new cancer medicines reflect their clinical benefits to patients. The association between the use of new cancer medicines and their clinical benefits is also strongest in the UK and US. However, even in settings where there is evidence to suggest a positive association between cancer drug spending and drug clinical benefits, that association may only be weak. Countries therefore differ in how successfully they mediate the relationship between cancer drug spending and clinical benefits to patients from

treatment, yet all can do more to improve value-for-money in cancer drug spending. In summary, there may be an opportunity to improve the degree to which spending on cancer medicines is value-based.

Key Learnings and Implications

- Per patient drug utilization and costs are generally higher in the US than in Australia, France, and the UK.
- Cancer drug costs and utilization may be weakly correlated with their impact on OS, QoL, and safety in Australia, France, the UK, and the US.
- There may be a positive interaction between drug-related improvements in OS and costs, though the strength of this association varies across countries, and is highest in the UK and France. Interaction terms between there being no drug-related effect on QoL and cancer drug costs in both the UK and France were also significant and negative.
- A positive, albeit non-significant, interaction between drug-related improvements in OS and incidence-adjusted utilization of new anticancer medicines was found, though the strength of this association was highest in the US and, particularly, the UK. Interaction terms between there being a drug-related reduction in QoL and France, as well as no effect on safety and the US, were also significant and negative.

6

Synthesis and Conclusion

Drug spending has grown significantly over recent years, with global pharmaceutical expenditures rising from approximately $750 billion to $1.1 trillion between 2007 and 2015.(24) New anticancer medicines, in particular, have driven recent increases in spending,(23) and projections estimate that they will contribute the most to global pharmaceutical spending growth through 2021, particularly in developed countries.(24)

As fiscal budgets have tightened, rapid increases in pharmaceutical spending have not gone unnoticed.(3) Over recent years, US policymakers have, for instance, launched investigations into drug pricing and price competition,(3) while UK policymakers have sought to reform the CDF to provide patients and the UK health system with greater value-for-money.(88,89) For their part, clinicians have criticized the growth in cancer drug prices as excessive and unsustainable,(44) and have argued that growing cancer drug costs may undermine patient access and clinical compliance.(44,90)

Contributing to this debate is the argument that increases in spending on medicines should nevertheless be considered alongside their clinical benefits. Recent publications

have argued that while cancer drug pricing may be excessive,(44) high costs may be justified if new cancer treatments bring equally large benefits to patients.(22,44,46) Fojo and colleagues (2014) take this one step further by arguing that pharmaceutical companies deserve to charge premium prices for therapies offering premium benefits, while marginal benefits should not be rewarded.(313) There is the notion that a value-based approach to drug spending—where payments are linked to drug clinical benefits—would incentivize the development of medicines that bring greater meaningful improvements to therapy.(313)

Yet, relatively little empirical evidence exists to examine whether spending on cancer medicines is worth it to patients and society.(22,32–35) This likely owes in part to two factors. First, the historical lack of a framework on how to measure value within the field of cancer therapeutics has made it difficult to reach consensus on the clinical objectives of cancer drug spending. The dearth of comparative evidence on the use or cost of cancer medicines has also made it difficult to assess whether and to what extent expenditures are value-based.

This thesis was designed to address these challenges, and to provide insights on the question of whether spending on new cancer medicines is providing value-for-money to patients and society. Briefly, Chapter 2 was the first to build on ASCO's recently published Value Framework to shed light on the clinical risks and benefits associated with all newly licensed cancer medicines. Chapter 3 (b) (4) to generate comparative evidence on their expected use and cost in Australia, France, the UK, and the US. Incorporating data from these chapters, Chapters 4 and 5 then took two approaches to examine whether cancer drug spending is value-based in

these countries. In particular, Chapter 4 adapted the methods used by Eggleston and colleagues (2009)(82) to analyze whether growing cancer drug expenditures generate net positive value, both at a societal- and drug-level. Chapter 5 then used regression analysis to test the value-based hypothesis that spending on new cancer medicines is associated with their beneficial impact to patients.

The following pages synthesize findings from this thesis, discuss their implications, and provide a conclusion on the issue of value-for-money from cancer drug spending.

Synthesis

Clinical Risks and Benefits from New Cancer Medicines

Chapter 2 of this thesis first adopted ASCO's recently published Value Framework for cancer therapeutics, and performed a systematic review with narrative synthesis of corresponding appraisals from Australian, English, and French HTA authorities, to assess their clinical risks and benefits.

62 new medicines with a primary anti-cancer indication were licensed by the US FDA or EU EMA between 2003-2013. Measures of clinical impact varied widely across the 53 cancer medicines that were eligible for inclusion, as well as across treatment indications. Throughout the entire eligible sample, 32% of new anti-cancer medicines increased overall survival by three months or more; 11% by an unknown magnitude of greater than three months; 11% by less than three months; and 15% by some unknown amount. A further 30% did not improve overall survival relative to alternative treatments. Just

under half of new cancer drugs increased cancer patients' quality of life, and the largest share (45%) reduced patient safety.

Taken together, this chapter found that approximately one in three newly approved cancer medicines are not associated with any overall survival benefit, while one in five neither extend life nor improve quality of life or safety.

Licensure however does not necessarily mean that new medicines are used by patients, or generously rewarded by payers. Subsequent chapters incorporate other streams of evidence to compare drug clinical benefits and levels of spending. Findings from this chapter nevertheless have several implications for health policy, clinical practice, and research.

Most immediately, they raise questions over whether there is any value from even minimal additional expense on a subset of new cancer medicines. Findings from Chapter 2 are however based on a review of expert, regulatory evaluations of explanatory clinical trial evidence. To better reveal the real-world clinical risks and benefits from new cancer medicines, future studies should periodically repeat this analysis using post-marketing,(150) observational or pragmatic clinical trial evidence. The National Cancer Institute's upcoming National Cancer Knowledge System may provide crucial insights in this regard.

From a policy perspective, limits to health resources would mean that spending on certain medicines may not benefit patients, and could instead come with significant

opportunity costs to society. As cancer drug spending grows, how should health systems therefore respond to these findings?

To address this question, it may be useful to first consider several points.

First, Chapter 2 focused on the overall survival, quality of life, and safety benefits of new cancer medicines. Briefly, ASCO's Value Framework is based on the notion that value-based clinical decision-making should consider cancer drug costs alongside their impact on efficacy, toxicity, and quality of life. With respect to efficacy, overall survival is generally taken as the gold standard among oncology efficacy endpoints,(64,93,94) and the FDA takes overall survival as the only "universally accepted direct measure of benefit" in oncology drug trials.(95) Whereas surrogate clinical endpoints such as PFS may be subject to assessment bias or variability in the measurement of radiologic or clinical measures and assessment schedules,(96,97) the interpretation of overall survival is objective and not prone to investigator bias.(98) Dodd and colleagues (2008) in fact claim overall survival to be the "most objective end point to measure patient benefit,"(99) and the FDA itself describes overall survival as the "most reliable cancer endpoint."(95) Perhaps as a result, surrogate efficacy measures are not regularly considered during regulatory evaluations,(95) and their predictive value in measuring clinical outcomes remains debated.(111) ASCO's Value Framework encapsulates this line of thinking by arguing that overall survival should be used, where it is reported, to assess the clinical efficacy benefit of treatments for advanced disease. Surrogate measures of efficacy were therefore not considered in this analysis. However, if surrogate efficacy markers do in fact represent unique clinical benefits, then their absence from Chapter 2

would mean that the findings described above represent an upper limit in the percentage of new cancer medicines that provide therapeutic advantages.

Second, cancer medicines can have a variable impact on real-world clinical populations. Biological response to new anticancer medicines may vary, and may partly depend on unknown factors.(332) Scientific advances on the mechanisms of disease, however, continue to emerge.(332) As they do, it may become increasingly possible to stratify patient subgroups and personalize clinical decision-making to improve the therapeutic effects from cancer drug use.(332) Trastuzumab has, for instance, achieved blockbuster status, yet is only efficacious in patients with breast cancer that is HER2/neu-positive.(332)

Variability in clinical response may in part reflect uncertainty over the mechanisms of disease, as 28% of Phase II/III trials still have unidentified targets.(333) This may make it difficult to measure the benefit from new treatments in any clinically relevant way within the limited timeframes of trial studies.(334) From a regulatory perspective, any misapprehension over the biological mediators of disease may therefore mean that regulators are unable to fully appreciate their value to patients.

The implications of there being any uncertainty in decision-making that can affect drug access are morally fraught in cancer, where medicines are often used to treat life-threatening diseases. Within this context, granting conditional marketing authorization may be in the interest of public health if the benefit of immediate availability outweighs the risk of incomplete data.(334) Even if early market authorization provides clinical

benefits to patients, it may also limit data availability for value-based pricing and reimbursement decisions,(334) and lead to hard increases in the cost of care for patients. Complementary efforts to resolve clinical uncertainty, which include phase IV post-marketing surveillance trials, may therefore ensure clinical benefits to patients and value-based spending. Coverage with evidence development and managed access schemes, including England's CDF,(43) are two policy tools that balance access to new treatments with evidence development. If the objective is to optimize the value obtained from spending on new and existing cancer medicines, policymakers should prioritize basic research into the mechanisms of disease. Moreover, drug access and evidence development are both needed to optimize patient well-being. Resources are therefore needed to assess the value from existing clinical and economic information, and to develop tools that can provide value insights using existing data.

Indeed, this thesis found evidence to indicate that clinical uncertainty can directly impact drug evaluations. Agreement between HTA agencies on the accepted overall survival benefit from new medicines, for instance, was found to decrease as the magnitude of the purported benefit increased, suggesting that the regulatory milieu may shape the interpretation of clinical evidence. For example, while both English and Australian regulators accepted that sunitinib extended life by 7.8 months relative to BSC for gastrointestinal stromal tumors, Australia's HTA agency expressed some unease with this claim, noting that this survival benefit "may be an overestimate" given limitations in the supporting evidence. Additional research is needed to help explain the causes of these differences in regulatory opinion.

How should health systems respond to the findings described above? New medicines with an uncertain impact on health may benefit certain patients. Yet, and if only to incentivize clinically meaningful drug innovation,(313) health systems may still be expected to link expenditure with therapeutic impact. They must therefore optimize use of limited resources and reward meaningful innovation, while also facilitating access to treatments and acting in the face of uncertainty.

Mechanisms for tiered drug use may provide health systems with an opportunity to balance these concerns. The UK provides a case study on how to design and implement such a system. In the UK, most care is funded by the public sector, which accounts for 83.3% of total healthcare expenditures in 2013.(335) As of 2016, England's NICE has been tasked with evaluating the clinical- and cost-effectiveness of all new anti-cancer medicines under an accelerated appraisal timetable, and issuing recommendations on whether they should be made available for routine commissioning throughout the country's publicly-funded healthcare system, the NHS.(43) NHS England and Wales is then legally obliged to fund new medicines that are recommended by NICE,(54) prioritizing the uptake of medicines that bring the greatest health benefit to society. To nevertheless alleviate concerns over accessibility, the agency can recommend that new medicines be made available through the CDF if it believes that they may satisfy the criteria for routine commissioning, but significant clinical uncertainty remains. As a managed access fund, the CDF is designed to provide access to cancer medicines that are not routinely available through the NHS, while also aiming to reduce clinical uncertainty.(43) Its annual budget is however capped at £340m: the CDF is not intended to substitute for NICE-recommended treatments, but to help promote drug access and evidence development of new medicines and, as is demonstrated by recent reforms to

the program,(43) drive stronger value-for-money in drug spending. Health systems can therefore prioritize the use of cost-efficient care that provides the greatest good to society, while at the same time providing access to treatments with unclear health benefits and incentivizing the development of clinically meaningful therapeutics.

Spending on New Cancer Medicines

Chapter 3 (b) (4)

[redacted] to generate comparative evidence on the use and cost of individual cancer medicines. Building on recent publications,(78,159) these methods offer a transparent and evidence-based approach to examine both elements to drug spending, (b) (4) [redacted]

The chapter finds that per patient drug costs vary widely across all newly licensed medicines, but also between countries. Per patient drug costs are consistently higher in the US compared with Australia, France, and the UK. This is true even when the drug sample is limited to those medicines that are marketed across all four countries. Holding all else equal, these findings suggest that the US regularly pays a premium for the same cancer medicines.

This finding may reflect national policies on pharmaceutical spending. To lower drug prices, the US Department of Commerce in 2004 characterized the American strategy as one that relies on added competitive pressures from a strong generic pharmaceutical industry, while OECD countries were said to instead rely on "governmental fiat rather

than competition."(336) In Australia, France, and the UK, this was represented by price-volume agreements for new medicines, price and profit controls, encouragement of use of generics and patient co-payments, publication of "negative lists" and "selected lists," and campaigns to encourage doctors to control drug expenditures.(336) Thesis findings have several implications for policy and research that extend from this characterization of national strategies for pharmaceutical spending.

First, findings from this thesis suggest that US payers and patients are willing to accept higher drug costs, without any clear difference in the pharmaceutical goods that are provided. Arguing that manufacturers may delay drug launches in certain countries due to potential 'spill-over' effects on drug pricing, Danzon and colleagues (2007) find that countries with lower expected drug prices or a smaller expected market size have fewer launches or longer launch delays.(337) Higher drug pricing in the US after initial entry, but before subsequent launch in other countries, may therefore represent an "innovation premium" for faster access to new cancer medicines. This thesis in fact shows that most new anti-cancer medicines are initially launched in the US, though the delay to subsequent licensure in Australia, France, and the UK is often less than one year. From the perspective of value, additional research should nevertheless build on these findings to examine whether and to what extent faster access to new treatments provides real-world health benefits to patients.

However, this thesis also finds that higher US drug costs persist over time, and most US patients are treated with new medicines in the years after market entry. It is therefore unclear whether consistently higher US drug costs provide any additional benefit to most US cancer patients, as equivalent medicines may be available at lower cost outside

of the US in the years after market entry. Kantarjian and colleagues (2013) have questioned whether this is fair to US patients, as they pay "two to four times the price paid by patients in other countries for the same drug."(32)

The US accounts for 5% of the world's population, but 30% of its drug revenue, leading some to argue that US patients and payers are "being asked to essentially fund [the world's] drug development."(338) The US does indeed often pay more for medicines than other countries, and higher US drug costs persist over time, suggesting that they may contribute proportionally more to pharmaceutical R&D. Recent studies have nevertheless found that the premiums pharmaceutical companies earn from charging higher drug prices in the US compared with other countries are considerably greater than how much they spend on global R&D, pointing to the notion that higher US drug prices are not necessary for its funding.(339) If new medicines are associated with objectively greater clinical benefits over existing treatments, then faster access to new medicines at higher cost may be to the benefit of US patients. The degree to which this may be true, however, diminishes once equivalent treatments are made available elsewhere at lower cost. In this sense, any additional expense borne by most US cancer patients may also represent a subsidy to those who are treated with new medicines immediately after their launch. Regardless, if higher US drug costs are justified by their impact on R&D, research is needed to evaluate whether US cancer drug price premiums incentivize clinically meaningful innovation.

As these questions are investigated, US policymakers could make drug price premiums fairer for US patients by making it easier for international patients to access new treatments in the US. Depending on its implementation, such a system could help

reduce drug spending by US patients proportional to those from abroad, while still promoting early access to new treatments. Over the longer-term, the US will have to decide if US cancer drug price premiums represent a net benefit to the US health system and US patients. What is clear is that other countries—in this thesis, Australia, France, and the UK—have taken different approaches to regulate cancer drug spending. Were foreign price controls to be eliminated, some have suggested that global pharmaceutical revenues and R&D spending would increase.(336) Assuming that it is unrealistic for this to occur, however, price regulation in the US may be an alternative approach to making cancer drug prices fairer for US patients.

Value-Based Spending on New Cancer Medicines

However, to justify additional governmental fiat in US cancer drug expenditures, evidence is first needed to determine whether current levels of spending are rational and worth the cost to patients and society. Building on evidence from prior chapters, Chapters 4 and 5 take two different approaches to evaluate whether cancer drug expenditures are value-based.

Chapter 4 extends the methods used by Eggleston and colleagues (2009) to determine whether the monetized value of health gains net of marginal increases in cancer drug spending result in positive value to US patients and society.(82) For this, evidence on the overall survival benefits associated with all new anti-cancer medicines was taken from Chapter 2, along with cancer drug spending data from Chapter 3.

The US promotes the generic pharmaceutical industry as a means of creating "added competitive pressure to lower drug prices,"(336) and therefore help moderate drug spending. Chapter 4 finds evidence to suggest that there is indeed a strong generic pharmaceutical industry in the US. However, the degree to which it has effectively helped lower drug prices and drug spending, in particular, is unclear. Between 2004-2014, the US consistently utilized higher volumes of generic cancer medicines than Australia, France, and the UK. The US also experienced a lower compounded annual rate of growth in spending on generic drugs than the latter two countries.

Yet, the US continued to outspend other countries across both generic and branded cancer drug markets. This finding was in spite it having the highest level of generic drug use and comparable levels of overall cancer drug utilization. It also persists after adjusting for population and cancer epidemiology,(74,75) and is consistent across cancer drug classes, many individual new medicines, and over time. These findings suggest that growth in US cancer drug expenditures is not primarily driven by utilization—arguably key to improving patient outcomes—but rather by high drug prices, particularly of branded medicines.

There is therefore some evidence to suggest that a strong generic pharmaceutical industry may help lower growth in total cancer drug spending. However, if comparative rates of price growth offer any guide, this may be driven primarily through competition among generic medicines, rather than between new and older treatments for the same indication. Competition with branded medicines may help lower growth in total cancer drug expenditures, while also incentivizing the development of clinically meaningful medicines. For this to occur, however, economic theory suggests that reliable

information is needed on the comparative clinical risks and benefits between new and older medicines. Unfortunately, this may not always exist: accelerated approval procedures, for instance, may not always provide conclusive information on drug efficacy, and may therefore require phase IV confirmatory studies.(101)

To moderate growth in total drug spending through competition among alternative treatments, policymakers may wish to consider providing additional support to the development of comparative clinical evidence, and re-doubling efforts on comparative efficacy research. In the US, this objective may be met by supporting the Patient-Centered Outcomes Research Institute.

With respect to the clinical impact from cancer drug spending, there was consistent evidence to suggest that the US can do more to improve value-for-money. Adapting the methods used by Eggleston and colleagues (2009),(82) this thesis found that country-level, neoplasm-related, drug-attributable survival gains between 2004-2014 were among the lowest in the US, in spite the country having the highest level of incidence-adjusted spending on cancer medicines. Unlike in Australia, France, and the UK, base-case, country-level analyses suggested that the monetized value of US survival gains that could be attributable to new medicines over this period were less than long-term increases in cancer drug costs. These findings suggest that US cancer drug costs are high compared to what is observed in Australia, France, and the UK, and that, at an aggregate level, the monetized value of survival benefits may not always be worth the cost to patients or society.

These findings were consistent with those from drug-level analyses. Again building on established methods,(82) and utilizing results from earlier chapters, Chapter 4 found that the net value from spending on individual cancer medicines was often lower in the US than in Australia, France, and the UK, due to generally higher cancer drug costs. However, this analysis also revealed that there is wide heterogeneity in the net economic value generated from spending on individual cancer medicines. Pharmaceutical innovations have, in some instances, brought large, positive economic returns from their impact on survival (e.g. pertuzumab). In other cases, the use of some new medicines has generated little, or indeed negative, net value. Even in the US, therefore, growth in cancer drug spending may, in some instances, provide net economic benefits to society. Rather than focus exclusively on growing cancer drug prices, policymakers may instead consider them alongside drug-related clinical benefits, and work to prioritize the development and use of cancer medicines that provide the greatest therapeutic good to patients.

Chapter 5 goes on to show that, when deciding among alternative treatments, clinical decision-making is inconsistently associated with drug-related clinical benefits. The UK showed the strongest, albeit still non-significant, positive association between survival benefits and adoption of new cancer medicines; reductions in quality of life were most likely to reduce incidence-adjusted cancer drug utilization in France; and reductions in, or no established effect on, safety were most likely to reduce cancer drug utilization in the US. Additional research is needed to determine whether these findings reflect differences in how health benefits are prioritized in the clinical decision-making process.

Moreover, little evidence was found to suggest that cancer-drug pricing is value-based, particularly in the US. Compared with France and the UK, the US was less likely to demonstrate evidence of an association between measures of clinical benefit and per patient drug costs. If we accept that the US relies more on market-based systems to moderate drug spending than other OECD countries,(336) these findings suggest that governmental fiat may, if properly designed, play an appropriate economic role in the VBP of cancer medicines.

To conclude, growing expenditures on cancer medicines have not always been met with meaningful gains in value to patients and health systems. The magnitude of clinical benefits associated with all newly licensed cancer medicines varies widely: some new medicines have brought patients notable improvements in therapy, while others have not, raising questions of the value from additional expense. The monetized value of survival gains, net of changes in drug spending, varies by medicine and country, with the US notably lagging Australia, France, and the UK due in part to higher drug costs. There is some evidence to suggest that cancer drug use and cost may only weakly be value-based, and the extent to which this is true also differs across country settings. Taken together, these findings raise several important questions about value-for-money in oncology, and they highlight the important role that health policy can have in value-base cancer drug spending.

Conclusion

Theory, Empirical Gaps, and Thesis Outline

This thesis collected data on the clinical impact, use, and cost associated with new cancer medicines, before then examining whether cancer drug spending provides patients and society with value-for-money. As is shown in Figure 3, these efforts were framed around ASCO's Value Framework, and were designed to reflect its approach for assessing the value of new cancer treatments.

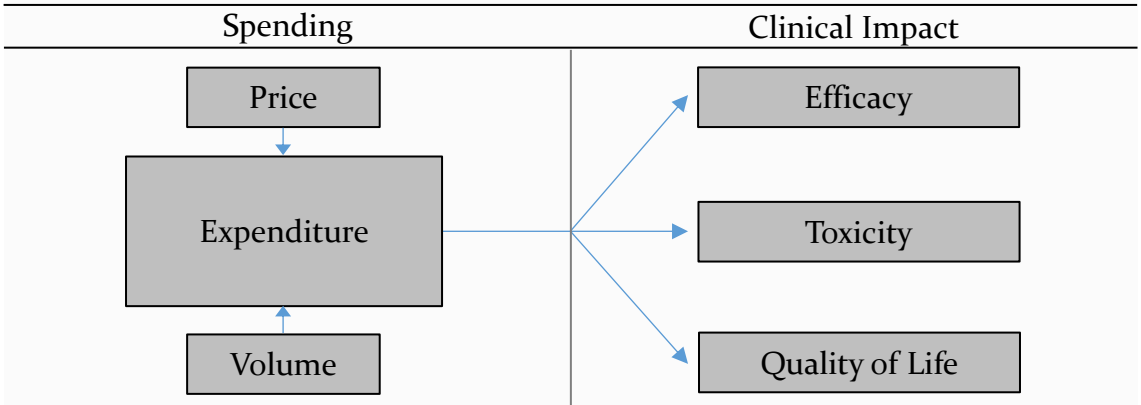
Chapter 2 of this thesis used ASCO's recently published Value Framework within the context of a systematic review with narrative synthesis to assess the clinical impact from new cancer medicines, while Chapter 3 (b) (4) to generate comparative evidence on their expected use and cost in Australia, France, the UK and the US. These data were then used in subsequent chapters to compare the costs and clinical impact from new medicines, and assess their value to patients and society.

In particular, Chapters 4 and 5 incorporated evidence on the clinical impact from new cancer medicines (Chapter 2), and their use and cost (Chapter 3), to examine whether cancer drug spending is providing patients and society with value-for-money. Chapter 4 adapted methods from previous studies to analyze whether the monetized value of survival gains attributable to cancer drug innovation exceeds growth in drug spending, both at a societal- and drug-level. Chapter 5 then incorporated evidence from prior chapters within a regression-based framework to test the value-based hypothesis that spending on new cancer medicines is associated with their beneficial impact to patients. The conceptual framework and empirical gaps underlying these efforts, as well as thesis research questions, outline, and key research findings are shown in Figure 19.

Figure 19. Overview of Conceptual Framework, Empirical Gaps, Research Questions, Thesis Outline, and Key Research Findings

Overarching Research Question: Is cancer drug spending providing patients and society with value-for-money?

Conceptual Framework (12):



Chapter 3:
Empirical Gap: There is a dearth of publicly available and comparable evidence on the use and cost associated with new cancer medicines.

Research Question: What is the utilization and cost (spending) associated with new cancer medicines?

Key Research Findings:

- There is a wide variation in the total dose and total duration of treatment that would be expected from (b) (4) treatment with new cancer medicines.
- Mean estimates of the total expected cost from treatment varied widely across all newly licensed cancer drugs, were highest for hematologicals, increased over time, and varied across countries, with mean total drug costs consistently highest in the US.
- Cancer drug utilization also varied over time and across medicines, and were highest for lung cancer indications and non-orphan medicines.

Chapter 2:
Empirical Gap: Without a conceptual framework in place, it is difficult to systematically assess the clinical impact to cancer patients from new medicines.

Research Question: What are the relative clinical risks and benefits (clinical impact) associated with new cancer medicines?

Key Research Findings:

- All newly licensed cancer medicines have extended OS by an average (SEM) of 3.43 (0.63 months) over 2003 treatment standards.
- Most newly approved cancer drugs were associated with some known (55%) or unknown (70%) benefit in OS, with the largest share (43%) extending life by ≥3 months.
- English HTA agencies were most likely to determine that new cancer medicines improved overall survival, QoL, and reduced patient safety.
- 1 in 3 of all newly approved cancer medicines were not associated with any OS benefit, while 1 in 5 neither extend life nor improve QoL or safety.

Chapters 4 & 5:
Empirical Gap: In the absence of information on the clinical impact **(Ch 2)**, utilization or cost **(Ch 3)**, associated with new cancer medicines, it is difficult to assess whether cancer drug spending provides patients and society with value-for-money.

Research Question (Ch 4): Building on data collected from earlier chapters, is the net monetized value of survival gains that can be attributed to cancer drug innovation positive, both at a societal- and drug-level?
Research Question (Ch 5): Building on data collected from earlier chapters, is spending on new cancer medicines associated with measures of their beneficial clinical impact to patients?

Key Research Findings (Ch 4):

- Base-case, country-level analyses found that Australia, France, and the UK obtained net positive economic returns of $2.52, $6.46, and $3.94 billion in 2014, respectively, from long-term increases in spending on cancer medicines.
- The US outspends other countries on cancer medicines, even after adjusting for population and cancer epidemiology, and was the only country of the four to be associated with a net negative economic return from total, long-term increases in aggregate cancer drug spending.
- At a drug level, the monetized value of drug-related survival gains has exceeded increases in cost for some new cancer medicines, but not for all.

Key Research Findings (Ch 5):

- Per patient drug utilization and costs are generally higher in the US than in Australia, France, and the UK.
- Cancer drug costs and utilization may be weakly correlated with their impact on OS, QoL, and safety in Australia, France, the UK, and the US.
- There may be a positive interaction between drug-related improvements in OS and costs, though the strength of this association varies across countries, and is highest in the UK and France. Interaction terms between there being no drug-related effect on QoL and cancer drug costs in both the UK and France were also significant and negative.
- A positive, albeit non-significant, interaction between drug-related improvements in OS and incidence-adjusted utilization of new anticancer medicines was found, though the strength of this association was highest in the US and, particularly, the UK. Interaction terms between there being a drug-related reduction in QoL and France, as well as no effect on safety and the US, were also significant and negative.

Overarching Conclusion: Generally-speaking, cancer drug spending may be providing patients and society with value-for-money, but the degree to which this is true varies by medicine and country.

Contributions to Policy, Clinical Practice, and Research

To the extent that it examined whether cancer drug spending is providing value-for-money, this thesis may offer several insights to policymakers. There is often uncertainty over the clinical impact from new cancer medicines, pointing to the need for continued investments in basic biomedical and comparative effectiveness research. Such efforts may not only help improve patient care, but also better inform regulatory evaluations and optimize the value that is obtained from spending on new and existing cancer medicines. Over the shorter term, if the objective is to make efficient use of limited resources, while also rewarding meaningful innovation and facilitating access to treatments, policymakers may consider mechanisms for managed entry of new cancer medicines that promote evidence development.

This thesis also finds that the magnitude of clinical benefits varies widely across newly licensed cancer medicines, clinical benefits often come at the cost of safety, and there may be reasons to doubt whether clinical efficacy has been matched by effectiveness in real-world clinical settings. By providing additional clarity on the potential risks and benefits of new cancer medicines, findings from this thesis provide an additional resource for clinical decision-making by patients and physicians.

More so than to policy or clinical practice, the primary contributions from this thesis are methodological and empirical (Figure 19). This thesis makes five major contributions to the literature on value-based spending on cancer medicines. First, adopting the recently published ASCO Value Framework, this thesis finds that approximately one in three

newly licensed cancer medicines provide no known overall survival benefit, while one in five provide no known overall survival, quality of life, or safety benefit. Second, making novel use of methodologies to model treatment course and duration, this thesis finds that cancer drug costs and utilization vary greatly between individual medicines, and across Australia, France, the UK, and the US. Third, it also finds that the monetized value of survival gains attributable to development of new cancer medicines, net of growth in cancer drug spending, varies across individual medicines, and, at a country-level, remains unambiguously positive in Australia, France, and the UK, but negative in the US. Fourth, spending on new cancer medicines is often only weakly associated with their clinical benefits. Fifth, the strength of this association nevertheless varies across countries, with the UK demonstrating the strongest evidence of value-based spending on new cancer medicines.

Pharmaceutical innovations have occasionally brought meaningful clinical benefits to patients. From the perspective of value, growth in cancer drug spending may sometimes, but not always, be justified. Similar arguments have been made elsewhere.(8,9) At a country-level, the strength of association between cancer drug spending and drug clinical benefits varies, yet the evidence suggests that all countries can do more to improve value-for-money.

Future Research Directions

The work that is presented in this thesis outlines several areas for additional research. First, in the absence of real-world data, this thesis was based on pivotal clinical trial evidence. Future studies should extend this analysis by examining post-marketing,

observational or pragmatic clinical trial data, as it becomes available, and comparing against explanatory clinical trial results. Moreover, regulatory assessments of the clinical impact from new cancer medicines may differ, raising questions over whether they consistently reflect the value that patients ascribe to clinical outcome measures. Future studies should therefore examine how evidence on the clinical impact from new treatments is measured, weighted, and rewarded in decision-making by regulators and payers. Finally, the magnitude of association between cancer drug spending and drug clinical benefits varies across countries. Future studies should therefore examine the effectiveness of individual policies and regulations in linking evidence on the clinical impact from new cancer medicines to drug spending.

7

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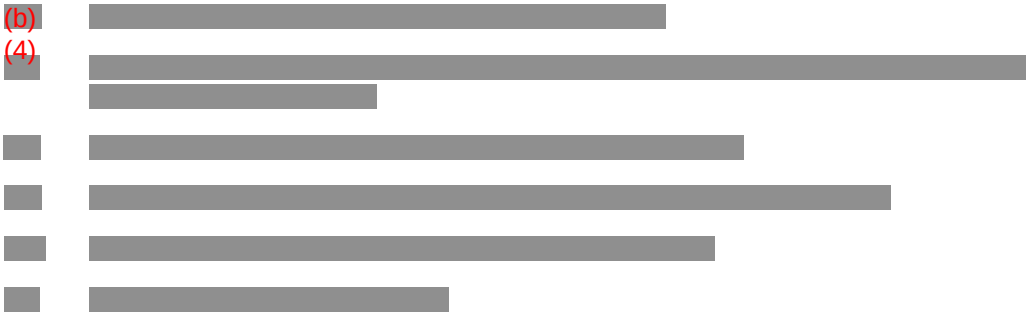

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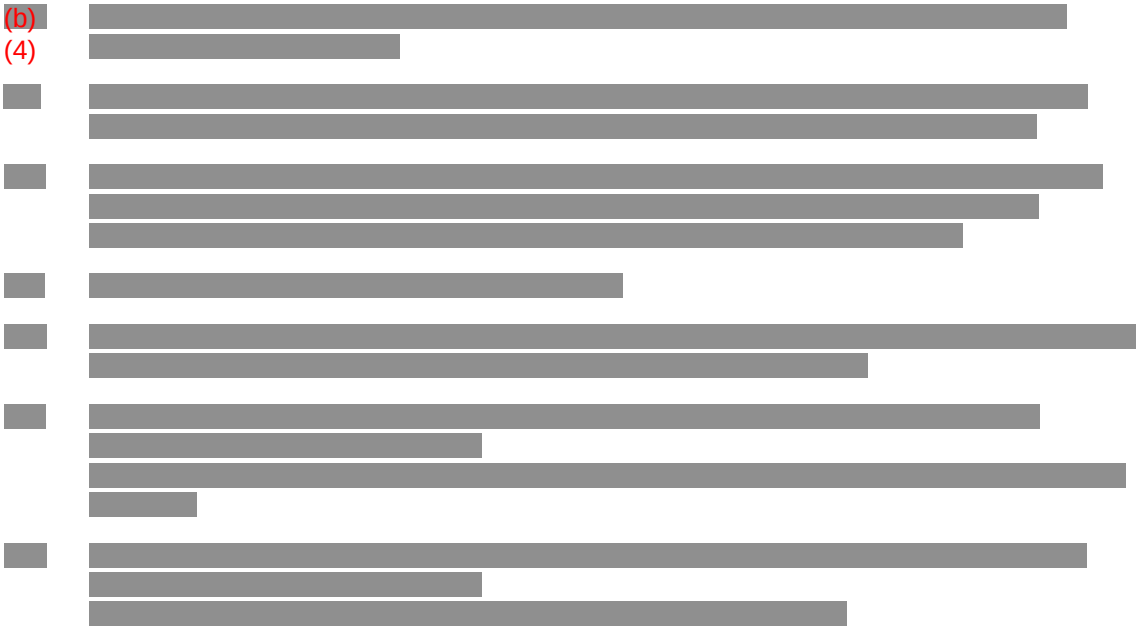

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8

Appendix

Appendix 1.1

eTable 1. Healthcare-Related Bills Introduced during the 114th US Congress

		Competition						Price Regulation							Insurance		Drug Use	Payment Method
Legislation	**Congress**	Barriers to Generic Competition	Generic Priority Review Voucher	Market Exclusivity	Drug Importation	"Pay-for-Delay" Prohibition	Federal Employee Drug Price Regulation	Part D Price Determination	Part D Price Negotiation	Orphan Drug Price Discounts	Price Inflation Reporting	Drug Rebate Provisions	Generic Drug Rebates	Cancer Drugs Insurance Coverage	Part D Coverage Gap	Prescription Drug Monitoring	Part C VBID Methodology
Pharmaceutical Supply and Value Enhancement Act (S.3455)	114th				X												
Value-Based Insurance Design Seniors Copayment Reduction Act (S.1396)	114th																X
Fair Accountability and Innovative Research Drug Pricing Act (S.3335)	114th										X						
Fair Accountability and Innovative Research Drug Pricing Act (H.R.6043)	114th										X						
Medicare Prescription Drug Savings and Choice Act (H.R.3261)	114th								X								
Medicare Prescription Drug Savings and Choice Act (S.1884)	114th								X								
Prescription Drug Affordability Act (H.R.3513)	114th			X	X	X			X			X	X		X		
Prescription Drug Affordability Act (S.2023)	114th			X	X	X			X			X	X		X		
Closing Loopholes for Orphan Drugs Act (H.R.6174)	114th									X							
Prescription Drug Monitoring Act (S.3209)	114th															X	
Prescription Drug and Health Improvement Act (S.2858)	114th								X								
Lower Drug Costs through Competition Act (H.R.4784)	114th	X	X														
Medicare Fair Drug Pricing Act (H.R.4207)	114th							X									
Medicare Prescription Drug Price Negotiation Act (H.R.3061)	114th								X								
Safe and Affordable Prescription Drugs Act (S.1790)	114th				X												
Cancer Drug Coverage Parity Act (H.R.2739)	114th													X			
Cancer Drug Coverage Parity Act (S.1566)	114th													X			
Medicaid Generic Drug Price Fairness Act (H.R.2391)	114th												X				
Medicaid Generic Drug Price Fairness Act (S.1364)	114th												X				
Medicare Drug Savings Act (H.R.2005)	114th											X					
Prescription Drug Accountability Act (H.R.2046)	114th															X	
Safe and Affordable Drugs from Canada Act (H.R.2228)	114th				X												
FEHBP Prescription Drug Oversight and Cost Savings Act (H.R.2175)	114th						X										
Medicare Drug Savings Act (S.1083)	114th											X					
Generic Complex Drugs Safety and Effectiveness for Patients Act (H.R.1576)	114th																
Safe and Affordable Drugs from Canada Act (S.122)	114th				X												
Medicare Prescription Drug Price Negotiation Act (S.31)	114th								X								

Source:

Author's coding of bills from congress.gov.

Notes:

[1] Search strategy: '114th congress' (2015-2016), 'drug', 'value' text words.

Appendix 2.1

eTable 2. Regulatory Evidence in Support of Classification of Drug Clinical Benefits

abiraterone acetate	FDA primary indication		
ATC code: L02BX03	A CYP17 inhibitor indicated for use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel.		
Orphan Status: –			
Licensure: FDA/EMA			
Target: Prostate			
Agency	NICE	HAS	PBAC
Appraisal date	Jun-12	Feb-12	Jul-12
Comparator	BSC (prednisolone)	BSC (prednisolone)	BSC (prednisolone)
Modelled/indirect comparison	No	No	No
Basis for classification	**OS**: 4.6-month increase in median OS compared to prednisolone; estimated mean overall survival gain was greater than 3 months, though exact value was "commercial in confidence" **QoL**: Committee concluded that abiraterone offers a step change in treatment because it is an oral drug taken by patients at home, and is associated with few adverse reactions. The benefit related to being an oral drug was not captured in the analysis because the model applied the same utility benefit to abiraterone as to mitoxantrone. Committee therefore acknowledged that abiraterone provides HRQoL benefits other than those captured in the QALY calculation for patients currently receiving mitoxantrone	**OS**: 3.9-month increase in median OS compared to placebo (prednisone or prednisolone) **QoL**: The patients' quality of life deteriorates less under treatment than with placebo **Safety**: No judgment given on comparative differences in safety	**OS**: 3.9-month increase in median OS compared to BSC (prednisone/ prednisolone plus other care); OS increase compared to mitoxantrone (based on indirect comparison), though magnitude of increase not given; no significant increase compared to cabazitaxel (based on indirect comparison) **QoL**: Statistically significant differences in functional assessment of cancer therapy – prostate (FACT-P) scores between the abiraterone and placebo arms of Trial 301 were demonstrated. However, the magnitude of changes in FACT-P Total Scores between trial arms were small and changes in subscale FACT-P scores were similar in both groups

		Safety: The Committee also noted that abiraterone is not associated with the more severe adverse reactions that can occur with cytotoxic drugs such as mitoxantrone. The Committee heard from the clinical specialists that abiraterone is a well-tolerated oral medication		**Safety**: Whilst PBAC considered there were uncertainties inherent from indirect comparisons, it accepted the submission's clinical claims: (1) abiraterone + prednisone/ prednisolone is equivalent in terms of comparative safety over BSC (prednisone/prednisolone alone); (2) abiraterone + prednisone/ prednisolone is superior in terms of comparative safety over mitozantrone plus prednisone/prednisolone alone; (3) abiraterone + prednisone/ prednisolone is superior in terms of comparative safety over cabazitaxel plus prednisone/prednisolone alone
Effects	Merged data			
OS increase	3.9–4.6 months	≥ 3 months	≥ 3 months	≥ 3 months
QoL change	+	+	+	+
Safety change	+	+	NA	No difference (BSC); + (mitoxantrone); + (cabazitaxel) = +
ado-trastuzumab emtansine		FDA primary indication		
ATC code: L01XC14 Orphan Status: – Licensure: FDA/EMA Target: Breast		HER2-targeted antibody and microtubule inhibitor conjugate indicated, as a single agent, for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: (a) Received prior therapy for metastatic disease, or (b) Developed disease recurrence during or within six months of completing adjuvant therapy.		
Agency		NICE	HAS	PBAC
Appraisal date		Aug-14	Mar-14	Nov-14
Comparator		lapatinib + capecitabine	lapatinib + capecitabine	lapatinib + capecitabine
Modelled/indirect comparison		No	No	No
Basis for classification		**OS**: 5.8-month increase in median OS compared to lapatinib + capecitabine **QoL**: The Committee was aware that EMILIA was an open- label trial, which may have	**OS**: 5.8-month increase in median OS compared to lapatinib + capecitabine **QoL**: In view of the available results from clinical trials, especially the EMILIA study, ado-	**OS**: 5.8-month increase in median OS compared to lapatinib + capecitabine **QoL**: The PBAC noted strong support for the listing of T-DM1 received through the consumer

		introduced bias in the outcomes reported by patients, but concluded that a marginally higher utility value for trastuzumab emtansine in the progression-free state could be accepted in this appraisal **Safety**: The Committee understood that fewer patients stopped treatment because of an adverse event in the trastuzumab emtansine group than in the lapatinib + capecitabine group	trastuzumab is expected to have a moderate impact in terms of morbidity, mortality and QoL **Safety**: A smaller proportion of AEs of grade 3 or worse and serious AEs (SAE) of grade 3 or worse was reported in the trastuzumab emtansine group compared to the control group	comments facility expressing a range of benefits from treatment including improved QoL **Safety**: T-DM1 second-line: the previous resubmission described T-DM1 as superior in terms of comparative safety over lapatinib plus capecitabine. In March 2014, the PBAC accepted this clinical claim, although noted that some of the toxicity profile of T-DM1 was less favourable than that of its comparator
Effects	Merged data			
OS increase	5.8 months	≥ 3 months	≥ 3 months	≥ 3 months
QoL change	+	+	+	+
Safety change	+/-	+	+	+/-
afatinib		FDA primary indication		
ATC code: L01XE13 Orphan Status: – Licensure: FDA/EMA Target: Lung		A kinase inhibitor indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.		
Agency		NICE	HAS	PBAC
Appraisal date		Apr-14	Feb-14	Jul-13
Comparator		erlotinib, gefitinib	cisplatin-based chemotherapy	erlotinib, gefitinib
Modelled/indirect comparison		No	No	No
Basis for classification		**OS**: Committee concluded that on balance afatinib is likely to have similar clinical efficacy to erlotinib and gefitinib. Because of the immaturity of the OS data available, there was uncertainty about whether treatment with afatinib resulted in OS benefit compared with	**OS**: In view of the available clinical data and in comparison with cisplatin-based chemotherapy, it should be noted that there is no improvement in terms of OS **QoL**: In view of the available clinical data and in comparison with cisplatin-based chemotherapy, a moderate additional impact	**OS**: PBAC noted that there was no significant survival advantage reported for afatinib or the other two TKIs in trials considered. Comparing afatinib with chemotherapy, there was no observed benefit in OS

		chemotherapy, therefore no increase was established **QoL**: The Committee did not draw any specific conclusions about the HRQoL benefits and utility values **Safety**: The Committee concluded that although afatinib has a different adverse reaction profile from erlotinib and gefitinib, overall the toxicity of the tyrosine kinase inhibitors was similar	QoL is expected in patients treated with first-line afatinib. In the absence of any clinical data comparing afatinib with other tyrosine kinase inhibitors, the medicinal product afatinib is not expected to have any additional impact on QoL in the current treatment strategy for these patients **Safety**: While HAS makes a few claims on AE rates, the agency gives no assessment of comparative differences in safety	**QoL**: PBAC considered that the benefit of afatinib was due only to a prolongation of PFS which is associated with some improvement in QoL **Safety**: PBAC considered that many serious adverse events including grade 3 or higher appeared more often in the afatinib arm compared to the cisplatin/pemetrexed arm. They noted that there were relatively high rates of adverse events (AEs) associated with afatinib relative to doublet platinum chemotherapy, including more Grade 3 or higher AEs, in the LUX Lung 3 trial. There was a higher proportion of dose reductions during treatment with afatinib compared to treatment with either gefitinib or erlotinib, although there were limitations for those indirect comparison
Effects	Merged data			
OS increase	None established	None established	None established	None established
QoL change	+	NA	+	+
Safety change	-	No difference	NA	-
asparaginase E. chrysanthemi		FDA primary indication		
ATC code: L01XX02 Orphan Status: EU Licensure: FDA Target: Hematological		An asparagine specific enzyme indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to E. coli-derived asparaginase.		
Agency		NICE	HAS	PBAC
Appraisal date		NA	NA	NA
Comparator		NA	NA	NA
Modelled/indirect comparison		NA	NA	NA

Basis for classification		NA	NA	NA
Effects	Merged data			
OS increase		NA	NA	NA
QoL change		NA	NA	NA
Safety change		NA	NA	NA
axitinib		FDA primary indication		
ATC code: L01XE17		A kinase inhibitor indicated for the treatment of advanced renal cell carcinoma after failure of one prior systemic therapy.		
Orphan Status: EU (w)				
Licensure: FDA/EMA				
Target: Renal				
Agency		NICE	HAS	PBAC
Appraisal date		Feb-15	Jan-13	Nov-14
Comparator		BSC	sorafenib	everolimus
Modelled/indirect comparison		Yes	No	Yes
Basis for classification		**OS**: More than 3-month increase compared to BSC was "likely" (based on indirect and simulated treatment comparisons), though exact magnitude of increase was uncertain as the comparison results were "improbable"; Committee concluded that axitinib "was likely to have clinical effectiveness comparable to pazopanib and sunitinib" **QoL**: NICE was satisfied with the HRQoL data collected and found no significant difference versus sorafenib in FKSI-15. QoL was maintined while patients remained in both treatment groups. For EQ-5D, the overall between-treatment comparison for axitinib compared with sorafenib was not statistically significant	**OS**: An increase compared to sorafenib was not established in the overall population or patient subgroups as no statistically significant difference was observed; Committee considered that the indirect comparison to everolius was "exploratory in nature from [which] no conclusions can be drawn with a sufficient level of evidence" **QoL**: In view of the clinical study results showing no gain in terms of overall survival or quality of life, the expected impact of axitinib in terms of morbidity, mortality and quality of life can only be small	**OS**: An increase compared to everolimus was not established given "the limitations of the comparative evidence and the methodological limitations of the simulated treatment comparison and matching-adjusted indirect comparison", though Committee accepted claim of non-inferiority **QoL**: NA **Safety**: PBAC accepted the clinical claim that axitinib is non-inferior to everolimus in terms of comparative effectiveness and safety

		(no p value given); however, QoL was maintained while patients remained on treatment and declined when patients stopped trial medication **Safety**: The Committee noted that diarrhoea occurred with similar frequency in the axitinib and sorafenib groups. It was aware that hypertension, dysphonia, nausea and hypothyroidism occurred more frequently in the axitinib group, although hand–foot syndrome, rash and alopecia occurred more frequently in the sorafenib group. The Committee concluded that axitinib has a manageable adverse event profile compared with other treatments	**Safety**: The frequency of serious adverse events was of the same order between axitinib and sorafenib	
Effects	Merged data			
OS increase	≥ 3 months (exact gain uncertain)	≥ 3 months (exact gain uncertain)	None established	None established
QoL change	None established	No difference	No difference	NA
Safety change	+/-	+/-	No difference	No difference
azacitidine		FDA primary indication		
ATC code: L01BC07		Indicated for treatment of patients with the following myelodysplastic syndrome subtypes: refractory anemia or refractory anemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia.		
Orphan Status: US/EU				
Licensure: FDA/EMA				
Target: Hematological				
Agency		NICE	HAS	PBAC
Appraisal date		Mar-11	Apr-09	Jul-09
Comparator		conventional care	conventional care	conventional care
Modelled/indirect comparison		No	No	No

Basis for classification		**OS**: 9.6-month increase in median OS compared to conventional care regimens (i.e. BSC, low-dose chemotherapy, and standard-dose chemotherapy); OS increase significant compared to BSC and low-dose chemotherapy, but not significant compared to standard-dose chemotherapy though the Committee "was aware that the small patient numbers limited the precision and certainty of the outcome estimates in these groups" **QoL**: Committee heard from the patient experts that compared with other treatment options, azacitidine was associated with relief from fatigue, fewer infection-related hospitalisations, a decreased need for blood and platelet transfusion, and increased ability to perform day-to-day activities. No QoL data were collected in AZA-001, although EORTC data collected in CALGB 9221 suggested improvements in overall health with azacitidine. **Safety**: No comparative assessment made on AEs and safety	**OS**: 9.4-month increase in median OS compared to conventional care regimens (i.e. no active treatment, low-dose cytarabine, and standard chemotherapy) **QoL**: In view of the available clinical data and current therapeutic strategies, azacitidine is expected to have a significant impact on morbidity, mortality and QoL **Safety**: No explicit judgment provided discussing the comparative evidence on drug-related changes in AEs and safety	**OS**: 9.4-month increase in median OS compared to conventional care regimens (i.e. BSC, low-dose cytarabine, and standard-dose chemotherapy) in patients with high risk MDS **QoL**: No explicit discussion on HRQoL data, though there is a brief discussion of the "paucity of available utility data" and the "uncertainty" in the values used in submitted health economic evaluations **Safety**: PBAC agreed that BSC (which included low dose cytarabine and standard chemotherapy) was the appropriate comparator and that the clinical trial data supported the claim that azacitidine was significantly more effective than conventional care but was associated with more toxicity when used for the treatment of INT-2/high risk MDS patients
Effects	Merged data			
OS increase	9.4–9.6 months	≥ 3 months	≥ 3 months	≥ 3 months
QoL change	+	+	+	NA
Safety change	-	NA	NA	-
bendamustine		FDA primary indication		
ATC code: L01AA09 Orphan Status: US Licensure: FDA/EMA Target: Hematological		An alkylating drug indicated for the treatment of patients with chronic lymphocytic leukemia. Efficacy relative to first line therapies other than chlorambucil has not been established.		

Agency		NICE	HAS	PBAC
Appraisal date		Feb-11	Oct-10	NA
Comparator		chlorambucil	chlorambucil	NA
Modelled/indirect comparison		No	No	NA
emBasis for classification		**OS**: No statistically significant difference in median OS between bendamustine and chlorambucil **QoL**: During the treatment period, patients' QoL was assessed using the EORTC questionnaires. Patients' overall QoL was modestly improved in both groups during treatment, with no significant differences between the groups. The manufacturer explained in its submission that the QOL data collected during the trial showed that patients receiving the more effective therapy (bendamustine) experienced a greater number of adverse events during the treatment period, leading to a QoL detriment in some health dimensions **Safety**: The only available treatment for these patients is chlorambucil. The Committee heard that although bendamustine is slightly more toxic and is associated with more AEs, the clinical specialists considered bendamustine to be the more effective treatment. The Committee also noted the views of the patient groups in their submissions to NICE that because of its improved efficacy compared with chlorambucil, people with the condition would be willing to accept the side effects	**OS**: Insignificant difference in terms of median OS compared to the benchmark (65.4 months in the chlorambucil group and not achieved in the bendamustine group) **QoL**: There is a lack of HRQoL data **Safety**: HAS noted that grade 3–4 adverse events were more common in the bendamustine group than in the chlorambucil group, especially haematological adverse events and infections	NA
Effects	Merged data			
OS increase	None established	None established	None established	NA
QoL change	-	-	NA	NA

Safety change	-	-	-	NA
bevacizumab		FDA primary indication		
ATC code: L01XC07 Orphan Status: – Licensure: FDA/EMA Target: GI		In combination with intravenous 5-fluorouracil–based chemotherapy is indicated for first- line treatment of patients with metastatic carcinoma of the colon or rectum.		
Agency		NICE	HAS	PBAC
Appraisal date		Jan-07	Jun-05	Jul-08
Comparator		IFL	IFL	IFL or 5-FU/LV
Modelled/indirect comparison		No	No	No
Basis for classification		**OS**: 4.7-month increase in median OS compared to IFL (irinotecan, bolus 5-FU and leucovorin); no significant difference compared to 5-FU/LV (two studies); Committee noted that the comparators "cannot be considered current standard practice in NHS," though was "persuaded that the results seen in the studies could be considered generalizable to NHS practice" **QoL**: Committee recommends studies to investigate the impact of bevacizumab and cetuximab treatment on HRQoL **Safety**: In all the studies there was a higher incidence of grade 3 and 4 adverse events in the groups receiving bevacizumab compared with the control groups	**OS**: 4.7-month increase in median OS compared to IFL (first-line); no significant difference in median OS was observed compared to FUFOL (5-FU plus folinic acid) **QoL**: Time to deterioration in QoL were similar in both groups **Safety**: In the pivotal study, grade 3-4 toxicity was higher in the IFL + Avastin group than in the IFL alone group	**OS**: 3- to 4-month increase in OS compared to first-line chemotherapy (i.e. IFL or 5-FU/LV), although the differences were not statistically significant in two of the three trials; Committee also noted that IFL was "no longer accepted as best practice in Australia or the USA" **QoL**: No HRQoL data presented **Safety**: Overall, the risk of several AEs, particularly hypertension, proteinuria and arterial thromboembolic events, was found to be elevated following the addition of bevacizumab to chemotherapy
Effects	Merged data			
OS increase	3.0–4.7 months	≥ 3 months	≥ 3 months	≥ 3 months
QoL change	None established	NA	No Difference	NA

Safety change	-	-	-	-
bortezomib		FDA primary indication		
ATC code: L01XX32 Orphan Status: US Licensure: FDA/EMA Target: Hematological		bortezomib for injection is indicated for the treatment of multiple myeloma patients who have received at least two prior therapies and have demonstrated disease progression on the last therapy. The effectiveness of VELCADE is based on response rates (see CLINICAL STUDIES section). There are no controlled trials demonstrating a clinical benefit, such as an improvement in survival.		
Agency		NICE	HAS	PBAC
Appraisal date		Oct-07	Oct-04	Mar-06
Comparator		high-dose dexamethasone	Not given	high-dose dexamethasone
Modelled/indirect comparison		No	Yes	No
Basis for classification		**OS**: 6.1-month increase in median OS compared to high-dose dexamethasone **QoL**: No HRQoL information provided. Further research into the effectiveness of bortezomib for the treatment of relapsed multiple myeloma is needed. Such studies should include: measurement of quality of life in patients with relapsed multiple myeloma, including the effect of treatment and adverse events **Safety**: Committee understood from the clinical specialists that there was a greater frequency of peripheral neuropathy and gastrointestinal adverse effects in the bortezomib arm, but that bortezomib was associated with less bone destruction and fewer infections than HDD	**OS**: 8.5- to 11.5-month improvement in median survival based on comparison of OS data from single-arm bortezomib study and OS data from literature for similar patient population **QoL**: Regarding QoL treatment, improved items including the overall score of QoL, the physical score and social score were observed in 2 of the three scales used (QLQ-C30 scale EORTC-QLQ Module MY24). Variation of the scores of the FACIT-Fatigue scale score was not statistically significant **Safety**: No comparative data	**OS**: Committee "acknowledged that bortezomib has significant advantages in the short term over the comparator HDD in terms of…increasing the proportion of individuals alive at one year" but noted that "a number of uncertainties arose over the interpretation of the…trial results," including wide 95% confidence intervals, significant patient crossover, and "doubts about the acceptability of HDD as being representative for the main comparator" **QoL**: NA **Safety**: Overall incidence of AEs were similar in both groups, with 100% of bortezomib patients and 98% of HDD patients experiencing one AE. Overall pattern of AE differed. Incidence of Grade 3 and those leading to discontinuation was higher in the bortezomib group
Effects	Merged data			
OS increase	6.1–11.5 months	≥ 3 months	≥ 3 months	Uncertain

QoL change	+	NA	+	NA
Safety change	+/-	+/-	NA	-
bosutinib		FDA primary indication		
ATC code: L01XE14		A kinase inhibitor indicated for the treatment of adult patients with chronic, accelerated, or blast phase Ph+ chronic myelogenous leukemia (CML) with resistance or intolerance to prior therapy.		
Orphan Status: US/EU				
Licensure: FDA/EMA				
Target: Hematological				
Agency		NICE	HAS	PBAC
Appraisal date		Nov-13	Feb-14	NA
Comparator		BSC	NA	NA
Modelled/indirect comparison		Yes	No	NA
Basis for classification		**OS**: At least 3-month extension compared to BSC, though exact magnitude of increase uncertain (based on modeled data) **QoL**: NA **Safety**: The Committee heard from a patient expert that, in their own experience, previous tyrosine kinase inhibitors had resulted in them being unable to work and needing cardiac and surgical interventions. However, bosutinib had been tolerated	**OS**: An increase was not established given the lack of comparative data presented to the Committee **QoL**: The proprietary medicinal product bosutinib is not expected to have any impact on morbidity, mortality or QoL in comparison with cited treatments **Safety**: No comparative data available	NA
Effects	Merged data			
OS increase	≥ 3 months (exact gain uncertain)	≥ 3 months (exact gain uncertain)	None established	NA
QoL change	None established	NA	No difference	NA
Safety change	+	+	NA	NA

brentuximab vedotin		FDA primary indication		
ATC code: L01XC12 Orphan Status: US/EU Licensure: FDA/EMA Target: Hematological		A CD30-directed antibody-drug conjugate indicated for: (a) Hodgkin lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates; and (b) Systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen. These indications are based on response rate.		
Agency		NICE	HAS	PBAC
Appraisal date		NA	Mar-13	Mar-14
Comparator		NA	non-comparative	multi-agent salvage chemotherapy
Modelled/indirect comparison		NA	No	No
Basis for classification		NA	**OS**: Median OS was not achieved during the primary analysis and does not enable conclusions to be drawn regarding this endpoint; available data are not sufficient (absence of comparative data in particular) to enable an evaluation of the expected impact of brentuximab vedotin on the morbidity, mortality and quality of life of patients treated **QoL**: NA **Safety**: No comparative data available	**OS**: The PBAC accepted the claim that BV is associated with significant additional OS and patient relevant efficacy in the first line salvage setting for patients that have had no prior SCT **QoL**: NA **Safety**: PBAC considered that the submission's claim of less toxicity relative to multi-agent salvage chemotherapy was reasonable with respect to most acute toxicity, but that severe peripheral neuropathy was an important toxicity more likely in BV treated patients
Effects	Merged data			
OS increase	Exact magnitude uncertain	NA	None established	Uncertain
QoL change	None established	NA	NA	NA
Safety change	+/-	NA	NA	+/-
cabazitaxel		FDA primary indication		

ATC code: L01CD04 Orphan Status: – Licensure: FDA/EMA Target: Prostate		A microtubule inhibitor indicated in combination with prednisone for treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen.		
Agency		NICE	HAS	PBAC
Appraisal date		May-12	Oct-12	Nov-11
Comparator		mitoxantrone	mitoxantrone	mitoxantrone
Modelled/indirect comparison		Yes	No	No
Basis for classification		**OS**: More than 3-month increase compared to mitoxantrone (4.2 months based on modeled mean OS gain); 2.4-month increase in median OS was observed in the trial **QoL**: No statistically significant difference in pain response between the treatment arms. No significant difference in time to pain progression between the treatment arms **Safety**: The Committee was initially concerned that in TROPIC more participants in the cabazitaxel arm died from cardiac and renal complications than in the mitoxantrone arm. The Committee concluded that there is no evidence of additional risk other than that included in the SPC and that the health economic model adequately reflected the disutility associated with adverse reactions. The Committee further heard that patient experts are aware that cabazitaxel is associated with serious ARs and that it would not be suitable for some patients who are not fit for chemotherapy	**OS**: 4.1-month increase in median OS compared to mitoxantrone in subgroup of patients who had stopped treatment due to disease progression and had a histologically poorly differentiated tumor; 2.4-month increase in median OS compared to mitoxantrone in the whole trial population **QoL**: In the absence of data, the impact on the QoL of treated patients is not quantifiable. Nevertheless, a negative impact (safety issues) on QoL cannot be ruled out **Safety**: Safety was not as good in the cabazitaxel group as in the mitoxantrone group	**OS**: 2.4-month increase in median OS compared to mitoxantrone; Committee stated that the modeled mean OS gain of 4.26 months appeared to be an overestimate and was uncertain **QoL**: A regulatory judgment of the submitted HRQoL (Q-TWIST) evidence is not given **Safety**: The PBAC agreed that the clinical claim that cabazitaxel is superior in terms of comparative effectiveness and inferior in terms of comparative safety over mitozantrone is reasonable
Effects	Merged data			
OS increase	2.4–4.2 months	≥ 3 months	≥ 3 months	≥ 3 months

QoL change	None established	No difference	NA	NA
Safety change	-	-	-	-
cabozantinib		FDA primary indication		
ATC code: L01XE26		A kinase inhibitor indicated for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC).		
Orphan Status: US				
Licensure: FDA/EMA				
Target: Thyroid				
Agency		NICE	HAS	PBAC
Appraisal date		NA	Dec-14	NA
Comparator		NA	placebo	NA
Modelled/indirect comparison		NA	No	NA
Basis for classification		NA	**OS**: The available data showed no benefit, and given current therapeutic strategies, low impact in terms of morbidity and mortality is expected **QoL**: The available clinical data (including a Phase III placebo-controlled trial) showed a gain of 7 months progression-free survival with better response rates, but no benefit on overall survival or profit (or worsening) of QoL **Safety**: Treatment discontinuations due to adverse events were higher for patients in the cabozantinib group versus placebo patients	NA
Effects	Merged data			
OS increase	None established	NA	None established	NA
QoL change	None established	NA	No difference	NA
Safety change	-	NA	-	NA

carfilzomib		FDA primary indication		
ATC code: L01XX45		A proteasome inhibitor indicated for the treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate.		
Orphan Status: US/EU				
Licensure: FDA/EMA				
Target: Hematological				
Agency		NICE	HAS	PBAC
Appraisal date		NA	NA	NA
Comparator		NA	NA	NA
Modelled/indirect comparison		NA	NA	NA
Basis for classification		NA	NA	NA
Effects	Merged data			
OS increase		NA	NA	NA
QoL change		NA	NA	NA
Safety change		NA	NA	NA
catumaxomab		FDA primary indication		
ATC code: L01XC09		indicated for the intraperitoneal treatment of malignant ascites in adults with EpCAM-positive carcinomas where standard therapy is not available or no longer feasible.		
Orphan Status: US/EU				
Licensure: EMA				
Target: Ascites				
Agency		NICE	HAS	PBAC
Appraisal date		NA	Dec-09	NA
Comparator		NA	paracentesis	NA
Modelled/indirect comparison		NA	No	NA

Basis for classification		NA	**OS**: Median OS did not differ between the two groups: 72 days in the REMOVAB group compared with 68 days in the control group **QoL**: In view of the methodology of the study (open-label), QoL data are difficult to interpret. The need for 11 days of hospitalisation for the treatment while no evidence is available of an improvement in QoL **Safety**: No comparative evidence presented	NA
Effects	Merged data			
OS increase	None established	NA	None established	NA
QoL change	None established	NA	No difference	NA
Safety change	None established	NA	NA	NA
cetuximab		FDA primary indication		
ATC code: L01XC06 Orphan Status: – Licensure: FDA/EMA Target: GI		Used in combination with irinotecan for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy. cetuximab administered as a single agent is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy.		
Agency		NICE	HAS	PBAC
Appraisal date		Jan-07	Mar-05	Mar-09
Comparator		cetuximab monotherapy	cetuximab monotherapy	BSC
Modelled/indirect comparison		No	No	Yes
Basis for classification		**OS:** No statistically significant difference in median OS between cetuximab-irinotecan combination therapy and cetuximab monotherapy. Relative effectiveness against	**OS:** No gain in OS has been demonstrated between cetuximab-irinotecan and cetuximab monotherapy	**OS:** PBAC noted 3.6-month survival gain over BSC arm in modeled data. However, submission estimate likely overestimated the OS. PBAC considered that the extent of OS benefit over BSC

		current standard care remains uncertain **QoL:** The Committee recommends studies to investigate the impact of bevacizumab and cetuximab treatment on health-related quality of life **Safety:** In the RCT the incidence of some AEs was higher in patients receiving cetuximab plus irinotecan compared with those receiving cetuximab alone: grade 3 and 4 adverse events; diarrhoea; neutropenia; grade 3 or 4 acne-like rash.	**QoL:** Available data do not allow to quantify the contribution of cetuximab in terms of quality of life vis-à-vis existing therapies **Safety:** 71% of patients in the combination group experienced at least one Grade 3–4 events against 53% monotherapy group	in the KRAS subgroup remained uncertain **QoL:** For key results, see Nov 2008 PSD. No information indicating drug-induced change **Safety:** For key results, see Nov 2008 PSD. Cetuximab in combination with irinotecan tended to have more serious AEs and Grade 3/4 AEs compared to cetuximab monotherapy. These AEs were expected to be less in the BSC group. Cetuximab monotherapy had a greater incidence of any adverse event of grade 3 or higher compared to the BSC group (p<0.001). Patients in the cetuximab monotherapy group had a higher incidence of rash, infection without neutropenia, confusion and other pain as well as hypomagnesemia and infusion reactions
Effects	Merged data			
OS increase	Exact magnitude uncertain	None established	None established	Uncertain
QoL change	None established	NA	NA	NA
Safety change	-	-	NA	-
clofarabine		FDA primary indication		
ATC code: L01BB06 Orphan Status: US/EU Licensure: FDA/EMA Target: Hematological		Treatment of pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens. This use is based on the induction of complete responses. Randomized trials demonstrating increased survival or other clinical benefit have not been conducted.		
Agency		NICE	HAS	PBAC
Appraisal date		NA	Dec-06	NA
Comparator		NA	non-comparative	NA

Modelled/indirect comparison		NA	Yes	NA
Basis for classification		NA	**OS**: Expected to have an impact in terms of morbi-mortality by facilitating access to an allograft. However, in the absence of a formalized comparison with historic data, the impact can only be small. Moreover, because of the uncertainty about drug tolerance, extrapolation of the test results to real life is itself uncertain. **QoL**: No comparative data presented to evaluate HRQoL **Safety**: Tolerance data are limited at present. No comparative evaluation of drug-related safety as comparator arm unavailable. Additional absence of "formalized comparisons with historical data on relapsed or refractory patients having had at least two previous treatments"	NA
Effects	Merged data			
OS increase	None established	NA	NA	NA
QoL change	None established	NA	None established	NA
Safety change	None established	NA	NA	NA
crizotinib		FDA primary indication		
ATC code: L01XE16		A kinase inhibitor indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test. This indication is based on response rate.		
Orphan Status: -				
Licensure: FDA/EMA				
Target: Lung				
Agency		NICE	HAS	PBAC

Appraisal date		Sep-13	Apr-13	Nov-14
Comparator		docetaxel	pemetrexed or docetaxel	pemetrexed
Modelled/indirect comparison		Yes	No	Yes
Basis for classification		**OS**: Committee "accepted that treatment would result in gain compared with docetaxel but the exact magnitude was uncertain; Committee "considered that the IPTCW2 method, which resulted in an OS benefit of 7.1 months, may be a reasonable assumption given the lack of robust data" but that "an exact value could not be reliably established" **QoL**: Committee heard from the clinical specialists that patients with progressed disease continued to experience some additional health-related QoL benefit for some time after treatment was withdrawn compared with those on chemotherapy, but that this would deteriorate over time. It accepted that some utility benefit might be expected from crizotinib discontinued at disease progression, though there are no data to suggest how great a benefit this might be or for how long it would persist. The Committee was also aware that there might be a benefit to utility of continuing crizotinib, but there were no data to show whether such continued treatment benefits patients or for how long **Safety**: The Committee concluded that crizotinib is associated with some ADRs but these would be tolerable for most patients and generally easily managed.	**OS**: An increase compared to chemotherapy (i.e. docetaxel or pemetrexed) not established as no statistically significant difference was observed **QoL**: In view of the available clinical data, crizotinib showed a significant improvement in QoL versus docetaxel or pemetrexed **Safety**: No judgment given on comparative differences in drug-related safety profile	**OS**: Committee considered the "likely incremental gain "is between 3.1 to 3.5 months compared to pemetrexed (based on modeled data); Committee concluded that "given both the limitations of the randomized trial (small sample size, immature follow-up and post-progression cross-over to crizotinib in the pemetrexed arm) and also the usual concerns with attempting comparative treatment effect inferences by comparing across results for different groups of patients, no completely compelling conclusions could be drawn about the extent of incremental overall survival gain for crizotinib over pemetrexed" **QoL**: Consumer comments described a range of benefits, including the ability to return to work **Safety**: The PBAC accepted the claims for crizotinib having superior effectiveness and non-inferior safety compared to pemetrexed
Effects	Merged data			
OS increase	3.1–3.5 months	Uncertain	None established	≥ 3 months
QoL change	+	+	+	+
Safety change	None established	NA	NA	No difference

dabrafenib		FDA primary indication		
ATC code: L01XE23 Orphan Status: – Licensure: FDA/EMA Target: Skin		A kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.		
Agency		NICE	HAS	PBAC
Appraisal date		Oct-14	May-14	Mar-13
Comparator		dacarbazine	dacarbazine	DTIC
Modelled/indirect comparison		No	No	No
Basis for classification		**OS**: The Committee concluded that compared with dacarbazine, dabrafenib probably improved OS, but it was unable to draw firm conclusions about the magnitude of the benefit **QoL**: The mean change in EQ-5D utility index score from baseline to week 15 was lower in the dabrafenib group than in the dacarbazine group **Safety**: The Committee concluded that the current evidence suggests that ADRs from dabrafenib treatment were not a major concern when compared with those from alternative treatments	**OS**: In view of the available data, which shows no increase, the impact of dabrafenib on morbidity and mortality is considered low. On this date, there was no difference between the two therapeutic groups, dabrafenib vs dacarbazine (at six months) **QoL**: evaluatation using EORTC QLQ-C30 and EuroQoL EQ-5D questionnaires did not show any difference between the two treatment groups **Safety**: Treatment discontinuations due to adverse events were similar in both groups	**OS**: Dabrafenib, unlike vemurafenib, has not demonstrated an unequivocal advantage over DTIC. There was no statistically significant difference both treatment groups. However, OS data at time of cut-off was not mature, therefore no conclusions could be drawn **QoL**: NA **Safety**: Dabrafenib and DTIC have different toxicity profiles, with dabrafenib being associated with manageable toxicity versus DTIC. PBAC noted that dabrafenib has a preferable toxicity profile vs vemurafenib as evidenced by fewer and less extensive dose intensity reductions and by favourable differences in rates for AEs such as photosensitivity, cutaneous squamous cell carcinoma – but not pyrexia
Effects	Merged data			
OS increase	Exact magnitude uncertain	Uncertain	None established	None established
QoL change	-	-	No difference	NA

Safety change	+	No difference	No difference	NA (dacarbazine); + (vemurafenib) = +
dasatinib		FDA primary indication		
ATC code: L01XE06 Orphan Status: US/EU Licensure: FDA/EMA Target: Hematological		Indicated for the treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib. Also indicated for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia with resistance or intolerance to prior therapy.		
Agency		NICE	HAS	PBAC
Appraisal date		Jun-12	Mar-07	Jul-07
Comparator		non-comparative	non-comparative	non-comparative
Modelled/indirect comparison		Yes	Yes	Yes
Basis for classification		**OS**: Clinical trials were non-comparative, of short duration and had used surrogate outcomes to predict OS. The Committee noted the poor quality of the evidence base **QoL**: No regulatory judgment made on comparative differences in HRQoL **Safety**: Committee concluded that dasatinib and nilotinib are better tolerated than imatinib, and that older treatments, particularly interferon alfa, can be poorly tolerated	**OS**: Available clinical studies do not evaluate OS benefits directly **QoL**: No comparative data presented with which to evaluate comparative differences in HRQoL **Safety**: While safety of dasatinib evaluated, no comparison against other treatments is made	**OS**: Clinical benefits as determined by number of patients achieving complete cytogenic response. Outstanding areas of concern for the Committee were whether cytogenetic response outcomes later in the course of the chronic phase of CML result in survival gain and, if so, what is the magnitude of the gain **QoL**: NA **Safety**: Evaluation indicated that dasatinib has significant advantages in effectiveness over imatinib but has more toxicity
Effects	Merged data			
OS increase	None established	None established	None established	None established
QoL change	None established	NA	NA	NA
Safety change	+/-	+	NA	-

decitabine		FDA primary indication		
ATC code: L01BC08		Indicated for treatment of patients with myelodysplastic syndromes (MDS) including previously treated and untreated, de novo and secondary MDS of all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.		
Orphan Status: US/EU				
Licensure: FDA/EMA				
Target: Hematological				
Agency		NICE	HAS	PBAC
Appraisal date		NA	NA	NA
Comparator		NA	NA	NA
Modelled/indirect comparison		NA	NA	NA
Basis for classification		NA	NA	NA
Effects	Merged data			
OS increase	NA	NA	NA	NA
QoL change	NA	NA	NA	NA
Safety change	NA	NA	NA	NA
degarelix		FDA primary indication		
ATC code: L02BX02		A GnRH receptor antagonist indicated for treatment of patients with advanced prostate cancer.		
Orphan Status: –				
Licensure: FDA/EMA				
Target: Prostate				
Agency		NICE	HAS	PBAC
Appraisal date		Apr-14	Sep-09	Jul-10
Comparator		LHRH agonists	leuproprelin	leuproprelin
Modelled/indirect comparison		No	No	No

Basis for classification		**OS**: Committee noted that duration of trials was short and were not sufficiently powered to detect differences between treatment groups. Mixed treatment comparison also did not show statistically significant differences. Lack of evidence to support OS benefit compared with LHRH agonists **QoL**: Patient experts noted that subcutaneous injections of degarelix are administered monthly and this dosing schedule may be inconvenient for some patients compared with subcutaneous administration of the LHRH agonists every 3 months. The manufacturer presented data for HRQoL, which was assessed using different measures and questionnaires. All the SF12 v2 scores were comparable across treatment groups and study days. **Safety**: The Committee heard from the patient experts that the safety profile is comparable to that of the LHRH agonists and the potential benefits of outweigh the adverse effects associated with it	**OS**: Not expected to have impact on morbidity and mortality. No clinical data demonstrating the benefits of this product in the treatment of prostate cancer **QoL**: Degarelix has not been shown to provide any improvement in treated patients **Safety**: The safety profiles of the two treatments were similar, apart from the emergence of anti-degarelix antibodies. There was no observed correlation between emergence of these antibodies and the efficacy and safety of degarelix after one year of treatment	**OS**: Submission provided no evidence to demonstrate whether outcomes observed in the first month of possible long-term treatment with degarelix would have significant effects on overall survival compared with leuproprelin **QoL**: NA **Safety**: The PBAC noted that there are more injection site reactions compared with leuprorelin and therefore degarelix may not be non-inferior with regards to safety. The majority of treatment-emergent ADRs were general disorders and administration site conditions including injection-site reactions which occurred in 73 patients in the degarelix 240/80 mg group compared with 1 patient in the leuprorelin arm
Effects	Merged data			
OS increase	None established	None established	None established	None established
QoL change	None established	No difference	No difference	NA
Safety change	-	No difference	No difference	-
enzalutamide		FDA primary indication		
ATC code: L02BB04 Orphan Status: - Licensure: FDA/EMA Target: Prostate		An androgen receptor inhibitor indicated for the treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel.		

Agency		NICE	HAS	PBAC
Appraisal date		Jul-14	Nov-13	Jul-14
Comparator		placebo	placebo	abiraterone
Modelled/indirect comparison		No	No	Yes
Basis for classification		**OS**: 4.5-month increase in median OS compared to placebo; no statistically significant difference compared to abiraterone (based on indirect comparison) **QoL**: There was a statistically significant difference in QoL for patients receiving enzalutamide compared with placebo, as measured using Functional Assessment of Cancer Therapy-Prostate (FACT-P) **Safety**: NICE noted that ADRs were generally manageable and reversible. However, the Committee was aware of the increased risk of seizures with enzalutamide treatment, and noted that the summary of product characteristics advises caution when treating people with a history of seizures or other predisposing factors for seizures	**OS**: 4.8-month increase in median OS compared to placebo; Committee noted that there was no comparison to active comparators **QoL**: The fragmented QoL data cannot quantify the impact of enzalutamide on the QoL of the patients treated **Safety**: Although the Committee refers to differences in the safety profile of enzalutamide versus placebo, the Committee judges neither the strength nor direction of difference	**OS**: An increase compared to abiraterone was not established given limitations associated with the indirect comparison, though Committee accepted claim of non-inferiority **QoL**: The comments describe a range of benefits from treatment with enzalutamide, including improvement in survival and QoL **Safety**: PBAC considered that the claim of non-inferior comparative safety was reasonable
Effects	Merged data			
OS increase	4.5-4.8 months	≥ 3 months	≥ 3 months	None established
QoL change	+	+	NA	+
Safety change	+/-	+/-	NA	No difference
eribulin		FDA primary indication		
ATC code: L01XX41 Orphan Status: – Licensure: FDA/EMU		A microtubule inhibitor indicated for the treatment of patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting.		

Target: Breast				
Agency		NICE	HAS	PBAC
Appraisal date		Nov-13	Jul-11	Nov-13
Comparator		TPC	TPC	TPC
Modelled/indirect comparison		No	No	No
Basis for classification		**OS**: 2.7-month increase in median OS compared with TPC in the overall ITT population. The Committee considered that it had not seen sufficient evidence to indicate that eribulin offers an extension to life of at least 3 months **QoL**: The Committee noted that no HRQoL data were collected during the EMBRACE trial and that data were presented from two phase II trials in which there was no comparator arm **Safety**: It was also aware of the importance of the side effects of hair loss, grade 3 and 4 peripheral neuropathy and febrile neutropenia, all of which occurred more frequently with eribulin than with TPC. The Committee concluded that eribulin was associated with a greater overall survival benefit compared with TPC but with a less favourable toxicity profile	**OS**: 2.5-month increase in median OS (primary endpoint) in the eribulin mesylate group versus TPC group **QoL**: The impact of the treatment on the QoL is not documented; no QoL data available **Safety**: The incidence of grade 3-4 adverse events was higher in the eribulin mesylate group than those treated with TPC	**OS**: 2.5-month increase in median OS (primary endpoint) in the eribulin mesylate group versus TPC group **QoL**: The impact of the treatment on the QoL is not documented; no QoL data available **Safety**: The incidence of grade 3-4 adverse events was higher in the eribulin mesylate group than those treated with TPC
Effects	Merged data			
OS increase	2.5–2.7 months	< 3 months	< 3 months	< 3 months
QoL change	None established	NA	NA	NA
Safety change	-	-	-	-
erlotinib		FDA primary indication		
ATC code: L01XE03		Indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen.		
Orphan Status: –				

Licensure: FDA/EMA				
Target: Lung				
Agency		NICE	HAS	PBAC
Appraisal date		Nov-08	Mar-06	Nov-07
Comparator		No treatment	placebo	BSC
Modelled/indirect comparison		No	No	No
Basis for classification		**OS**: 2.0-month increase in median OS compared to no treatment. Difference in benefit with docetaxel is uncertain in the absence of direct comparisons **QoL**: Committee noted that patients may prefer erlotinib treatment to docetaxel because it is orally administered and they would therefore need to spend less time in hospital receiving treatment **Safety**: Clinical specialists and patient experts emphasised erlotinib's favourable toxicity profile, with fewer serious AEs reported during treatment with erlotinib than with docetaxel	**OS**: 2.0-month increase in median OS (primary endpoint) compared to placebo. No survival benefit in patients treated whose tumor EGFR expression was negative **QoL**: Time to deterioration of the three symptoms (cough, dyspnoea and pain) was significantly increased in patients treated with erlotinib: cough 2.9 months, dyspnoea 2 months and pain approximately 1 month **Safety**: The most commonly reported undesirable effects in the comparative study were diarrhoea and a skin rash. The dose was reduced because of undesirable effects in 19% of patients in the erlotinib group compared with 2% in the placebo group. Treatment was withdrawn from 5% of patients in the erlotinib group. Although AE rates and incidence is given, overall assessment of drug-related change in safety is not given by HAS	**OS**: Statistically significant differences versus BSC regarding all event rates, including overall survival. Statistically significant differences versus BSC regarding all event rates, including overall survival. Although exact gain in OS is not given, the label refers to various, placebo-controlled trials in the NEJM (referred to as BSC in a PBAC label published in 2006) which indicate that gain in OS associated with treatment is 2.0 months. **QoL**: NA **Safety**: Study BR.21 showed that erlotinib was associated with significantly more rash and diarrhoea compared to placebo, although they were mild to moderate intensity. There was no relevant haematological toxicity reported. For PBAC's comments on these results, see Recommendation and Reasons
Effects	Merged data			
OS increase	2.0 months	< 3 months	< 3 months	< 3 months
QoL change	+	+	+	NA
Safety change	+/-	+	NA	-
everolimus		FDA primary indication		

ATC code: L01XE10		A kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.		
Orphan Status: EU (w)				
Licensure: FDA/EMA				
Target: Renal				
Agency		NICE	HAS	PBAC
Appraisal date		Apr-11	Jan-10	Nov-09
Comparator		BSC	placebo	BSC
Modelled/indirect comparison		Yes	No	No
Basis for classification		**OS**: More than 3-month increase compared to BSC (exact magnitude of was uncertain given that it was "based on modelled data as opposed to data directly observed in the trial"); Committee considered a modelled 5.2-month increase compared to BSC "more plausible" than the 8.2-month increase derived by the manufacturer **QoL**: Time to deterioration in functioning/symptoms was delayed with everolimus + BSC by 3.5 months compared with placebo + BSC. The median time to deterioration according to FKSI–DRS score was 7.4 months for everolimus + BSC and 3.9 months for placebo + BSC. Difference was statistically significant **Safety**: The Committee noted the increased frequency of AEs (including serious) associated with everolimus treatment. There was a greater incidence of AEs (including serious) reported in the everolimus + BSC arm (40.1%) than the placebo + BSC arm (22.6%)	**OS**: An increase compared to placebo (optimum symptomatic treatments) not established as no improvement was observed; Committee acknowledged that an assessment was difficult "given the premature termination of the pivotal study and the fact that patients whose disease had demonstrably progressed were allowed to transfer" **QoL**: No improvement was demonstrated in the pivotal study (QLQ-C30) **Safety**: More patients in the everolimus group stopped treatment as a result of adverse effects than in the placebo group	**OS**: No statistically significant difference was observed compared to BSC **QoL**: PBAC considered that the results for Karnofsky performance status, physical function, and QoL scores showed no statistically significant differences and performance status between everolimus and placebo treated patients. However, these results are difficult to interpret because of the substantial crossover of placebo patients to everolimus treatment **Safety**: Everolimus has significant on-treatment toxicity compared to placebo, including increased risk of serious infection, non-infectious pneumonitis, dyspnea, stomatitis, hyperglycaemia, anaemia, lymphopenia as well as neurotoxicity
Effects	Merged data			
OS increase	5.2 months	≥ 3 months	None established	None established

QoL change	+	+	No difference	No difference
Safety change	-	-	-	-
gefitinib		FDA primary indication		
ATC code: L01XE02 Orphan Status: – Licensure: FDA/EMA Target: Lung		Indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR-TK.		
Agency		NICE	HAS	PBAC
Appraisal date		Jul-2010	Nov-2009	Jul-2013
Comparator		paclitaxel + carboplatin	paclitaxel + carboplatin	paclitaxel + carboplatin
Modelled/indirect comparison		No	No	No
Basis for classification		**OS:** Committee was aware that the analysis of OS was an interim analysis of immature data. The Committee noted that a longer progression-free survival may correlate with improved overall survival in NSCLC, but there was uncertainty around this **QoL:** Committee agreed that treatment … offers an advantage because it can be taken at home. Committee accepted the ERG's view that EGFR-TK mutation-positive patients who were randomised to receive gefitinib had a clinically relevant improvement in health-related quality of life and disease symptoms compared with patients randomised to receive paclitaxel and carboplatin **Safety:** The Committee concluded that gefitinib was associated with an improved adverse effects profile compared with platinum-based chemotherapy. Clinical specialists confirms that	**OS:** Median overall survival did not differ between the two groups (18.6 months in the IRESSA group and 17.3 months in the comparator group). The overall survival results are not mature (number of events not reached) **QoL:** quality of life analysis results showed an improvement in the IRESSA group in two of the three scales used (FACT-L and TOI) **Safety:** No comparative data presented	**OS:** The data were updated for trials NEJ002 and WJTOG3405, but were still immature for the WJTOG3405 trial. As seen in the IPASS (paclitaxel + carboplatin) and First-SIGNAL (cisplatin + gemcitabine) trials, there was no significant difference between the two treatment arms in terms of OS (NEJ002 HR=0.89; 95% CI: 0.63, 1.24; WJTOG3405: HR=1.19; 95% CI: 0.77, 1.83) **QoL: T**he PBAC accepted that the clinical benefit of listing gefitinib in patients with EGFR M+ NSCLC as first-line treatment in addition to the current listing for second-line treatment is an improvement in quality of life **Safety:** Overall, safety profiles varied across the treatment arms, but gefitinib appeared to have less serious toxicity than platinum-based therapy … the PBAC accepted that gefitinib appears to have less serious toxicity than platinum-based doublet chemotherapy

		gefitinib had been shown to be well tolerated in clinical practice		
Effects	Merged data			
OS increase	None established	None established	None established	None established
QoL change	+	+	+	+
Safety change	+	+	NA	+
ibrutinib		FDA primary indication		
ATC code: L01XE27		A kinase inhibitor indicated for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. This indication is based on overall response rate.		
Orphan Status: US/EU				
Licensure: FDA/EMA				
Target: Hematological				
Agency		NICE	HAS	PBAC
Appraisal date		NA	NA	NA
Comparator		NA	NA	NA
Modelled/indirect comparison		NA	NA	NA
Basis for classification		NA	NA	NA
Effects	Merged data			
OS increase		NA	NA	NA
QoL change		NA	NA	NA
Safety change		NA	NA	NA
ipilimumab		FDA primary indication		
ATC code: L01XC11		A human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody indicated for the treatment of unresectable or metastatic melanoma.		
Orphan Status: –				

Licensure: FDA/EMA				
Target: Skin				
Agency		NICE	HAS	PBAC
Appraisal date		Jul-14	Nov-14	Nov-12
Comparator		dacarbazine	dacarbazine / temozolomide / vemurafenib	Dacarbazine
Modelled/indirect comparison		No	Yes	Yes
Basis for classification		**OS**: 5.7-month increase in mean OS compared to dacarbazine when given as first-line (2.1-month increase in median OS); mean OS was available because of the long duration of the trial and lack of crossover **QoL**: First- and second-line, no HRQoL data reported **Safety**: Severe, serious, drug-related and AEs leading to discontinuation were all more frequent in the ipilimumab 10 mg/kg + dacarbazine group than in dacarbazine alone group. In second-line treatment, the Committee concluded that the ADRs and mortality associated with ipilimumab seen in the MDX010-20 trial were considerable	**OS**: Committee noted that the results of an indirect comparison with several comparators (dacarbazine, temozolomide, and vemurafenib) suggested that OS improved with ipilimumab, but did not allow for a formal conclusion **QoL**: A negative impact on quality of life cannot be ruled out mainly because of significant side effects experienced. No explicit judgment on comparative differences in HRQoL given **Safety**: The safety data provided in this new indication are comparable to the safety profile seen to date for this specialty	**OS**: Committee considered that the "magnitude of the incremental benefit of ipilimumab remained uncertain" compared to dacarbazine as the submission was "reliant on extrapolation of trial results to a ten-year time horizon" **QoL**: NA **Safety**: Ipilimumab has a different safety profile than BSC (DTIC/fotemustine), with irAEs (immune-related adverse events) which are manageable and controllable. Even though the PBAC considers this claim reasonable, it does not indicate whether it believes differences to be clinically meaningful and does not give a value judgment
Effects	Merged data			
OS increase	5.7 months	≥ 3 months	Uncertain	Uncertain
QoL change	None established	NA	NA	NA
Safety change	-	-	No difference	NA
ixabepilone		FDA primary indication		
ATC code: L01DC04		A microtubule inhibitor, in combination with capecitabine is indicated for treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline and a taxane.		
Orphan Status: –				

Licensure: FDA Target: Breast		Also indicated as monotherapy for treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline, a taxane, and capecitabine.		
Agency		NICE	HAS	PBAC
Appraisal date		NA	NA	NA
Comparator		NA	NA	NA
Modelled/indirect comparison		NA	NA	NA
Basis for classification		NA	NA	NA
Effects	Merged data			
OS increase	NA	NA	NA	NA
QoL change	NA	NA	NA	NA
Safety change	NA	NA	NA	NA
lapatinib		FDA primary indication		
ATC code: L01XE07 Orphan Status: – Licensure: FDA/EMA Target: Breast		A kinase inhibitor, indicated in combination with capecitabine, for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.		
Agency		NICE	HAS	PBAC
Appraisal date		May-10	Jul-08	Nov-07
Comparator		capecitabine monotherapy	capecitabine monotherapy	capecitabine monotherapy
Modelled/indirect comparison		No	No	No
Basis for classification		**OS**: 2.4-month increase in overall median survival; certainly not enough evidence that the extension of life provided was 3 months or greater	**OS**: At the cut-off point for the first interim analysis, no difference was observed between the two treatment arms. In view of the premature termination of the study, the benefit of lapatinib + capecitabine compared with	**OS**: 1.1-week increase in median overall survival. However, study was terminated early by independent monitoring board, and patient crossover. Early termination reduces the likelihood of detecting a significant difference in overall survival. There is some evidence improves survival

		QoL: No HRQoL information presented in report **Safety**: The lapatinib + capecitabine group had a marginally higher incidence of diarrhoea and palmar-plantar erythrodysaesthesia than the capecitabine monotherapy group	capecitabine alone in terms of overall survival cannot be evaluated **QoL**: The available data are insufficient to estimate the impact of lapatinib + capecitabine in reducing the morbidity and mortality associated with metastatic breast cancer and in improving QoL, compared with the current form of management **Safety**: Main AEs were often raised in the lapatinib + capecitabine arm compared with the capecitabine arm, including for: diarrhoea, palmar-plantar erythrodysaesthesia, nausea, rash, and vomiting. However, the HAS does not make a judgment as to the statistical or clinical significance of these findings	compared to capecitabine alone, but full extent of survival benefit is not known and is not statistically different from comparator treatment alone **QoL**: NA **Safety**: The overall safety profile of lapatinib + capecitabine, in terms of the incidence, types and intensities of adverse events, appears similar to that reported in the published studies for different trastuzumab-containing chemotherapies for patients with metastatic breast cancer
Effects	Merged data			
OS increase	0.3–2.4 months	< 3 months	None established	Uncertain
QoL change	None established	NA	NA	NA
Safety change	-	-	NA	No difference
lenalidomide		FDA primary indication		
ATC code: L04AX04 Orphan Status: US/EU Licensure: FDA/EMA Target: Hematological		Indicated for the treatment of patients with transfusion-dependent anemia due to Low- or Intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.		
Agency		NICE	HAS	PBAC
Appraisal date		Sep-14	Nov-14	Mar-13
Comparator		placebo	placebo	placebo (BSC)
Modelled/indirect comparison		No	No	No

Basis for classification		**OS**: No statistically significant difference. Placebo arm could cross over to lenalidomide treatment, therefore benefit of lenalidomide may be underestimated. Lenalidomide could indirectly improve OS by improving transfusion independence, but this was uncertain **QoL**: Committee considered the results of the MDS-004 study: the rates of transfusion independence (at 26 weeks, lenalidomide 10 mg: 56.1%, placebo: 5.9%) and improvements in the FACT-An questionnaire (mean change, lenalidomide 10 mg: 5.8, placebo: -2.5) were significantly better in people treated with lenalidomide compared with placebo **Safety**: Committee was aware that lenalidomide may be associated with higher rates of venous thrombo-embolism than placebo. A higher proportion of people in the lenalidomide 10 mg (95.7%) and 5 mg groups (98.6%) had at least 1 drug-related AE compared with the placebo group (49.3%). However, it heard from the clinical specialist and patient experts that AEs associated with lenalidomide treatment are managed with dose interruptions and are generally well tolerated. The Committee concluded that, although lenalidomide is associated with some AEs, these can be managed by dose interruptions	**OS**: Available clinical data shows better cytogenic response but without benefit in OS **QoL**: Given current therapeutic strategies, the available clinical data indicates a moderate impact in terms of morbidity and mortality and quality of life should be expected from lenalidomide. The "transferability of test results to the practice can be regarded as assured" **Safety**: The safety profile observed in the lenalidomide MDS patients of low risk associated with a deletion 5q was comparable to that already experienced in patients with myeloma. Regarding the first 16 weeks of the double-blind phase, at least one adverse event was observed in all patients of lenalidomide group (69 patients in the 5 mg group and 69 patients in the 10 mg group) and in 96% of 67 patients in the placebo group	**OS**: While results did not show statistically significant change in OS, possibly owing to patient cross-over, the PBAC considered that there was a trend favoring lenalidomide **QoL**: For key results, see Mar 2011 PSD. PBAC noted clinical meaningful change in patients HRQoL after 24 weeks of treatment with lenalidomide and a worsening in placebo patients. However, the results were confounded due to loss to follow up **Safety**: PBAC considered that treatment with lenalidomide was associated with more toxicity than best supportive care and that dose reduction would be required to manage side effects in a number of patients
Effects	Merged data			
OS increase	Exact magnitude uncertain	Uncertain	None established	Uncertain
QoL change	+	+	+	NA
Safety change	-	-	No difference	-
nelarabine		FDA primary indication		

ATC code: L01BB07 Orphan Status: US?EU Licensure: FDA/EMA Target: Hematological		Indicated for the treatment of patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens. This use is based on the induction of complete responses. Randomized trials demonstrating increased survival or other clinical benefit have not been conducted.		
Agency		NICE	HAS	PBAC
Appraisal date		NA	Dec-07	NA
Comparator		NA	non-comparative	NA
Modelled/indirect comparison		NA	Yes	NA
Basis for classification		NA	**OS**: Facilitates the use of allografts, therefore expected to have an impact on morbidity and mortality, which can only be low. Because of the uncertainty about the tolerability of this drug, extrapolation of the trial results to real life is uncertain **QoL**: NA **Safety**: There are "currently few safety data". Safety-related data drawn from non-comparative adult and child studies	NA
Effects	Merged data			
OS increase	None established	NA	NA	NA
QoL change	None established	NA	None established	NA
Safety change	None established	NA	NA	NA
nilotinib		FDA primary indication		
ATC code: L01XE08 Orphan Status: US/EU Licensure: FDA/EMA		A kinase inhibitor indicated for the treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia (CML) in adult patients resistant to or intolerant to prior therapy that included imatinib.		

Target: Hematological				
Agency		NICE	HAS	PBAC
Appraisal date		Jan-12	Feb-08	Mar-08
Comparator		non-comparative	non-comparative	non-comparative
Modelled/indirect comparison		Yes	No	Yes
Basis for classification		**OS**: Clinical trials were non-comparative, of short duration and had used surrogate outcomes to predict OS. The Committee noted the poor quality of the evidence base **QoL**: No regulatory judgment made on comparative differences in HRQoL **Safety**: Committee concluded that dasatinib and nilotinib are better tolerated than imatinib, and that older treatments, particularly interferon alfa, can be poorly tolerated	**OS**: No comparative evaluation of OS relative to available treatments **QoL**: No comparative data presented Safety: There are currently few safety data. No comparative data presented	**OS**: Committee does not present any conclusion regarding OS benefits. Evidence for nilotinib after imatinib and dasatinib treatment is from single arm open-label nilotinib study for CML-CP and CML-AP **QoL**: NA **Safety**: PBAC noted that whilst nilotinib has a different safety profile to both high dose imatinib and dasatinib, there is considerable uncertainty around the claims that nilotinib has significant activity after failure of both imatinib and dasatinib and that nilotinib has a superior safety profile to dasatinib
Effects	Merged data			
OS increase	None established	None established	None established	None established
QoL change	None established	NA	NA	NA
Safety change	+	+	NA	NA
obinutuzumab		FDA primary indication		
ATC code: L01XC15		A CD20-directed cytolytic antibody and is indicated, in combination with chlorambucil, for the treatment of patients with previously untreated chronic lymphocytic leukemia.		
Orphan Status: US/EU				
Licensure: FDA/EMA				
Target: Hematological				

Agency		NICE	HAS	PBAC
Appraisal date		Mar-15	Feb-15	Jul-14
Comparator		chlorambucil	rituximab / chlorambucil	chlorambucil
Modelled/indirect comparison		No	No	No
Basis for classification		**OS**: Obinutuzumab + chlorambucil was associated with statistically significantly greater OS compared with chlorambucil monotherapy. However, the Committee acknowledged that the OS data were immature **QoL**: The clinical expert and patient expert acknowledged that some people may prefer oral treatment with chlorambucil instead of having to attend a day unit for intravenous treatment with obinutuzumab or bendamustine **Safety**: Some people may prefer to have obinutuzumab instead of bendamustine, because obinutuzumab is associated with fewer AEs. The Committee took into consideration the summary of product characteristics and concluded that obinutuzumab had an acceptable adverse event profile	**OS**: Impact compared to the comparator (R-Clb) is not quantifiable **QoL**: The impact compared to the comparator (R-Clb) is not quantifiable **Safety**: Compared to rituximab, the incidence of AEs ≥ grade 3 was higher in the G-Clb group than in the R-Clb group	**OS**: PBAC accepted the claim that obinutuzumab + chlorambucil is superior in terms of comparative effectiveness and inferior in terms of comparative safety over chlorambucil alone. While hazard ratio for OS was not statistically significant, the trend was in favor of obinutuzumab + chlorambucil and the more recent data is approaching statistical significance **QoL**: Consumer comments captured the notion that obinutuzumab provides a treatment option for older, less fit patients with CLL and prolongs remission during which time patients can live a "normal life" **Safety**: PBAC accepted the submission's claim that obinutuzumab + chlorambucil is inferior in terms of comparative safety over chlorambucil alone
Effects	Merged data			
OS increase	Exact magnitude uncertain	Uncertain	None established	Uncertain
QoL change	+/–	-	NA	+
Safety change	+/–	+	-	-
ofatumumab		FDA primary indication		
ATC code: L01XC10		A CD20-directed cytolytic monoclonal antibody indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab. The effectiveness of ofatumumab is based on the demonstration of durable objective responses.		
Orphan Status: US/EU				

Licensure: FDA/EMA				
Target: Hematological				
Agency		NICE	HAS	PBAC
Appraisal date		Oct-10	Oct-10	Nov-14
Comparator		non-comparative	non-comparative	chlorambucil
Modelled/indirect comparison		Yes	Yes	No
Basis for classification		**OS**: No data on median OS available for patients responding to treatment because data were immature. Although it was likely that ofatumumab is effective based on the observed ORRs, and partly based on manufacturer's model regarding extensions to life (">5 months relative to BSC"), it was not possible to estimate the size of the effect with certainty because of the absence of robust and comparative evidence and the immaturity of the data **QoL**: No HRQoL information presented in report. HRQoL had not been collected in the pivotal study **Safety**: The Committee concluded that ofatumumab may be associated with AEs, but the extent and impact of these was uncertain owing to a lack of robust evidence and the lack of a group of patients who did not receive ofatumumab in the trial	**OS**: The quality of the data available is not sufficient to allow an evaluation of the impact in terms of mortality of the medicinal product. Comparison of ofatumumab with historical data does not allows unbiased evaluation to be made of the size of effect, therefore it is not considered by the Committee **QoL**: NA Safety: The efficacy and tolerance data are limited, as they are drawn from a non-comparative phase II study	**OS**: No difference was observed in direct comparison with chlorambucil, which may be due to the limited follow-up of the trial for patients with indolent CLL. Overall, incomplete and less than rigorous comparison of ofatumumab with rituximab (modelled evaluation) **QoL**: NA Safety: PBAC noted no important overall differences in adverse events
Effects	Merged data			
OS increase	None established	None established	None established	None established
QoL change	None established	NA	NA	NA
Safety change	None established	NA	NA	No difference

omacetaxine mepesuccinate		FDA primary indication		
ATC code: L01XX40		Adult patients (injection) with chronic or accelerated phase chronic myeloid leukemia (CML) with resistance and/or intolerance to two or more tyrosine kinase inhibitors (TKI). This indication is based upon response rate.		
Orphan Status: US				
Licensure: FDA/EMA				
Target: Hematological				
Agency		NICE	HAS	PBAC
Appraisal date		NA	NA	NA
Comparator		NA	NA	NA
Modelled/indirect comparison		NA	NA	NA
Basis for classification		NA	NA	NA
Effects	Merged data			
OS increase		NA	NA	NA
QoL change		NA	NA	NA
Safety change		NA	NA	NA
panitumumab		FDA primary indication		
ATC code: L01XC08		Indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.		
Orphan Status: -				
Licensure: FDA/EMA				
Target: GI				
Agency		NICE	HAS	PBAC
Appraisal date		Jan-12	Apr-08	Nov-13
Comparator		BSC	palliative care	cetuximab
Modelled/indirect comparison		Yes	No	No

Basis for classification		**OS**: Approximately 3-month extension to life compared to BSC (mean life extension estimated to be 2.7 to 3.2 months after adjusting for patient crossover in the trial); no statistically significant difference in overall survival was observed in the trial **QoL**: No HRQoL data presented in report **Safety**: Committee did not discuss specific issues around the AEs to the technologies appraised but it was aware of the special warnings and precautions for use outlined in the SPCs	**OS**: An increase compared palliative care not established as no statistically significant difference was observed **QoL**: In light of the available data (just one post hoc analysis on subgroups of the pivotal study), the impact of panitumumab on morbidity, mortality and quality of life cannot be quantified **Safety**: Safety data are currently limited. There is no judgment of comparative differences in toxicity	**OS**: No statistically significant difference was observed compared to cetuximab (third-line) **QoL**: NA **Safety**: The PBAC considered the claim that panitumumab is non-inferior in terms of safety to cetuximab to be reasonable in the third-line setting where both drugs were used as monotherapy
Effects	Merged data			
OS increase	2.7–3.2 months	≥ 3 months	None established	None established
QoL change	None established	NA	NA	NA
Safety change	None established	NA	NA	No difference
pazopanib		FDA primary indication		
ATC code: L01XE11 Orphan Status: EU (w) Licensure: FDA/EMA Target: Renal		A kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma.		
Agency		NICE	HAS	PBAC
Appraisal date		Feb-11	Jun-13	Mar-12
Comparator		BSC/interferon-alfa	placebo/sunitinib	BSC/sunitinib
Modelled/indirect comparison		Yes	No	Yes
Basis for classification		**OS**: More than 3-month increase compared to BSC (based on RPSFT model) and interferon-	**OS**: An increase compared to sunitinib not established (first-line) as no statistically	**OS**: No statistically significant difference was observed compared to BSC (even after adjusting for

		alfa (based on indirect comparison), though exact magnitude of increase uncertain; no significant difference compared to sunitinib based on results from head-to-head trial the Committee noted would be available in 2012 **QoL**: For the VEG105192 trial, there were no statistically significant differences between pazopanib and placebo for any of the instruments used (European Organisation for Research and Treatment of Cancer [EORTC] QoL questionnaire – Core 30, EQ-5D, EQ-5D-VAS) **Safety**: Committee heard from the clinical specialists that the evidence presented by the manufacturer suggested that pazopanib has a more favourable toxicity profile than sunitinib, especially in relation to hand-foot syndrome. The clinical specialists and patient experts were of the opinion that pazopanib is a useful option because it has a more favourable toxicity profile than sunitinib	significant difference was observed; Committee noted that non-inferiority compared to sunitinib was "the subject of serious doubt"; increase compared to placebo not established as no statistically significant difference was observed **QoL**: No reliable conclusions could be drawn from evaluation scores as to any difference between the two treatments. In fact, results varied depending on the scale used: there was no difference on one scale (FACIT-F), although there were differences on the FKSI-19 and CTSQ scales but with values below the threshold for clinical relevance **Safety**: For 1st RCC, the safety profile differed between the two groups, with notably a higher incidence of abnormal liver function tests in the pazopanib group and a higher incidence of hand-foot syndrome in the sunitinib group. For 2nd RCC, treatment discontinuation due to AEs was twice as common in the pazopanib group as in the placebo group	patient crossover with IPCW and RPSFT models); no statistically significant difference was observed compared to sunitinib (based on indirect comparison) **QoL**: NA **Safety**: PBAC concluded that pazopanib has a different side-effect profile to sunitinib. Patients taking sunitinib tend to experience events such as diarrhoea, fatigue, hypertension, mucositis, hand-foot syndrome, and myelosuppression; patients taking pazopanib tend to experience diarrhoea, hypertension and liver dysfunction. These differences are insufficient to change an overall conclusion that pazopanib is non-inferior to sunitinib in terms of safety.
Effects	Merged data			
OS increase	Exact gain over 3 months uncertain	≥ 3 months (Exact gain over 3 months uncertain)	None established	None established
QoL change	None established	No difference	No difference	NA
Safety change	+/–	+	+/– (1st RCC); – (2nd RCC) = +/–	No difference
pemetrexed		FDA primary indication		
ATC code: L01BA04 Orphan Status: US/EU (w) Licensure: FDA/EMA		In combination with cisplatin for the treatment of patients with malignant pleural mesothelioma whose disease is either unresectable or who are otherwise not candidates for curative surgery.		

Target: Lung				
Agency		NICE	HAS	PBAC
Appraisal date		Jan-08	Mar-05	Nov-07
Comparator		cisplatin	cisplatin	cisplatin
Modelled/indirect comparison		No	No	No
Basis for classification		**OS**: 2.8-month increase in median OS compared to cisplatin **QoL**: Committee noted that there was some evidence showing that pemetrexed plus cisplatin was associated with significant symptomatic improvements compared with cisplatin alone. Committee agreed that the economic analyses may have underestimated the overall quality of life benefits of pemetrexed in people with MPM. Combination treatment appears to demonstrate advantages in QoL **Safety**: Severe to life-threatening or disabling adverse events were statistically significantly more frequent in patients receiving pemetrexed plus cisplatin than in those receiving cisplatin alone	**OS**: 3.3-month increase in median OS compared to cisplatin in subgroup of patients fully supplemented with vitamins; 2.8-month increase in median OS compared to cisplatin in the intention-to-treat population **QoL**: It was also observed a reduction of certain clinical symptoms (dyspnea, pain) related to the disease and improving lung function **Safety**: No comparative data presented	**OS**: 2.8-month increase in median OS **QoL**: data from the pivotal trial using the Patient Lung Cancer Symptom Scale (LCSS) were presented. There were significant improvements in fatigue, dyspnea, pain, symptom distress, activity level, and overall LCSS, except for hemoptysis, in the pemetrexed+ cisplatin treatment arm. Although the global QoL scale did not show significant changes, the total LCSS as an average of all nine items reached a statistically significant difference in favor of pemetrexed **Safety**: Serious AEs occurred more frequently in the PMT+cisplatin arm than the cisplatin alone arm. Overall, frequency of Grade 3/4 laboratory toxicity was higher in the PMT+cisplatin arm than in the cisplatin alone arm. Severe toxicity was uncommon in the cisplatin arm, compared to the PMT+cisplatin arm where Grade ¾ neutropenia were the most common haematologic toxicities
Effects	Merged data			
OS increase	2.8–3.3 months	< 3 months	≥ 3 months	< 3 months
QoL change	+	+	+	+
Safety change	-	-	NA	-
pertuzumab		FDA primary indication		
ATC code: L01XC13				

Orphan Status: – Licensure: FDA/EMA Target: Breast		A HER2/neu receptor antagonist indicated in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.		
Agency		NICE	HAS	PBAC
Appraisal date		NA	Jul-13	Mar-14
Comparator		NA	trastuzumab + docetaxel	trastuzumab + docetaxel
Modelled/indirect comparison		NA	No	No
Basis for classification		NA	**OS**: An increase compared to trastuzumab + docetaxel was observed (by a second interim analysis not scheduled in the protocol), but the size of the increase was uncertain given that median OS had not yet been achieved **QoL**: The treatment is not expected to have any impact on patients' quality of life evaluated using the FACT-B questionnaire specific to the disease **Safety**: In addition to similar drop-out rates from AEs, no difference was seen between the two groups (pertuzumab vs placebo) as regards the incidence of grade 3-4 events	**OS**: 15.7-month increase in median OS compared to trastuzumab + docetaxel **QoL**: PBAC noted strong support for pertuzumab received through the consumer comments facility expressing a range of benefits from treatment including improving QoL **Safety**: PBAC considered the claim that pertuzumab, when used in combination with trastuzumab + docetaxel, to be "slightly worse" in terms of comparative safety. PBAC considered the trial results indicated that adding pertuzumab to trastuzumab + docetaxel results in statistically significant increased toxicity in trastuzumab naïve (sensitive) compared to trastuzumab + docetaxel
Effects	Merged data			
OS increase	15.7 months	NA	Uncertain	≥ 3 months
QoL change	+	NA	No difference	+
Safety change	-	NA	No difference	-
pomalidomide		FDA primary indication		
ATC code: L04AX06 Orphan Status: US/EU		A thalidomide analogue indicated for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate.		

Licensure: FDA/EMA				
Target: Hematological				
Agency		NICE	HAS	PBAC
Appraisal date		Mar-15	Jan-14	Jul-14
Comparator		standard care	high-dose dexamethasone	high-dose dexamethasone
Modelled/indirect comparison		Yes	No	No
Basis for classification		**OS**: At least 3-month extension compared to standard NHS care (e.g. bendamustine) (based on modeled data); Committee was "not able to judge with any confidence how much more effective pomalidomide was compared with the current treatment options based on the available evidence"; nevertheless, the Committee was "persuaded that pomalidomide extends life for at least 3 months on average when compared with standard NHS care" based on data modeled data that was "not considered robust" **QoL**: HRQoL was measured using the EORTC questionnaire for patients with cancer (QLQ-C30), the EORTC multiple myeloma module (QLQ-MY20) and the EuroQol-5 dimensions survey (EQ-5D). Most results presented by the company suggest favourable trends with pomalidomide compared with dexamethasone **Safety**: The Committee noted that the proportion of patients with adverse reactions were similar between those taking pomalidomide and high-dose dexamethasone	**OS**: An increase compared palliative care not established; median OS was not reached in pomalidomide treatment arm; Committee noted that 29% of patients in the high-dose dexamethasone group had received pomalidomide because of disease progression **QoL**: In light of the available clinical trial data, no impact in terms of morbidity and mortality and QoL is expected for the proprietary medicinal product pomalidomide in combination with dexamethasone **Safety**: The most commonly observed serious AEs had a comparable incidence in the two groups, in particular pneumonia and deterioration in general health	**OS**: Committee considered that OS increased compared to high-dose dexamethasone, but the magnitude of the increase was redacted **QoL**: The PBAC also noted that the EQ-5D showed a trend towards improved QoL with pomalidomide + LDD compared with HDD, noting however that the differences in the EQ-5D utility index score between treatment arms were generally not statistically significant **Safety**: The PBAC considered that pomalidomide has inferior, but manageable, safety compared with HDD
Effects	Merged data			
OS increase	≥ 3 months (exact gain uncertain)	≥ 3 months (exact gain uncertain)	None established	Uncertain
QoL change	+	+	No difference	+

Safety change	-	No difference	-	-
ponatinib		FDA primary indication		
ATC code: L01XE24 Orphan Status: EU Licensure: FDA/EMA Target: Hematological		A kinase inhibitor indicated for the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) that is resistant or intolerant to prior tyrosine kinase inhibitor therapy or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL) that is resistant or intolerant to prior tyrosine kinase inhibitor therapy. This indication is based upon response rate.		
Agency		NICE	HAS	PBAC
Appraisal date		NA	Jan-15	Nov-14
Comparator		NA	non-comparative	dasatinib / nilotinib
Modelled/indirect comparison		NA	Yes	Yes
Basis for classification		NA	**OS**: No expected impact in terms of morbidity and mortality compared with current therapeutic management **QoL**: There is no expected impact in terms of morbidity and mortality and QoL for the specialty ponatinib compared with current management **Safety**: No comparative data available	**OS**: There is no direct evidence available for the comparative efficacy of ponatinib vs dasatinib or nilotinib. Based on single-arm comparative evidence, it is not clear whether ponatinib is better or worse than dasatinib or nilotinib in the treatment of chronic phase CML **QoL**: NA **Safety**: The PBAC considered that ponatinib had an inferior toxicity profile to imatinib, dasatinib, and nilotinib, especially with regard to serious vascular occlusive event
Effects	Merged data			
OS increase	None established	NA	None established	None established
QoL change	None established	NA	No difference	NA
Safety change	-	NA	NA	-
pralatrexate		FDA primary indication		

ATC code: L01BA05 Orphan Status: EU Licensure: FDA/EMU Target: Hematological		A folate analogue metabolic inhibitor indicated for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). This indication is based on overall response rate.		
Agency		NICE	HAS	PBAC
Appraisal date		NA	NA	NA
Comparator		NA	NA	NA
Modelled/indirect comparison		NA	NA	NA
Basis for classification		NA	NA	NA
Effects	Merged data			
OS increase	NA	NA	NA	NA
QoL change	NA	NA	NA	NA
Safety change	NA	NA	NA	NA
radium Ra 223 dichloride		FDA primary indication		
ATC code: V10XX03 Orphan Status: – Licensure: FDA/EMA Target: Prostate		An alpha particle-emitting radioactive therapeutic agent indicated for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease.		
Agency		NICE	HAS	PBAC
Appraisal date		NA	Apr-14	NA
Comparator		NA	Placebo	NA
Modelled/indirect comparison		NA	No	NA
Basis for classification		NA	**OS**: 2.8-month increase vs placebo demonstrated in available studies	NA

			QoL: The expected impact on preserving QoL remains difficult to assess, improved time observed to degradation of FACT-P score and the EQ-5D utility score are not considered clinically relevant and the absence of pain assessment. In the absence of comparative data versus currently used treatments, the expected impact of radium-223 dichloride in terms of improving QoL compared to those treatments currently used cannot be quantified **Safety**: Although HAS discusses several adverse events that were observed more frequently in the radium-223 dichloride group than in the placebo group, the agency does not provide an overall assessment of drug-related changes in safety	
Effects	Merged data			
OS increase	2.8 months	NA	< 3 months	NA
QoL change	None established	NA	NA	NA
Safety change	None established	NA	NA	NA
regorafenib		FDA primary indication		
ATC code: L01XE21		A kinase inhibitor indicated for the treatment of metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.		
Orphan Status: -				
Licensure: FDA/EMA				
Target: GI				
Agency		NICE	HAS	PBAC
Appraisal date		NA	May-14	Jul-14
Comparator		NA	placebo	placebo

Modelled/indirect comparison		NA	No	No
Basis for classification		NA	**OS**: 1.4-month increase in median OS in regorafenib group relative to placebo (primary analysis) **QoL**: It is not expected that this and a proprietary medicinal product will provide any additional impact in terms of morbidity and mortality or quality of life **Safety**: The overall incidence of serious adverse events considered as being treatment-related was higher in the regorafenib group	**OS**: 1.4-month increase in median OS. PBAC considered that clinical evidence from the CORRECT clinical trial was mature, there was not cross-over and subsequent therapy was relatively balanced between treatment groups. CORRECT unlikely to have underestimated the effectiveness of regorafenib compared to BSC. However OS benefit not considered to be clinically significant **QoL**: PBAC noted that no patients in the trial had a complete response and that EQ-5D data showed no improvement compared to BSC **Safety**: PBAC agreed that regorafenib was inferior in comparative safety to BSC and noted severe AEs associated with the drug, particularly hepatotoxicity and hand-foot skin reactions
Effects	Merged data			
OS increase	1.4 months	NA	< 3 months	< 3 months
QoL change	None established	NA	No difference	No difference
Safety change	-	NA	-	-
romidepsin		FDA primary indication		
ATC code: L01XX39 Orphan Status: US/EU Licensure: EMA Target: Hematological		A histone deacetylase (HDAC) inhibitor indicated for treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy.		
Agency		NICE	HAS	PBAC
Appraisal date		NA	NA	NA
Comparator		NA	NA	NA

Modelled/indirect comparison		NA	NA	NA
Basis for classification		NA	NA	NA
Effects	Merged data			
OS increase		NA	NA	NA
QoL change		NA	NA	NA
Safety change		NA	NA	NA
ruxolitinib		FDA primary indication		
ATC code: L01XE18		A kinase inhibitor indicated for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.		
Orphan Status: US / EU (w)				
Licensure: FDA/EMA				
Target: Hematological				
Agency		NICE	HAS	PBAC
Appraisal date		Jun-13	Jan-13	Jul-13
Comparator		BSC	placebo	BSC (hydroxyurea and placebo)
Modelled/indirect comparison		Yes	No	Yes
Basis for classification		**OS**: The Committee concluded that it was plausible that ruxolitinib could offer a survival benefit. However, the reason for this benefit remained unclear **QoL**: The Committee noted that in COMFORT-I significantly more patients treated had a 50% or more reduction in total symptom score than those on placebo, and that there was a significantly greater reduction in mean change from baseline total symptom score with ruxolitinib than placebo.	**OS**: The impact of the treatment on OS and leukaemic transformation cannot be evaluated at present because of the small number of events reported **QoL**: Ruxolitinib is expected to have a low impact on the morbidity of patients treated. However, the impact of treatment on quality of life is difficult to evaluate (several reasons given) **Safety**: The overall incidence of serious adverse effects was similar in the treatment groups in the two pivotal studies at around 30%.	**OS**: PBAC accepted the clinical claim of superior efficacy likely in OS, although the magnitude of the survival benefit is uncertain due to high number of cross-over and confounding factors **QoL**: PBAC accepted the claim of superior efficacy demonstrated in spleen response and QoL measures **Safety**: PBAC did not accept the claim for equivalence in comparative safety. Patients experienced significantly more drug-related AEs than patients treated with either BAT (in COMFORT-II) or placebo (in COMFORT-I). There

		Safety: The Committee concluded that ruxolitinib did have a negative impact on haematological outcomes in the short term, but agreed that these were manageable		were also significantly more cases of thrombocytopenia and anaemia in ruxolitinib treated patients compared to BAT treated patients in COMFORT-II
Effects	Merged data			
OS increase	Exact magnitude uncertain	Uncertain	None established	Uncertain
QoL change	+	+	NA	No difference
Safety change	-	-	+	-

sipuleucel-T	FDA primary indication		
ATC code: L03AX17 Orphan Status: – Licensure: FDA/EMA Target: Prostate	An autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.		
Agency	NICE	HAS	PBAC
Appraisal date	Feb-15	NA	NA
Comparator	BSC	NA	NA
Modelled/indirect comparison	No	NA	NA
Basis for classification	**OS**: 4.0-month median extension compared to BSC (based on meta-analysis of three trials) in subgroup of patients who had not previously received chemotherapy; two of the showed that sipuleucel-T extended life, including the pivotal trial with a 4.1-month increase in median OS; Committee concluded that "it would be reasonable to assume that sipuleucel-T and abiraterone had similar effectiveness in prolonging overall survival" (based on indirect comparison).	NA	NA

		QoL: Patient organisations expected sipuleucel-T to reduce pain, improve mental and physical health, and offer an additional treatment option at an early stage of disease. The Committee concluded that patients would like to have the option of having treatment with sipuleucel-T within the NHS. **Safety**: The Committee noted that the European public assessment report stated that sipuleucel-T is considered less toxic than other therapies (such as abiraterone, enzalutamide, docetaxel and cabazitaxel) that are currently used for treating metastatic hormone-resistant prostate cancer		
Effects	Merged data			
OS increase	4.0 months	≥ 3 months	+	+
QoL change	+	NA	NA	NA
Safety change	+	NA	NA	NA
sorafenib		FDA primary indication		
ATC code: **L01XE05**		Indicated for the treatment of patients with advanced renal cell carcinoma.		
Orphan Status: US/EU				
Licensure: FDA/EMU				
Target: Renal				
Agency		NICE	HAS	PBAC
Appraisal date		Aug-09	Sep-06	Mar-08
Comparator		BSC	placebo	BSC
Modelled/indirect comparison		Yes	No	No
Basis for classification		**OS**: More than 3-month increase compared to BSC was "likely" for people in whom	**OS**: An increase compared to placebo not established (second-line); median OS was not	**OS**: No statistically significant difference was observed compared to BSC, though Committee

		immunotherapy has failed (second-line), though exact magnitude was uncertain; trial was "terminated early, on ethical grounds, after an independent review decided that sorafenib should be offered to participants who were receiving placebo" **QoL**: No HRQoL difference between placebo and sorafenib groups in mean FACT-G physical well-being score, nor any significant difference in mean FKSI–10 total score over the first 32 weeks of treatment. However, median time to health status deterioration, as defined by a four-point or more drop in FKSI-10 total score, was significantly greater than placebo. Those who had received sorafenib scored significantly better on the following items of the FKSI-15 index: coughing; fever; worry about their disease; ability to enjoy life. **Safety**: associated with more AEs than BSC, particularly hand–foot skin reactions and hypertension. A significantly greater number of people reported 'bothersome side effects of treatment' than those receiving placebo. Skin rashes, hypertension, diarrhoea and hand–foot syndrome were more common in the sorafenib arm.	reached in the sorafenib group before patients receiving placebo were allowed to switch to sorafenib on the basis of "encouraging" progression-free survival results **QoL**: After 24 weeks of treatment, an improvement was observed: in the FKSI-10 score (44% in sorafenib versus 22% in placebo); in the FACT-G score (47% in sorafenib versus 21% in placebo). According to the results of clinical trials sorafenib is expected, in theory, to have a moderate effect on morbidity, mortality and quality of life. **Safety**: No Committee evaluation provided to describe comparative differences in safety	noted the influence that patient crossover had on the ability of the submission to demonstrate efficacy in terms of OS; Committee agreed that trial data suggested increase in progression-free survival as second-line treatment but "considered that the clinical importance of this gain had not been demonstrated…as a surrogate to predict future survival gain" **QoL**: NA **Safety**: PBAC noted that sorafenib is associated with a variety of AEs including dermatologic and gastrointestinal events, hypertension, sensory neuropathy, and neutropenia. Additionally, a six-fold increase in cardiac ischaemia/infarction was found in Trial 11213 for sorafenib treated patients compared to placebo. Diarrhoea, rash, fatigue, hand-foot syndrome, alopecia and nausea were reported in >20% patients
Effects	Merged data			
OS increase	≥ 3 months (exact gain uncertain)	≥ 3 months (exact gain uncertain)	None established	None established
QoL change	+	+	+	NA
Safety change	-	-	NA	-
sunitinib		FDA primary indication		
ATC code: L01XE04				

Orphan Status: EU Licensure: FDA/EMA Target: Renal		Indicated for the treatment of gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate. Aso indicated for the treatment of advanced renal cell carcinoma. Approval for advanced renal cell carcinoma is based on partial response rates and duration of responses. There are no randomized trials of sunitinib demonstrating clinical benefit such as increased survival or improvement in disease-related symptoms in renal cell carcinoma.		
Agency		NICE	HAS	PBAC
Appraisal date		Sept-09 (GIST) Mar-09 (RCC)	Sept-06 (GIST) May-07 (RCC)	Jul-09 (GIST) Jul-08 (RCC)
Comparator		BSC (GIST) / interferon-alfa (RCC)	BSC (GIST) / interferon-alfa (RCC)	BSC
Modelled/indirect comparison		Yes	No	Yes
Basis for classification		**OS**: More than 3-month increase compared to BSC as GIST treatment (7.8 months based on RPSFT model); more than 3-month increase compared to interferon-alfa as first-line RCC treatment (10 months according to model based on "Committee's preferred assumptions") **QoL**: More than 75% of people completed the EQ-5D questionnaire at each time point and there were no statistically significant differences reported. For RCC, overall results for HRQoL (total score and all subscales) were significantly better in the sunitinib arm compared with the IFN-α arm. **Safety**: For GIST, treatment-related AEs and serious AEs were more common in the sunitinib arm (83%) than in the placebo arm (59%). For RCC, the frequency of adverse events associated with sunitinib is comparable to that associated with IFN-α monotherapy. A total of 8% of participants receiving sunitinib discontinued treatment because of adverse events compared with 13% in the IFN-α arm.	**OS**: An increase compared to placebo not established in GIST treatment given that median OS was not reached in both treatment arms; increase not established compared to interferon-alfa in first-line RCC treatment as median OS was not reached in either treatment arm before patients receiving interferon-alfa were allowed to cross over to sunitinib based on progression-free survival results **QoL**: For GIST, NA. For RCC, a moderate theoretical impact may be expected of sunitinib in terms of reducing morbidity and improving quality of life in comparison to interferon alpha, as a first-line treatment. Statistically and clinically significant improvement in QoL, analysed through 3 FACT-G, FKSI and EQ-5D questionnaires, was observed in the sunitinib group compared to the interferon alpha group **Safety**: For GIST, no regulatory judgment is given on the comparative differences in safety across groups. For RCC, Grade III AEs were more frequent in the sunitinib group compared to IFN-α arm	**OS**: Committee considered that the magnitude of increase compared to BSC for treatment of GIST was "uncertain", noting that the 7.8-month survival benefit estimated by the RPSFT model "may be an overestimate"; no statistically significant difference was observed compared to interferon-alfa for treatment of RCC was observed, though Committee "acknowledged that because patients that progressed were allowed to cross-over this would bias later overall survival analyses towards the null, thereby underestimating the likely true difference between the therapies" **QoL**: NA **Safety**: For GIST, sunitinib is described as inferior in terms of comparative safety over placebo. For RCC, the PBAC noted the increase in AEs with sunitinib over BSC/placebo. Of particular concern to the PBAC was more recent evidence of cardiac side effects of ischemia and heart failure
Effects	Merged data			
OS increase	7.8 months (GIST);	≥ 3 months	None established	Uncertain

	10 months (RCC)			
QoL change	+	No Difference (GIST); + (RCC) = +	NA (GIST); + (RCC) = +	NA (GIST); NA (RCC) = NA
Safety change	-	– (GIST); No Difference (RCC) = –	NA (GIST); – (RCC) = –	– (GIST); – (RCC) = –
tegafur/gimeracil/oteracil		FDA primary indication		
ATC code: L01BC53		Indicated in adults for the treatment of advanced gastric cancer when given in combination with cisplatin.		
Orphan Status: EU (w)				
Licensure: EMA				
Target: GI				
Agency		NICE	HAS	PBAC
Appraisal date		NA	Oct-12	NA
Comparator		NA	fluorouracil (5-FU) / cisplatin	NA
Modelled/indirect comparison		NA	No	NA
Basis for classification		NA	**OS**: There was very little difference in median OS (primary endpoint) between the two groups: 8.6 months in the TEYSUNO group vs 7.9 months in the 5-FU group (HR = 0.92, 95% CI: [0.80; 1.05]). The median overall survival (primary endpoint) was similar across the two groups. As this was a superiority study, the primary objective was not achieved **QoL**: the overall FACT-Ga score, which evaluates quality of life, was also similar between the two groups. Available data do not show … the improvement in quality of life **Safety**: Similar overall incidence of AEs of any grade across both groups. Treatment stopped due to AE in 10.7% of treated patients vs 14.4% of comparator patients. Incidence profile for AEs were different between groups, with	NA

			treatment producing greater number of AEs in some cases, and comparator producing greater number of AEs in other cases. However, the primary superiority objective was not achieved (OS) … the results for the secondary endpoints, including safety, were of an exploratory nature and did not allow any conclusions to be drawn"	
Effects	Merged data			
OS increase	None established	NA	None established	NA
QoL change	None established	NA	No difference	NA
Safety change	None established	NA	No difference	NA
temsirolimus		FDA primary indication		
ATC code: L01XE09 Orphan Status: US/EU Licensure: FDA/EMA Target: Renal		A kinase inhibitor indicated for the treatment of advanced renal cell carcinoma.		
Agency		NICE	HAS	PBAC
Appraisal date		Aug-09	Feb-08	Jul-08
Comparator		interferon-alfa	interferon-alfa	BSC
Modelled/indirect comparison		No	No	Yes
Basis for classification		**OS**: 3.6-month increase in median OS **QoL**: Participants receiving temsirolimus had a significantly longer time in both TWiST and Q-TWiST health states compared with participants receiving IFN-α alone	**OS**: 3.6-month increase in median OS **QoL**: The available data are too limited for an evaluation of the product's impact on quality of life **Safety**: Grades 3–4 adverse effects were more common in the interferon alpha arm	**OS**: Committee considered "there was uncertainty about the magnitude of the treatment effect of temsirolimus compared with BSC" (based on indirect comparison); Committee was aware of the 3.6-month increase in median OS compared to IFN-α but did not consider IFN-α to be an appropriate comparator

		Safety: The frequency of treatment-related toxic events associated with bevacizumab plus IFN-α, sunitinib and temsirolimus appears to be comparable or slightly better than IFN-α, based on the data reported in these trials		**QoL**: PBAC considered that there was uncertainty regarding the effect of temsirolimus on QoL, as the two trials in the submission used different QoL instruments **Safety**: PBAC noted that AEs occurred at a significantly greater frequency in temsirolimus-treated patients compared to IFN-α patients and concluded that the profile of side effects for was different to I IFN-α, rather than that temsirolimus was better tolerated than IFN-α. However, PBAC considered that the submission did not consider the relative harms in comparison with BSC, including their impact on incremental QALYs and cost-effectiveness
Effects	Merged data			
OS increase	3.6 months	≥ 3 months	≥ 3 months	Uncertain
QoL change	+	+	NA	NA
Safety change	+	+	+	NA
tositumomab		FDA primary indication		
ATC code: V10XA53 Orphan Status: US/EU (w) Licensure: FDA/EMA Target: Hematological		Tositumomab and Iodine-131. Tositumomab is indicated for the treatment of patients with CD20 positive, follicular, non-Hodgkin's lymphoma, with and without transformation, whose disease is refractory to Rituximab and has relapsed following chemotherapy.		
Agency		NICE	HAS	PBAC
Appraisal date		NA	NA	NA
Comparator		NA	NA	NA
Modelled/indirect comparison		NA	NA	NA
Basis for classification		NA	NA	NA
Effects	Merged data			

OS increase	NA	NA	NA	NA
QoL change	NA	NA	NA	NA
Safety change	NA	NA	NA	NA
trabectedin		EMA primary indication		
ATC code: L01CX01 Orphan Status: – Licensure: EMA Target: Soft Tissue		Indicated for the treatment of adult patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents.		
Agency		NICE	HAS	PBAC
Appraisal date		Feb-2010	Apr-2008	
Comparator		BSC	non-comparative	NA
Modelled/indirect comparison		Yes	No	NA
Basis for classification		**OS**: Median OS was 13.9 months (95% CI 12.5 to 18.6). The Committee concluded that the use of historical controls (BSC) was appropriate. The manufacturer reported increased median OS over historical control patients treated with ifosfamide 6.6 months (95% CI 5.0 to 9.0), dacarbazine 6.6 months (95% CI 4.3 to 8.4) and etoposide 6.3 months (95% CI 4.4 to 8.9). Although the Committee "considered the clinical effectiveness data presented by the manufacturer, and noted the median OS for patients randomised to the licensed dosage of trabectedin exceeded that for patients receiving BSC", it does not indicate specify the exact gain in OS **QoL**: No comparative HRQoL data presented **Safety**: The Committee heard from the clinical specialist and patient experts that there were	**OS**: There was no difference between the two groups with regard to median overall survival time: 13.9 months in the group receiving treatment once every three weeks versus 10.8 months in the group receiving treatment every week **QoL**: No comparative evidence provided **Safety**: No comparative evidence provided	NA

		fewer, less severe and less frequent AEs than with the other agents. It understood that the AEs associated with trabectedin were manageable, but nevertheless important, as with other chemotherapy agents used to treat soft tissue sarcoma.		
Effects	Merged data			
OS increase	≥ 3 months (exact gain uncertain)	≥ 3 months (exact gain over uncertain)	None established	NA
QoL change	No difference	No difference	NA	NA
Safety change	+	+	NA	NA
trametinib		FDA primary indication		
ATC code: L01XE25		A kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.		
Orphan Status: –				
Licensure: FDA/EMA				
Target: Skin				
Agency		NICE	HAS	PBAC
Appraisal date		NA	NA	Nov-14
Comparator		NA	NA	dabrafenib
Modelled/indirect comparison		NA	NA	No
Basis for classification		NA	NA	**OS**: PBAC was satisfied that trametinib + dabrafenib, is more effective than dabrafenib alone, however the size of the incremental treatment effect is still uncertain, particularly for OS **QoL**: Report recalls consumer comments remarking on some benefits, including ability to return to work

				Safety: PBAC considered that the revised claim of different, but no worse comparative safety of trametinib + dabrafenib to dabrafenib monotherapy was reasonable, noting a decrease in rate of cutaneous hyperproliferative events and photosensitivity, but increase in rate of pyrexia and ejection fraction decrease
Effects	Merged data			
OS increase	Exact magnitude uncertain	NA	NA	Uncertain
QoL change	+	NA	NA	+
Safety change	None established	NA	NA	No difference
vandetanib		FDA primary indication		
ATC code: L01XE12		A kinase inhibitor indicated for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease.		
Orphan Status: US / EU (w)				
Licensure: FDA / EMA				
Target: Thyroid				
Agency		NICE	HAS	PBAC
Appraisal date		NA	Jun-12	NA
Comparator		NA	Placebo	NA
Modelled/indirect comparison		NA	No	NA
Basis for classification		NA	**OS**: Did not differ between the two groups during the analysis of the progression-free survival **QoL**: Impact is not measurable **Safety**: The Committee indicated that during the double-blind treatment period, treatment	NA

			was stopped due to adverse events for 12% of patients in the vandetanib arm and 3% of patients in the placebo arm. Grades ≥ 3 events involved 55% of patients in the vandetanib group and 24% of patients in the placebo group. However, the Committee did not provide an overall assessment of comparative changes in drug-related safety	
Effects	Merged data			
OS increase	None established	NA	None established	NA
QoL change	None established	NA	NA	NA
Safety change	None established	NA	NA	NA
vemurafenib		FDA primary indication		
ATC code: L01XE15 Orphan Status: – Licensure: FDA/EMA Target: Skin		A kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAFV600E mutation as detected by an FDA-approved test.		
Agency		NICE	HAS	PBAC
Appraisal date		Dec-12	Oct-12	Mar-13
Comparator		dacarbazine	dacarbazine	dacarbazine
Modelled/indirect comparison		No	No	No
Basis for classification		**OS**: 3.3-month increase in median OS; Committee "agreed it that it was appropriate to adjust the OS results…to control for switching using statistical modelling or other techniques" but "agreed that any estimate obtained using these techniques would be subject to uncertainty"	**OS**: 3.6-month increase in median OS compared to dacarbazine (based on follow-up OS analysis not scheduled in protocol); 1.5-month increase in median OS compared to dacarbazine (based on OS analysis scheduled in protocol)	**OS**: 3.3-month increase in median OS compared to dacarbazine (without censoring at crossover); 3.9-month increase in median OS compared to dacarbazine (with censoring at crossover); Committee considered "the true estimate" of OS gain would lie between those two points

		QoL: The Committee agreed with the manufacturer's assumption of a higher utility value for progression-free survival, given its improved clinical profile, including oral administration compared with intravenous administration for dacarbazine **Safety**: Treatment-related AEs were recorded for more people who received vemurafenib, may be explained by the fact that they stayed on treatment longer than those on dacarbazine	**QoL**: Although HAS indicates that a negative impact on quality of life cannot be ruled out, particularly in view of the safety problems encountered, there is no indication that it believes that worsened QoL is most likely outcome. The statement that worsened QoL can occur does not provide definitive proof one way or the other **Safety**: Safety data is limited due to the short follow-up period, especially in the pivotal study	**QoL**: NA **Safety**: The PBAC concluded that vemurafenib and DTIC have different toxicity profiles, with vemurafenib being associated with manageable toxicity. PBAC also noted that dabrafenib has a preferable toxicity profile as evidenced by fewer and less extensive dose intensity reductions and by favourable differences in rates for AEs such as photosensitivity, cutaneous squamous cell carcinoma – but not pyrex
Effects	Merged data			
OS increase	3.3–3.9 months	≥ 3 months	≥ 3 months	≥ 3 months
QoL change	+	+	NA	NA
Safety change	-	-	NA	NA (dacarbazine); – (dabrafenib) = –
vinflunine		EMA primary indication		
ATC code: L01CA05 Orphan Status: – Licensure: EMA Target: Bladder		Indicated in monotherapy for the treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen.		
Agency		NICE	HAS	PBAC
Appraisal date		Jan-2013	Dec-2009	Nov-2011
Comparator		BSC	BSC	BSC
Modelled/indirect comparison		No	No	No
Basis for classification		**OS:** The Committee noted that the difference between the study arms was not statistically significant for the ITT population, but was significant for the eligible ITT population … It considered that the results from the ITT	**OS**: The study objective was not reached in the ITT population: median overall survival was 6.9 months (95% CI [5.7 – 8.0 months]) in the JAVLOR arm versus 4.6 months (95% CI [4.1 – 7.0 months]) in the comparator arm (RR= 0.88;	**OS:** The PBAC noted that the increment is uncertain and, at best, is between 2.3 (ITT) and 2.6 months (eligible ITT) … the selection of the eligible ITT population was considered highly uncertain … The PBAC agreed that the ITT

		population were the most appropriate basis for its deliberations because randomisation had not been broken. It concluded that the extent of clinical effectiveness of vinflunine compared with BSC had not been conclusively demonstrated because of the uncertainty of the overall survival results **QoL:** There were no statistically significant differences in overall EORTC QLQ-C30 global health status score between the two arms (p=0.658). [The Committee] noted that there were no significant differences in HRQoL between patients receiving vinflunine and those receiving BSC alone **Safety**: Grade 3 or 4 toxicities relating to neutropenia, anaemia and constipation occurred in 50%, 19% and 16% respectively of patients in the vinflunine arm of study 302, compared with 1%, 8% and 1% of patients respectively in the best supportive care arm. Febrile neutropenia occurred in 6% of patients receiving vinflunine (none in the best supportive care arm). The Committee concluded that there were concerns about the tolerability of vinflunine	95% CI [0.69 – 1.12], NS). Two other types of analyses (multivariate, eligible ITT) discussed, but focus given on describing results for ITT population **QoL**: There was no difference in the quality of life assessment and clinical benefit between the two [study] arms. **Safety**: Treatment discontinuations more likely in the vinflunine arm compared with BSC alone arm. Grade 3-4 neutropenia and anaemia was higher in treatment arm. Higher incidence of non-haematological AEs reported in treatment arm.	population should be used in considering the effectiveness of vinflunine. The PBAC accepted that vinflunine may be superior in terms of comparative efficacy over BSC although the magnitude of the overall survival gain is uncertain (less than 3 months) **QoL:** No comparative data presented **Safety:** AEs significantly more frequent in treatment arm included abdominal pain, constipation, diarrhea, nausea, stomatitis, vomiting, among others. Grade III/IV AEs experienced more frequently included abdominal pain, constipation, nausea, vomiting, fatigue, among others. One death directly related to vinflunine, though 6% in vinflunine and 1% in BSC died within 30 days of final dose. PBAC noted that rates of AEs were higher in the treatment arm than in the BSC alone arm, and that the pattern of AE and serious AEs suggested very high levels of toxicity.
Effects	Merged data			
OS increase	Exact magnitude uncertain	None established	None established	None established
QoL change	None established	No difference	No difference	NA
Safety change	-	-	-	-
vismodegib		FDA primary indication		
ATC code: L01XX43		A hedgehog pathway inhibitor indicated for the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation.		
Orphan Status: –				

Licensure: FDA/EMA				
Target: Skin				
Agency		NICE	HAS	PBAC
Appraisal date		NA	Dec-13	NA
Comparator		NA	non-comparative	NA
Modelled/indirect comparison		NA	No	NA
Basis for classification		NA	**OS**: In light of the available clinical trial data in a non-comparative phase II study, an impact in terms of morbidity is not expected. In the efficacy trial (ERIVANCE), median OS was deemed not evaluable in the mBCC or laBCC cohorts **QoL**: In light of the available clinical trial data, an impact in terms of morbidity or QoL is not expected **Safety**: No comparative data presented	NA
Effects	Merged data			
OS increase	None established	NA	None established	NA
QoL change	None established	NA	No difference	NA
Safety change	None established	NA	NA	NA

vorinostat	FDA primary indication
ATC code: L01XX38	A histone deacetylase (HDAC) inhibitor indicated for: treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma (CTCL) who have progressive, persistent or recurrent disease on or following two systemic therapies.
Orphan Status: US	
Licensure: FDA/EMA	
Target: Hematological	

Agency		NICE	HAS	PBAC
Appraisal date		NA	NA	Mar-11
Comparator		NA	NA	BSC
Modelled/indirect comparison		NA	NA	No
Basis for classification		NA	NA	**OS**: No survival data are available from study P001 or from the non-comparative chemotherapy studies. Quality of data is extremely limited. Vorinostat has superior efficacy to palliative care, however, no conclusion can be reach with respect to other available therapies **QoL**: NA **Safety**: The PBAC agreed that vorinostat has significant toxicities, and is inferior in safety to palliative care. However, expert testimony suggests it is less toxic than cytotoxic chemotherapies
Effects	Merged data			
OS increase	None established	NA	NA	None established
QoL change	None established	NA	NA	NA
Safety change	+/-	NA	NA	– (placebo); + (chemotherapy) = +/–
ziv-aflibercept		FDA primary indication		
ATC code: L01XX44 Orphan Status: – Licensure: FDA/EMA Target: GI		In combination with 5-fluorouracil, leucovorin, irinotecan- (FOLFIRI) indicated for metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen.		
Agency		NICE	HAS	PBAC
Appraisal date		Mar-14	Jul-13	Jul-13

Comparator		placebo	placebo	placebo
Modelled/indirect comparison		Yes	No	No
Basis for classification		**OS**: 1.4-month increase in median OS. The Committee was not satisfied that estimates produced by the model were sufficiently robust to accept that the 3-month life extension criterion is fulfilled **QoL**: Although the Committee, echoing comments from a patient expert, would have liked the manufacturer to have collected trial data on HRQoL, the Committee noted that patients consider therapies such as ziv-aflibercept to improve QoL compared with chemotherapy **Safety**: The Committee concluded that treatment with aflibercept + ziv-aflibercept was associated with a considerable burden of AEs, but that, being a new treatment, less is known about its AE profile than for other available treatments.	**OS**: 1.4-month increase in median OS **QoL**: The expected additional impact of this medicinal product in terms of morbidity and mortality and QoL can only be very small **Safety**: Comparing ziv-aflibercept arm to placebo arm, frequency of treatment discontinuations due to AEs was greater	**OS**: 1.4-month increase in median OS compared to placebo for the K-RAS mutant patient population. The PBAC considered this survival gain to be modest and the clinical relevance and importance to be doubtful **QoL**: NA **Safety**: PBAC considered the claim that ziv-aflibercept is non-inferior in terms of comparative safety over cetuximab to not be a reasonable assumption, considering treatment to be potentially worse in comparative harms
Effects	Merged data			
OS increase	1.4 months	< 3 months	< 3 months	< 3 months
QoL change	+	+	No difference	-
Safety change	-	-	-	-

Source:

Authors' analysis of data, as described in Methods section.

Notes:

[1] '+' denotes improvement; '–' denotes reduction; '+/–' denotes mixed evidence. Orphan drug status obtained from Orphanet for the US and EU, with withdrawn, (w).

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Appendix 4.1

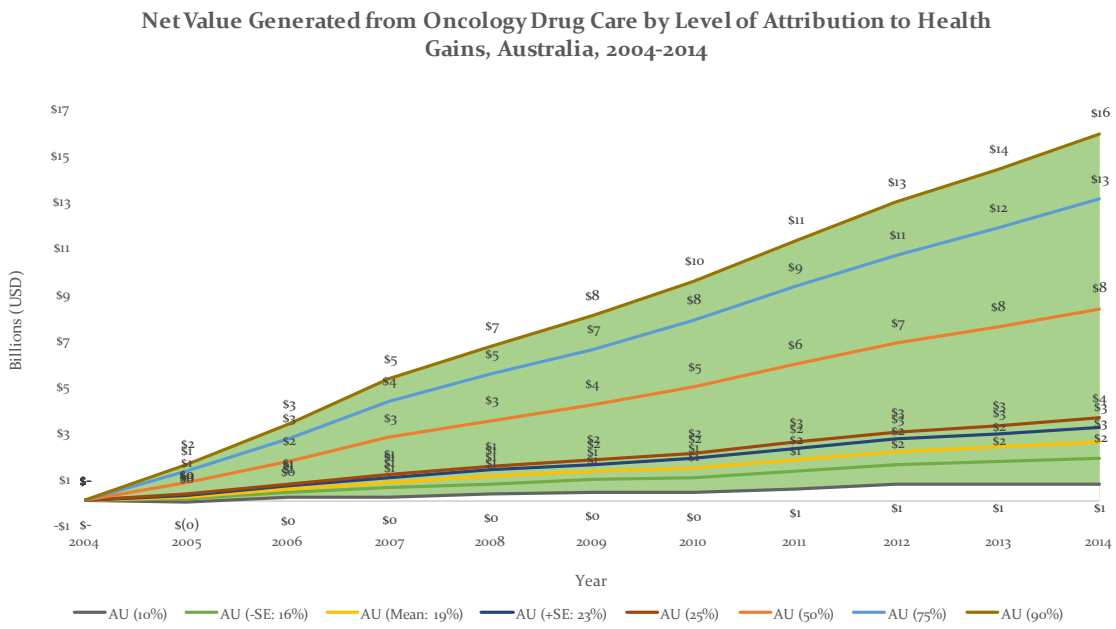
Overview of IHME methods to calculate global YPLLs

A thorough explanation of IHME methods for calculating country- and cause-specific YPLLs are provided elsewhere.(281,282) A brief overview of methods that are key to this study is nevertheless provided for reference. The IHME GBD study computes YPLLs by multiplying deaths from each cause in each age group by the reference standard life expectancy for that age group. One standard reference life table is used for both sexes across all countries,(353) and was developed by the IHME using the lowest observed death rate in each age group across countries with a population greater than 5 million. These methods reflect the IHME's assumption that, in the absence of any influence from outside factors, everyone should be expected to live equally long life in health.(354) By applying a normative standard life expectancy, IHME methods enable the use of GBD YPLL data as a neoplasm-related mortality indicator that is globally comparable and which tracks over time. Age-standardized YPLLs are also computed using an update to the world population age standard issues by the WHO in 2001.(282) Mathematically, YPLLs are calculated using the following equation:

$$\sum_{x=0}^{L} d_x(L-x) \qquad (13)$$

Appendix 4.2

eFigure 1. Net Value Generated from Oncology Drug Care by Level of Attribution to Health Gains, Australia, 2004-2014

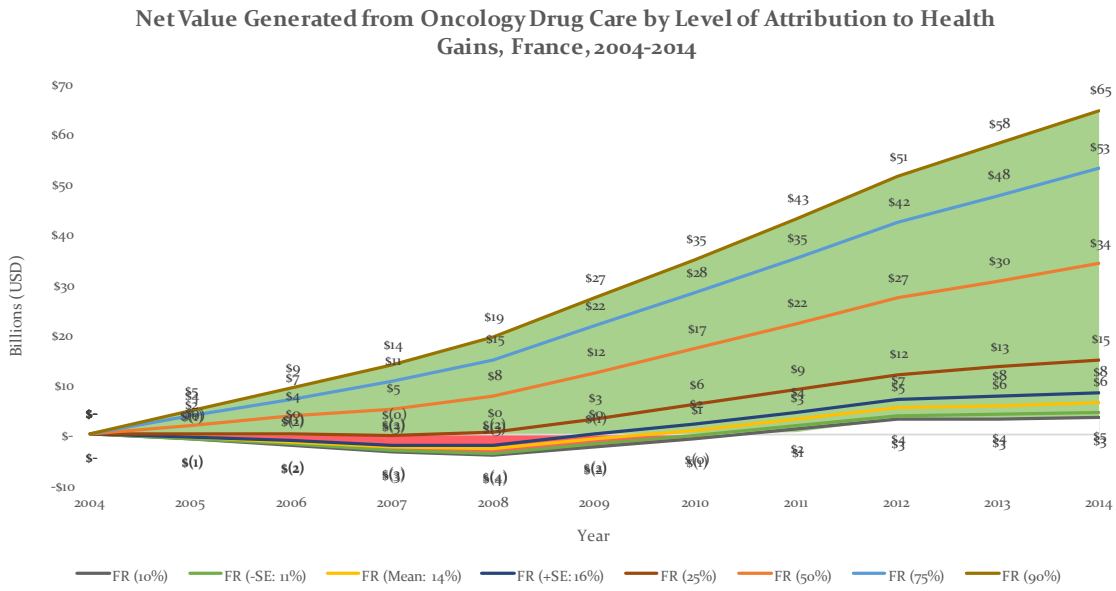


Source:

Authors' analysis of data, as described in Methods section.

Appendix 4.3

eFigure 2. Net Value Generated from Oncology Drug Care by Level of Attribution to Health Gains, France, 2004-2014

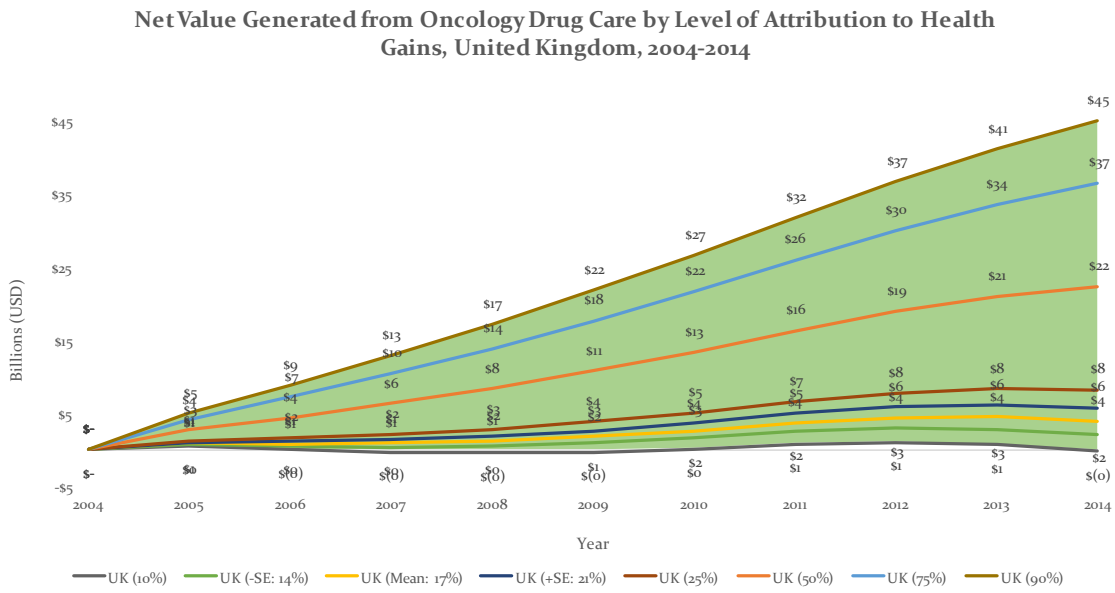


Source:

Authors' analysis of data, as described in Methods section.

Appendix 4.4

eFigure 3. Net Value Generated from Oncology Drug Care by Level of Attribution to Health Gains, United Kingdom, 2004-2014



Source:

Authors' analysis of data, as described in Methods section.

Appendix 4.5

eTable 9. Net Long-Term Value per Patient, First Year of Marketing, Assuming Treatment Duration (b) (4) (2015 USD)

Drug	Measure	AU			FR			UK			US		
		10%	50%	90%	10%	50%	90%	10%	50%	90%	10%	50%	90%
abiraterone	mean	$68,764.33	$60,822.31	$52,253.17	.	.	.	$66,250.83	$48,320.98	$28,850.73	$66,020.46	$47,175.25	$26,705.91
	p5	$43,945.59	$34,059.92	$21,375.08	.	.	.	$41,109.22	$14,843.53	$-21,235.40	$40,769.96	$12,919.01	$-25,188.06
	p25	$57,781.34	$49,541.64	$39,624.13	.	.	.	$55,288.42	$34,754.47	$10,413.56	$55,099.92	$33,402.92	$7,434.56
	p50	$68,402.60	$61,066.07	$52,781.71	.	.	.	$66,023.59	$49,466.36	$31,708.36	$65,727.58	$48,478.26	$29,601.81
	p75	$79,239.15	$71,917.46	$64,922.63	.	.	.	$76,681.61	$62,324.69	$49,241.87	$76,527.63	$61,578.22	$47,894.68
	p95	$94,118.60	$87,066.20	$82,665.17	.	.	.	$92,038.08	$80,068.19	$73,550.10	$91,846.01	$79,475.79	$72,486.66
afatinib	mean	$-3,811.55	$-19,138.03	$-34,458.33	$-3,996.96	$-20,069.00	$-36,134.57	$-5,917.69	$-29,713.10	$-53,498.91	$-10,326.44	$-51,849.71	$-93,356.24
	p5	$5,938.13	$29,491.07	$53,173.74	$-6,227.00	$-30,925.66	$-55,760.39	$-9,219.36	$-45,786.89	$-82,555.86	$-16,087.89	$-79,898.67	$-144,060.95
	p25	$4,710.59	$23,503.03	$42,574.92	$-4,939.73	$-24,646.34	$-44,645.98	$-7,313.51	$-36,490.06	$-66,100.47	$-12,762.16	$-63,675.59	$-115,346.10
	p50	$3,737.53	$19,261.51	$34,311.43	$-3,919.34	$-20,198.49	$-35,980.52	$-5,802.77	$-29,904.80	$-53,270.84	$-10,125.91	$-52,184.24	$-92,958.25
	p75	$2,894.22	$14,620.78	$26,452.14	$-3,035.01	$-15,332.01	$-27,738.91	$-4,493.47	$-22,699.76	$-41,068.75	$-7,841.16	$-39,611.35	$-71,665.46
	p95	$1,691.62	$8,582.85	$16,122.78	$-1,773.91	$-9,000.36	$-16,907.08	$-2,626.35	$-13,325.46	$-25,031.72	$-4,583.02	$-23,253.08	$-43,680.64
azacitidine	mean	$156,009.48	$145,320.82	$133,127.38	$151,542.78	$123,674.25	$95,281.25	$146,039.09	$95,716.56	$41,978.93	$151,156.37	$121,388.26	$88,911.16
	p5	$100,394.74	$87,216.87	$63,640.18	$95,858.56	$32,451.02	$-54,797.67	$88,990.85	$-46,424.91	$-205,006.62	$95,772.65	$30,687.18	$-62,637.77
	p25	$132,878.30	$121,094.03	$107,726.24	$128,166.69	$96,604.38	$63,736.94	$121,974.26	$66,505.16	$-8,192.07	$127,610.54	$94,906.74	$55,507.40
	p50	$156,048.27	$146,740.64	$135,858.12	$152,338.58	$129,648.67	$110,248.63	$147,240.96	$110,287.68	$77,323.42	$151,870.83	$127,185.41	$105,961.92
	p75	$179,141.67	$169,573.74	$161,535.62	$175,030.42	$158,806.96	$146,480.75	$170,110.55	$143,449.03	$126,140.45	$174,437.42	$154,434.53	$141,433.06
	p95	$209,692.86	$201,199.76	$195,218.95	$206,090.33	$194,476.83	$184,306.49	$201,345.49	$183,165.98	$169,299.44	$205,280.04	$191,568.66	$180,495.70
bendamustine	mean	.	.	.	$-825.71	$-4,122.79	$-7,412.56	$-1,454.13	$-7,274.94	$-12,853.25	$-6,239.54	$-31,392.10	$-55,395.91
	p5	.	.	.	$-1,751.40	$-8,484.46	$-15,798.91	$-2,518.74	$-12,744.88	$-22,118.69	$-10,780.61	$-54,674.32	$-96,356.51
	p25	.	.	.	$-1,096.67	$-5,508.35	$-9,826.17	$-1,883.10	$-9,302.00	$-16,384.34	$-7,990.21	$-40,141.07	$-70,075.12
	p50	.	.	.	$-743.77	$-3,728.64	$-6,753.04	$-1,365.61	$-6,942.99	$-12,075.84	$-5,948.88	$-30,108.63	$-52,846.18
	p75	.	.	.	$-458.67	$-2,346.07	$-4,229.78	$-966.38	$-4,869.44	$-8,689.84	$-4,165.03	$-21,187.77	$-37,650.89
	p95	.	.	.	$-189.41	$-941.72	$-1,712.53	$-601.59	$-3,007.08	$-5,357.77	$-2,515.75	$-12,581.66	$-23,001.18
bevacizumab	mean	$51,316.39	$-2,981.53	$-54,199.29	$61,210.19	$49,883.94	$39,455.89	$60,222.92	$44,424.84	$29,495.29	$58,114.26	$33,799.74	$9,254.44
	p5	$21,298.82	$123,078.11	$259,858.90	$37,403.41	$18,193.24	$-5,751.04	$36,165.57	$5,139.94	$-30,744.22	$33,496.07	$-19,337.16	$-96,867.34
	p25	$39,174.06	$30,150.70	$101,500.62	$51,060.75	$37,924.92	$26,235.36	$49,756.03	$31,757.22	$13,325.11	$47,592.13	$18,754.29	$-13,037.26
	p50	$51,888.81	$12,882.73	$27,218.43	$60,657.42	$50,395.71	$42,640.83	$59,785.41	$46,253.90	$33,996.87	$57,713.78	$38,282.20	$22,093.01
	p75	$63,543.09	$40,681.23	$19,593.47	$71,128.57	$62,702.24	$56,422.60	$70,356.34	$58,757.55	$51,501.02	$68,497.06	$54,631.54	$45,900.53
	p95	$80,394.23	$65,483.99	$55,071.08	$86,540.99	$79,519.34	$74,732.31	$85,774.01	$76,895.08	$71,652.18	$84,567.77	$73,384.25	$68,565.32
bortezomib	mean	$146,752.36	$144,241.65	$143,880.83	$143,225.22	$126,707.33	$112,066.26	$143,182.74	$126,289.59	$111,836.71	$143,898.71	$129,879.22	$118,286.45
	p5	$93,066.83	$88,507.33	$90,418.30	$89,727.01	$69,764.69	$51,604.46	$89,242.95	$70,732.20	$56,169.94	$89,918.52	$74,429.25	$63,703.71

	p25	$120,116.88	$119,013.94	$117,543.10	$116,459.23	$100,562.05	$84,879.04	$116,504.01	$101,204.66	$86,061.47	$117,088.15	$104,739.53	$92,613.84
	p50	$145,319.12	$141,109.89	$141,280.06	$141,645.20	$123,926.05	$109,921.95	$141,668.59	$123,415.56	$109,458.20	$142,341.83	$126,806.87	$115,917.34
	p75	$171,052.33	$167,810.71	$167,493.17	$166,826.59	$150,376.05	$137,975.00	$167,361.62	$149,411.97	$136,052.57	$168,096.97	$153,092.86	$142,602.82
	p95	$207,595.23	$208,692.14	$206,670.11	$203,778.17	$193,084.55	$180,529.81	$204,113.49	$190,730.22	$175,710.16	$204,825.82	$193,778.49	$181,226.22
cabazitaxel	mean	.	.	.	$49,659.15	$27,907.70	$5,353.15	$47,655.43	$17,823.01	$-13,206.10	$45,109.72	$5,455.43	$-35,556.76
	p5	.	.	.	$27,637.59	$-14,003.99	$-69,174.52	$24,522.90	$-38,468.96	$-111,736.36	$20,502.43	$-66,201.30	$-164,956.57
	p25	.	.	.	$39,993.42	$14,446.10	$-15,557.46	$37,602.11	$1,880.54	$-39,672.83	$34,539.14	$-15,091.93	$-70,946.50
	p50	.	.	.	$49,062.97	$30,525.85	$12,369.42	$47,081.37	$22,365.70	$-2,257.58	$44,598.55	$12,867.48	$-22,378.03
	p75	.	.	.	$59,157.31	$44,344.64	$32,145.14	$57,526.08	$38,987.14	$23,816.74	$55,418.22	$32,866.41	$13,039.73
	p95	.	.	.	$72,629.52	$61,105.14	$54,049.80	$71,221.24	$58,098.82	$48,857.74	$69,626.20	$54,207.91	$43,988.52
cabozantinib	mean	.	.	.	.	.	.	$-11,072.90	$-56,527.56	$-99,093.49	.	.	.
	p5	.	.	.	.	.	.	$-28,076.20	$-139,544.71	$-251,180.48	.	.	.
	p25	.	.	.	.	.	.	$-15,435.94	$-79,569.16	$-137,633.14	.	.	.
	p50	.	.	.	.	.	.	$-9,103.86	$-45,997.19	$-78,924.00	.	.	.
	p75	.	.	.	.	.	.	$-4,587.77	$-23,655.70	$-43,225.41	.	.	.
	p95	.	.	.	.	.	.	$-1,361.99	$-6,690.50	$-12,903.11	.	.	.
catumaxomab	mean	.	.	.	.	.	.	$-2,116.09	$-10,583.09	$-19,095.58	.	.	.
	p5	.	.	.	.	.	.	$-2,450.16	$-12,250.80	$-22,051.44	.	.	.
	p25	.	.	.	.	.	.	$-2,450.16	$-12,250.80	$-22,051.44	.	.	.
	p50	.	.	.	.	.	.	$-2,450.16	$-12,250.80	$-22,051.44	.	.	.
	p75	.	.	.	.	.	.	$-2,450.16	$-12,250.80	$-22,051.44	.	.	.
	p95	.	.	.	.	.	.	$-852.23	$-4,261.15	$-7,670.06	.	.	.
clofarabine	mean	$-7,376.29	$-36,726.23	$-65,600.30	$-10,990.07	$-54,624.37	$-96,354.37	$-16,639.44	$-82,421.12	$-149,763.75	$-17,243.59	$-85,915.13	$-153,027.58
	p5	$14,337.96	$73,093.96	$129,491.62	$-22,193.38	$-111,292.18	$-202,755.36	$-33,649.84	$-166,299.11	$-311,226.44	$-32,265.07	$-167,285.36	$-292,896.71
	p25	$9,693.10	$48,634.05	$86,280.84	$-14,348.27	$-72,214.04	$-124,334.30	$-21,680.69	$-108,821.77	$-196,310.08	$-22,812.32	$-112,640.02	$-201,948.58
	p50	$6,658.64	$33,225.16	$59,473.71	$-9,971.07	$-49,233.37	$-88,173.91	$-15,230.59	$-75,561.29	$-136,375.50	$-15,358.18	$-76,895.29	$-138,109.97
	p75	$3,616.15	$17,741.34	$32,186.58	$-5,987.42	$-28,757.75	$-51,734.76	$-8,883.44	$-43,339.02	$-78,311.88	$-8,096.32	$-40,077.87	$-72,666.41
	p95	$2,969.79	$14,813.65	$26,655.07	$-3,854.82	$-19,538.81	$-34,619.58	$-6,090.27	$-29,966.05	$-54,890.54	$-7,077.21	$-35,738.42	$-64,156.64
crizotinib	mean	$54,614.96	$53,058.16	$51,374.12	$49,228.40	$26,386.64	$3,266.73	$47,689.22	$18,765.38	$-10,479.72	$46,032.59	$10,562.61	$-25,275.05
	p5	$35,954.57	$33,767.49	$32,459.15	$29,875.58	$-6,252.41	$-48,074.95	$27,871.47	$-19,311.91	$-74,115.39	$25,756.56	$-33,895.01	$-102,269.32
	p25	$46,132.00	$44,733.39	$43,413.92	$40,800.26	$13,960.78	$-14,615.94	$39,235.88	$4,531.95	$-32,672.86	$37,270.44	$-5,732.35	$-51,906.89
	p50	$54,769.64	$52,841.02	$51,349.40	$49,514.19	$27,253.10	$6,157.48	$48,184.56	$20,180.97	$-7,058.88	$46,446.14	$12,514.57	$-20,707.70
	p75	$62,920.65	$61,338.43	$59,495.40	$57,758.22	$39,706.00	$24,017.94	$56,326.15	$34,467.42	$15,370.98	$54,784.57	$29,087.48	$6,202.68
	p95	$73,104.75	$72,511.04	$69,830.37	$68,746.52	$55,748.81	$45,064.66	$67,213.42	$52,588.15	$40,222.67	$66,322.90	$49,711.88	$35,459.75
degarelix	mean	$-206.60	$-1,037.95	$-1,860.33	$-200.99	$-1,009.76	$-1,809.80	$-239.18	$-1,201.64	$-2,153.71	$-266.48	$-1,338.76	$-2,399.47
	p5	$255.74	$1,278.68	$2,301.63	$-248.79	$-1,243.95	$-2,239.11	$-296.07	$-1,480.33	$-2,664.60	$-329.85	$-1,649.26	$-2,968.66
	p25	$221.64	$1,108.19	$1,994.75	$-215.62	$-1,078.09	$-1,940.56	$-256.59	$-1,282.96	$-2,309.32	$-285.87	$-1,429.35	$-2,572.84
	p50	$204.59	$1,022.95	$1,841.30	$-199.03	$-995.16	$-1,791.29	$-236.85	$-1,184.27	$-2,131.68	$-263.88	$-1,319.40	$-2,374.93
	p75	$187.54	$937.70	$1,687.86	$-182.45	$-912.23	$-1,642.01	$-217.12	$-1,085.58	$-1,954.04	$-241.89	$-1,209.45	$-2,177.02
	p95	$153.44	$767.21	$1,380.98	$-149.27	$-746.37	$-1,343.47	$-177.64	$-888.20	$-1,598.76	$-197.91	$-989.55	$-1,781.20
enzalutamide	mean	$74,851.70	$63,077.56	$51,986.50	$74,465.18	$61,136.74	$48,547.01	$72,419.23	$50,863.47	$30,340.88	$69,067.28	$34,032.47	$513.21
	p5	$47,884.24	$34,760.97	$19,039.87	$47,589.79	$32,363.43	$14,099.45	$45,435.47	$16,888.26	$-15,406.09	$41,845.43	$-8,393.50	$-68,189.03

	p25	$63,694.86	$50,785.22	$38,736.14	$63,277.77	$48,711.98	$34,632.42	$61,261.33	$37,132.45	$12,480.13	$57,800.63	$16,566.48	$-25,187.00
	p50	$75,039.42	$63,200.49	$52,710.23	$74,638.85	$61,431.72	$49,335.68	$72,501.31	$51,552.83	$31,739.60	$69,091.60	$34,682.04	$3,164.09
	p75	$85,593.77	$74,850.68	$66,023.66	$85,303.43	$73,147.83	$63,213.32	$83,394.13	$64,643.54	$49,850.53	$80,176.43	$51,343.14	$28,838.09
	p95	$101,429.95	$90,732.59	$83,553.21	$100,998.24	$89,523.53	$81,336.09	$98,865.96	$82,942.52	$72,464.70	$96,018.44	$73,793.53	$59,234.78
eribulin	mean	.	.	.	$41,735.54	$34,213.53	$26,758.83	$40,289.82	$26,825.97	$13,755.29	$38,485.59	$17,679.12	$-2,301.69
	p5	.	.	.	$26,902.34	$16,347.11	$3,682.67	$25,281.61	$2,742.21	$-22,807.14	$22,901.22	$-15,698.20	$-58,201.43
	p25	.	.	.	$35,403.79	$27,460.32	$18,196.76	$34,056.13	$18,612.77	$1,597.85	$32,125.72	$7,035.69	$-18,797.77
	p50	.	.	.	$41,898.86	$34,580.19	$27,671.06	$40,466.81	$27,756.53	$16,039.59	$38,650.59	$19,642.45	$2,191.22
	p75	.	.	.	$48,079.91	$41,568.16	$36,204.06	$46,723.92	$36,457.91	$28,387.60	$45,193.36	$30,808.77	$19,222.78
	p95	.	.	.	$56,326.44	$50,946.05	$47,017.53	$55,285.35	$47,532.84	$41,625.49	$53,818.33	$44,096.05	$36,441.81
erlotinib	mean	$31,844.13	$25,581.85	$19,548.36	$32,616.34	$29,428.65	$26,308.49	$31,702.26	$24,875.10	$18,306.37	$32,081.61	$26,764.86	$21,627.31
	p5	$20,380.84	$9,554.93	$3,355.67	$21,394.17	$17,001.55	$11,221.14	$20,206.40	$7,804.20	$-6,185.89	$20,779.59	$12,158.92	$1,408.50
	p25	$26,966.57	$19,698.72	$12,401.51	$27,749.13	$24,017.21	$20,787.40	$26,809.88	$18,950.79	$10,766.96	$27,130.78	$21,135.93	$15,002.07
	p50	$31,794.97	$25,908.63	$21,165.99	$32,607.37	$29,699.43	$26,856.78	$31,684.74	$25,239.30	$20,349.18	$32,038.34	$27,039.71	$22,886.36
	p75	$36,892.83	$32,345.59	$28,378.03	$37,563.68	$34,802.65	$32,347.40	$36,803.25	$31,893.84	$27,663.18	$37,107.70	$33,046.92	$29,649.05
	p95	$43,131.37	$39,268.84	$37,253.33	$43,864.67	$41,459.97	$39,639.56	$43,040.97	$38,862.59	$36,686.23	$43,346.57	$39,851.35	$37,905.71
everolimus	mean	.	.	.	$85,691.30	$81,365.37	$77,483.31	$85,674.75	$81,282.29	$77,332.05	$85,131.96	$78,558.38	$72,372.88
	p5	.	.	.	$56,423.19	$51,144.05	$47,381.17	$56,410.91	$50,992.84	$47,170.01	$55,915.89	$48,027.43	$41,482.33
	p25	.	.	.	$72,924.11	$68,142.05	$64,317.87	$72,904.90	$68,064.79	$64,172.85	$72,204.54	$65,191.62	$58,915.39
	p50	.	.	.	$85,285.10	$81,172.11	$77,286.32	$85,275.89	$81,094.62	$77,168.31	$84,706.92	$78,828.74	$72,051.90
	p75	.	.	.	$98,545.86	$94,333.24	$90,612.59	$98,540.87	$94,230.60	$90,497.09	$98,121.95	$91,714.48	$86,178.64
	p95	.	.	.	$114,974.10	$112,384.16	$107,406.51	$114,955.12	$112,294.06	$107,316.10	$114,583.63	$109,623.15	$103,525.41
gefitinib	mean	$-331.81	$-1,636.00	$-2,970.73	.	.	.	$-1,084.35	$-5,346.39	$-9,708.23	$-516.12	$-2,544.73	$-4,620.85
	p5	$777.97	$3,856.21	$7,142.96	.	.	.	$-2,542.38	$-12,601.98	$-23,342.97	$-1,210.10	$-5,998.19	$-11,110.60
	p25	$457.36	$2,264.40	$4,176.82	.	.	.	$-1,494.65	$-7,400.00	$-13,649.70	$-711.41	$-3,522.19	$-6,496.88
	p50	$278.01	$1,390.03	$2,502.06	.	.	.	$-908.51	$-4,542.57	$-8,176.63	$-432.43	$-2,162.14	$-3,891.85
	p75	$161.42	$762.27	$1,372.09	.	.	.	$-527.52	$-2,491.09	$-4,483.96	$-251.09	$-1,185.69	$-2,134.24
	p95	$44.84	$246.62	$403.56	.	.	.	$-146.53	$-805.94	$-1,318.81	$-69.75	$-383.61	$-627.72
ipilimumab	mean	.	.	.	$95,295.83	$95,334.24	$95,631.98	$81,942.72	$27,839.27	$-26,198.63	$81,378.06	$25,015.52	$-31,341.63
	p5	.	.	.	$63,985.23	$63,630.22	$63,666.55	$49,046.02	$-24,145.86	$-108,582.20	$47,432.55	$-40,123.24	$-141,324.48
	p25	.	.	.	$81,510.13	$81,473.85	$81,603.26	$67,381.79	$8,175.22	$-55,099.56	$66,813.53	$1,669.79	$-69,803.03
	p50	.	.	.	$95,407.97	$94,841.96	$95,777.98	$82,175.40	$29,259.53	$-23,059.17	$81,108.18	$27,298.70	$-28,291.49
	p75	.	.	.	$108,409.71	$108,833.55	$109,414.73	$96,100.10	$49,380.08	$6,213.59	$95,872.81	$51,712.70	$15,039.26
	p95	.	.	.	$128,177.18	$128,095.78	$127,542.03	$115,292.37	$74,426.67	$46,125.12	$115,431.29	$81,680.63	$60,587.04
lapatinib	mean	$21,155.15	$16,335.90	$11,369.71	$21,359.22	$17,377.09	$13,200.41	$21,185.60	$16,491.26	$11,642.87	$21,022.92	$15,661.25	$10,183.48
	p5	$8,066.10	$256.78	$9,786.66	$8,352.30	$1,677.38	$-5,480.36	$8,106.05	$156.54	$-9,184.53	$7,900.62	$-1,903.46	$-12,438.01
	p25	$14,680.64	$9,495.45	$4,052.39	$14,903.93	$10,621.73	$5,887.56	$14,717.24	$9,634.04	$4,254.83	$14,560.85	$8,980.65	$2,754.59
	p50	$20,312.17	$16,037.65	$12,063.32	$20,538.78	$17,079.45	$13,562.14	$20,333.09	$16,163.18	$12,283.21	$20,139.28	$15,431.05	$11,128.26
	p75	$26,715.35	$22,982.20	$19,689.63	$26,859.93	$23,774.56	$20,910.49	$26,742.89	$23,146.16	$19,866.73	$26,581.60	$22,550.93	$18,872.13
	p95	$36,908.03	$33,616.36	$30,470.72	$37,140.63	$34,348.04	$31,463.09	$36,950.69	$33,715.22	$30,648.01	$36,822.58	$32,949.55	$29,553.24
nelarabine	mean	.	.	.	$-2,559.73	$-12,768.42	$-22,968.91	$-3,139.44	$-15,731.52	$-28,171.93	$-3,954.37	$-19,762.89	$-35,488.56
	p5	.	.	.	$-4,530.97	$-22,348.27	$-39,745.33	$-5,653.73	$-27,686.20	$-49,741.03	$-6,818.84	$-34,302.52	$-60,889.34

	p25	.	.	.	$-3,189.58	$-16,023.33	$-28,379.66	$-3,929.41	$-19,935.45	$-35,304.77	$-4,912.50	$-24,822.28	$-43,530.42
	p50	.	.	.	$-2,460.30	$-12,490.53	$-22,399.46	$-2,934.80	$-14,979.75	$-27,126.15	$-3,997.70	$-19,980.57	$-36,171.24
	p75	.	.	.	$-1,787.30	$-8,963.27	$-16,328.10	$-2,183.56	$-10,915.36	$-19,845.35	$-2,772.06	$-13,819.91	$-24,907.52
	p95	.	.	.	$-915.39	$-4,536.36	$-8,234.08	$-1,122.25	$-5,389.52	$-10,171.50	$-1,412.03	$-6,928.04	$-12,445.18
ofatumumab	mean	.	.	.	$-5,177.81	$-26,310.75	$-47,126.35	$-7,160.37	$-36,385.01	$-65,170.81	$-11,465.04	$-58,258.94	$-104,350.17
	p5	.	.	.	$-7,553.20	$-37,765.99	$-67,978.78	$-10,445.28	$-52,226.41	$-94,007.54	$-16,724.77	$-83,623.86	$-150,522.95
	p25	.	.	.	$-6,485.61	$-32,428.04	$-58,370.47	$-8,968.92	$-44,844.59	$-80,720.25	$-14,360.85	$-71,804.23	$-129,247.62
	p50	.	.	.	$-5,418.02	$-27,090.09	$-48,762.16	$-7,492.55	$-37,462.76	$-67,432.97	$-11,996.92	$-59,984.61	$-107,972.29
	p75	.	.	.	$-3,816.63	$-21,752.14	$-39,153.86	$-5,278.00	$-30,080.94	$-54,145.69	$-8,451.03	$-48,164.98	$-86,696.96
	p95	.	.	.	$-2,749.04	$-13,745.22	$-24,741.39	$-3,801.64	$-19,008.20	$-34,214.76	$-6,087.11	$-30,435.54	$-54,783.97
panitumumab	mean	$46,144.32	$35,542.85	$24,069.53	$46,986.33	$39,740.97	$32,189.19	$46,216.45	$35,523.47	$24,782.12	$43,768.34	$22,718.43	$3,121.97
	p5	$29,461.70	$12,633.36	$10,025.21	$30,355.17	$20,987.14	$7,197.99	$29,463.73	$13,965.13	$-5,022.36	$26,636.57	$-14,935.98	$-57,273.96
	p25	$38,340.03	$26,794.57	$13,126.21	$39,285.53	$31,654.55	$23,318.76	$38,584.97	$26,918.25	$14,219.55	$35,742.68	$10,989.34	$-13,295.19
	p50	$46,100.22	$36,041.00	$26,252.56	$47,031.42	$39,738.23	$32,924.03	$46,220.80	$35,898.41	$26,101.43	$43,765.91	$25,233.99	$8,124.53
	p75	$53,633.31	$44,837.55	$36,631.27	$54,437.00	$48,039.49	$42,128.95	$53,625.67	$44,435.10	$36,600.06	$51,481.64	$36,782.60	$25,505.38
	p95	$62,926.43	$56,436.11	$50,651.39	$63,829.59	$58,766.04	$53,623.08	$63,021.37	$56,220.65	$50,336.60	$61,458.72	$51,173.83	$44,366.60
pertuzumab	mean	$254,063.84	$235,267.30	$211,401.28	$253,046.02	$230,219.22	$202,497.46	$249,425.36	$212,261.89	$170,824.22	$248,579.01	$208,064.28	$163,420.45
	p5	$163,806.30	$141,591.11	$111,709.13	$162,298.87	$137,548.60	$100,145.08	$157,671.77	$114,475.70	$55,647.87	$156,481.51	$108,922.31	$43,259.03
	p25	$214,198.64	$196,143.83	$169,882.05	$213,021.72	$190,225.11	$160,975.86	$209,756.77	$171,164.26	$125,063.68	$209,067.44	$165,795.77	$116,081.93
	p50	$255,175.49	$236,376.85	$212,206.09	$254,052.63	$231,086.43	$203,652.80	$250,299.23	$213,366.82	$173,009.26	$249,569.02	$208,886.08	$165,548.68
	p75	$292,071.23	$273,655.85	$253,112.16	$291,139.85	$269,391.60	$244,570.92	$287,861.80	$253,541.84	$218,893.02	$286,987.97	$250,144.10	$213,750.18
	p95	$345,396.55	$327,651.71	$308,832.94	$344,551.66	$323,321.84	$302,098.77	$341,070.71	$308,614.50	$282,085.02	$340,502.05	$305,246.78	$278,238.33
regorafenib	mean	$7,986.16	$-52,561.56	$-107,988.15	$21,119.12	$13,410.10	$6,207.73	$20,402.78	$9,811.68	$-21.08	$19,121.10	$3,373.29	$-11,165.82
	p5	$12,549.25	$152,790.97	$285,789.96	$13,025.47	$-1,914.95	$-18,019.03	$12,080.28	$-9,789.65	$-32,569.03	$10,305.94	$-24,973.17	$-58,707.39
	p25	$2,265.69	$82,187.93	$139,321.33	$17,499.17	$8,632.79	$-169.55	$16,777.23	$4,093.51	$-8,140.70	$15,342.73	$-4,267.16	$-22,212.85
	p50	$9,919.31	$40,274.13	$90,660.14	$21,100.03	$14,306.40	$8,409.45	$20,438.14	$11,427.68	$3,438.98	$19,251.41	$6,210.31	$-5,831.81
	p75	$15,607.35	$15,839.67	$48,944.09	$24,678.91	$19,113.85	$15,127.87	$24,013.19	$16,844.83	$11,966.80	$22,853.29	$13,382.08	$6,421.53
	p95	$22,741.02	$5,846.27	$11,745.60	$29,374.23	$25,766.59	$22,499.81	$28,837.22	$24,477.41	$20,138.78	$28,028.14	$22,005.43	$16,639.72
temsirolimus	mean	.	.	.	$59,436.90	$55,997.53	$51,959.00	$57,503.43	$46,628.25	$34,975.57	.	.	.
	p5	.	.	.	$38,571.17	$34,554.38	$28,399.96	$36,458.73	$14,836.36	$-12,470.03	.	.	.
	p25	.	.	.	$50,287.37	$46,792.02	$42,579.51	$48,379.55	$36,312.66	$22,005.23	.	.	.
	p50	.	.	.	$59,233.55	$55,934.89	$52,346.59	$57,124.88	$48,058.26	$38,584.96	.	.	.
	p75	.	.	.	$68,703.74	$65,397.49	$61,842.67	$67,016.59	$58,589.34	$52,176.71	.	.	.
	p95	.	.	.	$80,101.75	$77,257.09	$74,305.46	$78,750.49	$72,874.08	$67,628.28	.	.	.
trastuzumab emtansine	mean	$90,800.33	$74,622.49	$56,266.90	$89,577.93	$68,573.33	$44,165.64	$84,905.70	$45,926.93	$1,118.15	$83,521.84	$38,656.74	$-9,630.43
	p5	$57,454.01	$28,913.14	$10,031.32	$55,893.74	$15,986.91	$-36,080.83	$50,527.81	$-27,126.07	$-125,032.01	$47,552.66	$-55,196.13	$-154,622.76
	p25	$75,621.75	$57,274.97	$36,692.22	$74,311.91	$51,092.65	$21,730.31	$69,538.67	$21,926.59	$-34,960.84	$67,964.69	$12,978.32	$-51,289.94
	p50	$90,428.27	$76,749.08	$60,418.72	$89,285.18	$71,668.62	$50,031.08	$84,664.69	$50,569.04	$13,328.80	$83,498.47	$47,312.89	$7,948.67
	p75	$105,581.77	$93,305.48	$81,241.11	$104,401.78	$89,107.74	$74,010.65	$100,053.45	$75,308.06	$49,952.82	$98,974.15	$74,420.86	$47,779.70
	p95	$125,736.36	$116,129.38	$108,454.95	$125,133.22	$113,627.39	$103,437.39	$120,627.75	$105,177.13	$88,807.72	$120,115.47	$104,263.91	$87,884.28
vorinostat	mean	.	.	.	.	.	.	.	.	.	$-5,696.81	$-28,156.07	$-51,618.32
	p5	.	.	.	.	.	.	.	.	.	$-10,063.74	$-49,830.15	$-89,401.16

	p25	.	.	.	.	.	.	.	.	.	$-7,295.39	$-36,314.13	$-65,951.67
	p50	.	.	.	.	.	.	.	.	.	$-5,536.68	$-27,357.73	$-49,830.15
	p75	.	.	.	.	.	.	.	.	.	$-3,891.96	$-19,215.55	$-35,174.23
	p95	.	.	.	.	.	.	.	.	.	$-1,937.84	$-9,282.09	$-17,880.23
ziv-aflibercept	mean	.	.	.	$22,137.06	$17,594.28	$13,541.52	$21,085.56	$12,253.53	$4,369.94	$17,027.63	$-8,402.34	$-31,269.26
	p5	.	.	.	$14,164.19	$6,335.22	$-3,740.68	$12,871.05	$-5,623.72	$-25,203.67	$4,563.32	$-62,352.60	$-122,372.77
	p25	.	.	.	$18,603.83	$13,628.37	$8,807.00	$17,455.71	$6,961.40	$-3,430.63	$12,887.18	$-21,353.56	$-51,394.14
	p50	.	.	.	$22,145.51	$18,080.37	$14,756.57	$21,158.84	$13,729.65	$7,791.32	$17,690.91	$-826.68	$-17,910.59
	p75	.	.	.	$25,509.50	$22,151.42	$19,925.89	$24,645.47	$19,127.52	$15,235.94	$21,961.37	$10,623.78	$2,102.29
	p95	.	.	.	$30,038.77	$27,360.41	$25,784.12	$29,519.35	$25,404.15	$23,281.17	$27,816.70	$21,647.58	$17,251.53

Source:

Authors' analysis of data, as described Methods section.

Notes:

[1] Currencies are given in terms of 2015 US dollars. As explained in Chapter 3, outliers where the mean drug cost per patient was >$250,000 were censored (abiraterone, FR, Yo-2; erlotinib, (b) (4) ; cabazitaxel, AU, Yo; ipilimumab, AU, Yo).
[2] SD: standard deviation; p25: 25th percentile; p50: 50th percentile; p75: 75th percentile.
[3] DoT modeled as: (b) (4)

Appendix 4.6

eTable 10. Net Long-Term Value Generated to Society, First Year of Marketing, Assuming Treatment Duration Follows (b) (4) (Million 2015 USD).

Drug	Measure	AU			FR			UK			US		
		10%	50%	90%	10%	50%	90%	10%	50%	90%	10%	50%	90%
abiraterone	mean	$3.684	$3.283	$2.942	.	.	.	$26.571	$21.657	$17.185	$665.962	$538.066	$421.255
	p5	$0.770	$0.543	$0.306	.	.	.	$5.165	$1.525	$-2.180	$128.539	$32.623	$-64.920
	p25	$1.305	$1.059	$0.810	.	.	.	$9.096	$5.315	$1.523	$227.230	$127.787	$28.045
	p50	$1.983	$1.811	$1.514	.	.	.	$14.076	$10.844	$6.693	$352.264	$266.595	$157.833
	p75	$3.424	$3.304	$2.864	.	.	.	$24.666	$21.813	$16.610	$618.142	$541.989	$406.829
	p95	$9.943	$9.654	$8.552	.	.	.	$72.555	$68.464	$58.395	$1,820.461	$1,713.219	$1,455.898
afatinib	mean	$-0.009	$-0.046	$-0.082	$-0.120	$-0.599	$-1.077	$-0.043	$-0.217	$-0.391	$-0.700	$-3.500	$-6.300
	p5	$0.009	$0.046	$0.082	$-0.120	$-0.599	$-1.077	$-0.043	$-0.217	$-0.391	$-0.700	$-3.500	$-6.300
	p25	$0.009	$0.046	$0.082	$-0.120	$-0.599	$-1.077	$-0.043	$-0.217	$-0.391	$-0.700	$-3.500	$-6.300
	p50	$0.009	$0.046	$0.082	$-0.120	$-0.599	$-1.077	$-0.043	$-0.217	$-0.391	$-0.700	$-3.500	$-6.300
	p75	$0.009	$0.046	$0.082	$-0.120	$-0.599	$-1.077	$-0.043	$-0.217	$-0.391	$-0.700	$-3.500	$-6.300
	p95	$0.009	$0.046	$0.082	$-0.120	$-0.599	$-1.077	$-0.043	$-0.217	$-0.391	$-0.700	$-3.500	$-6.300
azacitidine	mean	$5.340	$5.338	$5.241	$195.678	$217.327	$182.866	$15.393	$14.008	$12.469	$280.327	$269.394	$252.255
	p5	$0.517	$0.394	$0.277	$11.266	$3.456	$-5.433	$1.155	$-0.514	$-2.280	$24.348	$7.035	$-12.913
	p25	$1.287	$1.152	$0.934	$35.597	$25.613	$15.230	$3.479	$1.792	$-0.193	$65.223	$48.148	$25.015
	p50	$2.778	$2.613	$2.315	$83.824	$73.670	$60.053	$7.848	$5.929	$3.926	$145.978	$123.257	$99.803
	p75	$6.502	$6.091	$6.298	$209.814	$197.087	$194.857	$18.541	$16.419	$15.672	$338.089	$315.897	$310.656
	p95	$21.985	$23.086	$23.166	$743.122	$763.784	$753.327	$63.234	$66.939	$64.583	$1,151.461	$1,204.786	$1,178.814
bendamustine	mean	.	.	.	$-0.000	$-0.001	$-0.002	$-0.052	$-0.259	$-0.466	$-9.273	$-46.364	$-83.456
	p5	.	.	.	$-0.000	$-0.001	$-0.002	$-0.052	$-0.259	$-0.466	$-9.273	$-46.364	$-83.456
	p25	.	.	.	$-0.000	$-0.001	$-0.002	$-0.052	$-0.259	$-0.466	$-9.273	$-46.364	$-83.456
	p50	.	.	.	$-0.000	$-0.001	$-0.002	$-0.052	$-0.259	$-0.466	$-9.273	$-46.364	$-83.456
	p75	.	.	.	$-0.000	$-0.001	$-0.002	$-0.052	$-0.259	$-0.466	$-9.273	$-46.364	$-83.456
	p95	.	.	.	$-0.000	$-0.001	$-0.002	$-0.052	$-0.259	$-0.466	$-9.273	$-46.364	$-83.456
bevacizumab	mean	$1.175	$0.740	$0.336	$88.202	$76.388	$68.972	$7.097	$6.085	$5.068	$1,347.571	$1,015.531	$821.524
	p5	$0.059	$0.274	$0.591	$9.845	$3.830	$-1.147	$0.846	$0.091	$-0.516	$92.693	$-45.226	$-195.537
	p25	$0.202	$0.134	$0.450	$21.694	$15.529	$10.191	$1.837	$1.021	$0.422	$234.945	$82.122	$-57.191
	p50	$0.439	$0.108	$0.219	$41.680	$34.640	$28.391	$3.521	$2.605	$1.889	$485.167	$304.187	$176.507
	p75	$1.082	$0.707	$0.306	$88.794	$77.916	$72.297	$7.533	$6.301	$5.446	$1,084.290	$900.568	$754.389
	p95	$4.392	$3.635	$3.005	$314.148	$292.353	$256.861	$26.687	$23.617	$20.724	$4,041.768	$3,835.847	$3,650.629
bortezomib	mean	$12.475	$12.233	$12.296	$40.489	$40.872	$41.084	$8.919	$7.849	$7.071	$927.908	$834.510	$773.418
	p5	$6.853	$6.798	$6.788	$13.910	$10.343	$7.394	$4.938	$3.896	$3.052	$516.008	$429.111	$360.946

	p25	$9.505	$9.381	$9.288	$21.484	$18.315	$14.662	$6.838	$5.788	$4.949	$710.961	$618.435	$545.222
	p50	$11.804	$11.536	$11.661	$30.180	$26.856	$23.706	$8.490	$7.364	$6.650	$886.540	$782.080	$729.105
	p75	$14.748	$14.322	$14.510	$43.671	$42.072	$37.320	$10.484	$9.407	$8.731	$1,087.221	$998.719	$949.070
	p95	$20.327	$20.178	$19.972	$92.362	$95.376	$90.331	$14.388	$13.301	$12.652	$1,510.941	$1,395.991	$1,345.148
cabazitaxel	mean	.	.	.	$1.206	$0.944	$0.649	$3.593	$2.493	$1.294	$125.192	$72.509	$15.447
	p5	.	.	.	$0.195	$-0.079	$-0.366	$0.510	$-0.630	$-1.812	$14.127	$-39.513	$-95.487
	p25	.	.	.	$0.415	$0.144	$-0.141	$1.185	$0.057	$-1.121	$38.610	$-15.649	$-70.451
	p50	.	.	.	$0.744	$0.479	$0.193	$2.220	$1.071	$-0.115	$75.439	$22.397	$-35.418
	p75	.	.	.	$1.412	$1.173	$0.861	$4.230	$3.203	$1.958	$147.598	$97.749	$36.804
	p95	.	.	.	$4.106	$3.983	$3.489	$12.586	$11.733	$10.156	$436.337	$395.101	$338.195
cabozantinib	mean	.	.	.	.	.	.	$-0.051	$-0.253	$-0.456	.	.	.
	p5	.	.	.	.	.	.	$-0.051	$-0.253	$-0.456	.	.	.
	p25	.	.	.	.	.	.	$-0.051	$-0.253	$-0.456	.	.	.
	p50	.	.	.	.	.	.	$-0.051	$-0.253	$-0.456	.	.	.
	p75	.	.	.	.	.	.	$-0.051	$-0.253	$-0.456	.	.	.
	p95	.	.	.	.	.	.	$-0.051	$-0.253	$-0.456	.	.	.
catumaxomab	mean	.	.	.	.	.	.	$-0.021	$-0.107	$-0.192	.	.	.
	p5	.	.	.	.	.	.	$-0.021	$-0.107	$-0.192	.	.	.
	p25	.	.	.	.	.	.	$-0.021	$-0.107	$-0.192	.	.	.
	p50	.	.	.	.	.	.	$-0.021	$-0.107	$-0.192	.	.	.
	p75	.	.	.	.	.	.	$-0.021	$-0.107	$-0.192	.	.	.
	p95	.	.	.	.	.	.	$-0.021	$-0.107	$-0.192	.	.	.
clofarabine	mean	$-0.013	$-0.063	$-0.113	$-0.085	$-0.423	$-0.761	$-0.074	$-0.372	$-0.669	$-0.281	$-1.406	$-2.530
	p5	$0.013	$0.063	$0.113	$-0.085	$-0.423	$-0.761	$-0.074	$-0.372	$-0.669	$-0.281	$-1.406	$-2.530
	p25	$0.013	$0.063	$0.113	$-0.085	$-0.423	$-0.761	$-0.074	$-0.372	$-0.669	$-0.281	$-1.406	$-2.530
	p50	$0.013	$0.063	$0.113	$-0.085	$-0.423	$-0.761	$-0.074	$-0.372	$-0.669	$-0.281	$-1.406	$-2.530
	p75	$0.013	$0.063	$0.113	$-0.085	$-0.423	$-0.761	$-0.074	$-0.372	$-0.669	$-0.281	$-1.406	$-2.530
	p95	$0.013	$0.063	$0.113	$-0.085	$-0.423	$-0.761	$-0.074	$-0.372	$-0.669	$-0.281	$-1.406	$-2.530
crizotinib	mean	$1.118	$1.131	$1.024	$1.849	$1.381	$0.702	$0.236	$0.157	$0.050	$11.797	$6.757	$0.316
	p5	$0.313	$0.298	$0.281	$0.430	$-0.088	$-0.608	$0.051	$-0.034	$-0.120	$2.372	$-3.000	$-8.383
	p25	$0.512	$0.493	$0.477	$0.780	$0.257	$-0.263	$0.097	$0.011	$-0.075	$4.698	$-0.710	$-6.090
	p50	$0.735	$0.726	$0.709	$1.173	$0.668	$0.146	$0.148	$0.064	$-0.022	$7.308	$2.021	$-3.374
	p75	$1.181	$1.145	$1.123	$1.960	$1.406	$0.877	$0.250	$0.160	$0.073	$12.530	$6.923	$1.478
	p95	$2.894	$2.953	$2.451	$4.981	$4.596	$3.220	$0.642	$0.574	$0.377	$32.594	$28.103	$17.033
degarelix	mean	$-0.000	$-0.002	$-0.004	$-0.199	$-0.995	$-1.790	$-0.006	$-0.029	$-0.053	$-0.588	$-2.940	$-5.293
	p5	$0.000	$0.002	$0.004	$-0.199	$-0.995	$-1.790	$-0.006	$-0.029	$-0.053	$-0.588	$-2.940	$-5.293
	p25	$0.000	$0.002	$0.004	$-0.199	$-0.995	$-1.790	$-0.006	$-0.029	$-0.053	$-0.588	$-2.940	$-5.293
	p50	$0.000	$0.002	$0.004	$-0.199	$-0.995	$-1.790	$-0.006	$-0.029	$-0.053	$-0.588	$-2.940	$-5.293
	p75	$0.000	$0.002	$0.004	$-0.199	$-0.995	$-1.790	$-0.006	$-0.029	$-0.053	$-0.588	$-2.940	$-5.293
	p95	$0.000	$0.002	$0.004	$-0.199	$-0.995	$-1.790	$-0.006	$-0.029	$-0.053	$-0.588	$-2.940	$-5.293
enzalutamide	mean	$3.999	$3.786	$3.246	$12.152	$11.320	$9.489	$11.122	$9.435	$6.814	$32.188	$22.669	$10.355
	p5	$1.354	$0.926	$0.483	$4.084	$2.596	$1.061	$3.587	$1.287	$-1.058	$9.624	$-1.730	$-13.218

	p25	$2.141	$1.656	$1.253	$6.485	$4.823	$3.409	$5.830	$3.366	$1.135	$16.340	$4.497	$-6.651
	p50	$3.016	$2.539	$2.168	$9.155	$7.516	$6.199	$8.323	$5.882	$3.742	$23.806	$12.029	$1.155
	p75	$4.585	$4.028	$3.695	$13.942	$12.056	$10.858	$12.794	$10.122	$8.093	$37.194	$24.727	$14.184
	p95	$9.749	$9.585	$9.217	$29.693	$29.009	$27.702	$27.506	$25.956	$23.825	$81.247	$72.141	$61.291
eribulin	mean	.	.	.	$22.383	$19.628	$17.458	$2.369	$1.869	$1.426	$4.217	$2.851	$1.586
	p5	.	.	.	$5.356	$2.773	$0.646	$0.525	$0.047	$-0.388	$0.843	$-0.487	$-1.743
	p25	.	.	.	$9.415	$7.163	$4.744	$0.968	$0.508	$0.047	$1.659	$0.346	$-0.938
	p50	.	.	.	$15.125	$12.605	$10.237	$1.572	$1.082	$0.631	$2.796	$1.429	$0.164
	p75	.	.	.	$26.455	$23.237	$21.639	$2.770	$2.258	$1.858	$5.030	$3.566	$2.304
	p95	.	.	.	$63.224	$58.635	$58.387	$6.915	$6.242	$5.916	$12.764	$11.016	$10.120
erlotinib	mean	$0.628	$0.593	$0.596	$69.123	$67.498	$70.107	$4.657	$4.363	$4.358	$59.742	$56.962	$57.863
	p5	$0.071	$0.029	$0.010	$8.365	$5.975	$4.009	$0.523	$0.178	$-0.139	$6.929	$3.485	$0.410
	p25	$0.144	$0.105	$0.066	$16.253	$14.246	$12.280	$1.060	$0.741	$0.424	$13.786	$10.674	$7.599
	p50	$0.262	$0.219	$0.184	$29.186	$26.781	$25.194	$1.940	$1.593	$1.302	$25.028	$21.570	$18.824
	p75	$0.534	$0.484	$0.456	$58.876	$55.652	$54.854	$3.959	$3.557	$3.320	$50.835	$46.665	$44.604
	p95	$1.972	$1.904	$2.097	$215.788	$210.620	$233.948	$14.634	$14.099	$15.504	$187.226	$181.367	$200.277
everolimus	mean	.	.	.	$5.264	$5.276	$4.902	$6.113	$6.124	$5.687	$297.386	$293.084	$266.880
	p5	.	.	.	$1.481	$1.307	$1.173	$1.719	$1.514	$1.355	$82.765	$67.897	$55.311
	p25	.	.	.	$2.436	$2.230	$2.041	$2.829	$2.586	$2.364	$136.974	$120.280	$104.595
	p50	.	.	.	$3.536	$3.429	$3.243	$4.106	$3.980	$3.760	$199.362	$188.333	$172.788
	p75	.	.	.	$5.614	$5.493	$5.455	$6.520	$6.376	$6.329	$317.241	$305.383	$298.255
	p95	.	.	.	$13.773	$13.249	$13.517	$15.997	$15.385	$15.693	$780.181	$745.453	$755.637
gefitinib	mean	$-0.031	$-0.157	$-0.282	.	.	.	$-0.028	$-0.141	$-0.253	$-29.418	$-147.092	$-264.766
	p5	$0.031	$0.157	$0.282	.	.	.	$-0.028	$-0.141	$-0.253	$-29.418	$-147.092	$-264.766
	p25	$0.031	$0.157	$0.282	.	.	.	$-0.028	$-0.141	$-0.253	$-29.418	$-147.092	$-264.766
	p50	$0.031	$0.157	$0.282	.	.	.	$-0.028	$-0.141	$-0.253	$-29.418	$-147.092	$-264.766
	p75	$0.031	$0.157	$0.282	.	.	.	$-0.028	$-0.141	$-0.253	$-29.418	$-147.092	$-264.766
	p95	$0.031	$0.157	$0.282	.	.	.	$-0.028	$-0.141	$-0.253	$-29.418	$-147.092	$-264.766
ipilimumab	mean	.	.	.	$68.124	$67.035	$66.704	$3.590	$1.523	$-0.389	$430.738	$205.445	$281.465
	p5	.	.	.	$29.049	$28.968	$29.335	$1.401	$-0.621	$-2.592	$98.243	$-74.943	$-257.561
	p25	.	.	.	$43.689	$42.109	$42.715	$2.236	$0.274	$-1.728	$181.900	$3.903	$-178.278
	p50	.	.	.	$57.828	$56.439	$57.630	$3.098	$1.104	$-0.869	$285.339	$94.324	$-93.308
	p75	.	.	.	$79.556	$78.458	$78.507	$4.316	$2.284	$0.301	$439.825	$246.644	$68.767
	p95	.	.	.	$134.118	$132.509	$131.864	$7.095	$5.113	$3.347	$895.408	$682.969	$594.845
lapatinib	mean	$0.012	$0.010	$0.009	$9.371	$8.238	$7.272	$6.421	$5.541	$4.776	$286.026	$242.475	$204.083
	p5	$0.001	$0.000	$0.001	$1.151	$0.194	$-0.565	$0.767	$0.008	$-0.615	$33.225	$-4.912	$-36.959
	p25	$0.004	$0.002	$0.001	$2.824	$1.985	$1.122	$1.917	$1.240	$0.545	$84.667	$50.178	$14.917
	p50	$0.007	$0.006	$0.004	$5.277	$4.525	$3.679	$3.605	$2.987	$2.305	$160.115	$128.300	$93.572
	p75	$0.014	$0.013	$0.011	$10.817	$10.268	$8.709	$7.415	$6.938	$5.765	$330.502	$304.924	$248.270
	p95	$0.044	$0.039	$0.038	$33.399	$30.401	$29.247	$22.949	$20.786	$19.892	$1,025.031	$924.129	$879.937
nelarabine	mean	.	.	.	$-0.030	$-0.152	$-0.274	$-0.008	$-0.039	$-0.071	$-0.585	$-2.927	$-5.269
	p5	.	.	.	$-0.030	$-0.152	$-0.274	$-0.008	$-0.039	$-0.071	$-0.585	$-2.927	$-5.269

	p25	.	.	.	$-0.030	$-0.152	$-0.274	$-0.008	$-0.039	$-0.071	$-0.585	$-2.927	$-5.269
	p50	.	.	.	$-0.030	$-0.152	$-0.274	$-0.008	$-0.039	$-0.071	$-0.585	$-2.927	$-5.269
	p75	.	.	.	$-0.030	$-0.152	$-0.274	$-0.008	$-0.039	$-0.071	$-0.585	$-2.927	$-5.269
	p95	.	.	.	$-0.030	$-0.152	$-0.274	$-0.008	$-0.039	$-0.071	$-0.585	$-2.927	$-5.269
ofatumumab	mean	.	.	.	$-0.039	$-0.197	$-0.354	$-0.027	$-0.135	$-0.243	$-0.302	$-1.509	$-2.716
	p5	.	.	.	$-0.039	$-0.197	$-0.354	$-0.027	$-0.135	$-0.243	$-0.302	$-1.509	$-2.716
	p25	.	.	.	$-0.039	$-0.197	$-0.354	$-0.027	$-0.135	$-0.243	$-0.302	$-1.509	$-2.716
	p50	.	.	.	$-0.039	$-0.197	$-0.354	$-0.027	$-0.135	$-0.243	$-0.302	$-1.509	$-2.716
	p75	.	.	.	$-0.039	$-0.197	$-0.354	$-0.027	$-0.135	$-0.243	$-0.302	$-1.509	$-2.716
	p95	.	.	.	$-0.039	$-0.197	$-0.354	$-0.027	$-0.135	$-0.243	$-0.302	$-1.509	$-2.716
panitumumab	mean	$0.275	$0.243	$0.203	$14.643	$12.904	$11.839	$1.553	$1.288	$1.072	$72.289	$61.432	$44.133
	p5	$0.062	$0.024	$0.018	$3.764	$2.254	$0.765	$0.426	$0.168	$-0.054	$13.272	$-5.893	$-23.175
	p25	$0.110	$0.072	$0.036	$6.577	$5.063	$3.866	$0.746	$0.483	$0.256	$25.428	$7.392	$-9.134
	p50	$0.172	$0.136	$0.102	$10.106	$8.511	$7.477	$1.111	$0.864	$0.640	$43.352	$24.973	$8.201
	p75	$0.299	$0.262	$0.223	$16.438	$15.144	$13.993	$1.802	$1.508	$1.329	$77.522	$56.362	$43.845
	p95	$0.698	$0.733	$0.665	$40.555	$35.532	$35.288	$4.055	$3.651	$3.386	$210.949	$186.408	$168.093
pertuzumab	mean	$2.486	$2.340	$2.192	$1.124	$1.044	$0.964	$36.223	$32.111	$27.983	$245.204	$214.891	$184.460
	p5	$0.835	$0.705	$0.546	$0.375	$0.303	$0.218	$11.844	$7.969	$3.670	$79.770	$51.062	$19.471
	p25	$1.317	$1.181	$1.043	$0.594	$0.519	$0.443	$18.964	$14.996	$11.014	$128.087	$98.745	$69.310
	p50	$1.886	$1.785	$1.656	$0.852	$0.793	$0.721	$27.365	$23.923	$20.067	$185.093	$159.328	$130.742
	p75	$2.803	$2.808	$2.652	$1.267	$1.256	$1.173	$40.905	$39.021	$34.779	$276.977	$261.782	$230.578
	p95	$6.115	$6.000	$5.806	$2.769	$2.704	$2.603	$89.817	$86.169	$81.354	$608.898	$581.728	$546.635
regorafenib	mean	$0.006	$-0.011	$-0.028	$11.887	$9.549	$7.042	$0.213	$0.151	$0.087	$17.523	$9.390	$0.993
	p5	$0.002	$0.019	$0.036	$2.661	$-0.275	$-2.961	$0.044	$-0.028	$-0.096	$3.056	$-6.015	$-14.692
	p25	$0.000	$0.017	$0.034	$5.274	$2.425	$-0.045	$0.092	$0.021	$-0.043	$7.153	$-1.780	$-10.120
	p50	$0.003	$0.014	$0.030	$9.071	$6.278	$3.822	$0.161	$0.091	$0.028	$13.107	$4.260	$-4.057
	p75	$0.008	$0.008	$0.025	$15.060	$13.432	$11.231	$0.271	$0.222	$0.163	$22.499	$15.479	$7.562
	p95	$0.022	$0.006	$0.012	$32.350	$30.759	$27.346	$0.587	$0.539	$0.458	$49.610	$42.648	$32.830
temsirolimus	mean	.	.	.	$150.076	$154.665	$157.533	$5.180	$5.088	$4.937	.	.	.
	p5	.	.	.	$18.395	$14.766	$11.784	$0.580	$0.201	$-0.154	.	.	.
	p25	.	.	.	$37.384	$36.309	$32.094	$1.243	$0.954	$0.555	.	.	.
	p50	.	.	.	$71.865	$73.537	$65.236	$2.447	$2.254	$1.713	.	.	.
	p75	.	.	.	$141.393	$152.762	$154.454	$4.876	$5.022	$4.829	.	.	.
	p95	.	.	.	$563.022	$566.708	$645.863	$19.604	$19.482	$21.995	.	.	.
trastuzumab emtansine	mean	$0.628	$0.601	$0.535	$36.573	$35.624	$41.214	$57.504	$49.744	$28.784	$503.639	$407.552	$250.324
	p5	$0.099	$0.040	$0.014	$6.186	$1.388	$-3.134	$10.375	$-4.456	$-20.312	$65.553	$-61.413	$-182.011
	p25	$0.197	$0.151	$0.098	$12.442	$8.126	$3.334	$20.240	$6.293	$-9.189	$145.443	$26.125	$-102.018
	p50	$0.355	$0.314	$0.246	$21.691	$18.258	$12.229	$35.521	$22.980	$5.640	$264.126	$159.857	$23.809
	p75	$0.659	$0.656	$0.579	$39.336	$37.782	$31.662	$62.152	$55.922	$36.368	$511.452	$463.204	$291.467
	p95	$1.988	$2.101	$1.926	$116.841	$125.858	$106.229	$177.596	$187.552	$145.593	$1,588.745	$1,602.605	$1,358.096
vorinostat	mean	.	.	.	.	.	.	.	.	.	$-0.189	$-0.943	$-1.697
	p5	.	.	.	.	.	.	.	.	.	$-0.189	$-0.943	$-1.697

	p25	.	.	.	.	.	.	.	.	.	$-0.189	$-0.943	$-1.697
	p50	.	.	.	.	.	.	.	.	.	$-0.189	$-0.943	$-1.697
	p75	.	.	.	.	.	.	.	.	.	$-0.189	$-0.943	$-1.697
	p95	.	.	.	.	.	.	.	.	.	$-0.189	$-0.943	$-1.697
ziv-aflibercept	mean	.	.	.	$31.210	$26.441	$25.403	$0.008	$0.006	$0.005	$39.090	$15.255	$128.831
	p5	.	.	.	$4.364	$1.694	$-0.883	$0.001	$-0.000	$-0.002	$1.249	$-15.563	$-32.223
	p25	.	.	.	$9.471	$6.299	$4.267	$0.002	$0.001	$-0.000	$6.831	$-10.064	$-26.252
	p50	.	.	.	$16.921	$13.498	$12.046	$0.004	$0.003	$0.002	$16.186	$-0.743	$-16.514
	p75	.	.	.	$33.213	$28.262	$28.643	$0.009	$0.007	$0.006	$36.931	$17.944	$3.828
	p95	.	.	.	$111.218	$96.538	$93.203	$0.031	$0.024	$0.024	$151.669	$107.569	$97.493

Source:

Authors' analysis of data, as described in Methods section.

Notes:

[1] Currencies are given in terms of 2015 billion US dollars. As explained in Chapter 3, outliers where the mean drug cost per patient was >$250,000 were censored (abiraterone, FR, Yo-2; erlotinib, (b) (4) ; cabazitaxel, AU, Yo; ipilimumab, AU, Yo).
[2] SD: standard deviation; p25: 25th percentile; p50: 50th percentile; p75: 75th percentile.
[3] DoT modeled as: (b) (4)

Appendix 4.7

eTable 11. Incidence-Adjusted Cost, Effect and Incremental Cost-Effectiveness Ratio, Adjusted to Reflect a Maximum Expected Patient Population Equal to 1.5x the Yearly Number of Incident Cases, 2004-2014

Country	Cost[1,2]			Effect[1,3]			ICER[1,2,4]
	t = 2004	t = 2014	Δ t	t = 2004	t = 2014	Δ t[4]	
Australia	**$11,676.36**	**$17,665.41**	**$5,989.05**	**4.203**	**3.221**	**0.981**	**$5,305.78**
France	**$17,067.51**	**$24,553.63**	**$7,486.11**	**5.248**	**3.837**	**1.411**	**$6,102.50**
UK	**$10,307.28**	**$21,743.14**	**$11,435.86**	**4.820**	**3.683**	**1.138**	**$10,050.91**
US	**$25,714.15**	**$49,279.66**	**$23,565.51**	**4.465**	**3.750**	**0.715**	**$32,973.07**

Source:

Authors' analysis of data, as described Methods section.

Notes:

[1] Adjusted to reflect incidence-adjusted expenditure (cost, C) or YPLLs (effect, E), where incidence is adjusted to reflect 1.5x the expected number of incident neoplasm cases.

[2] Figures given in terms of constant 2014 US dollars.

[3] Effect is given in terms of YPLLs.

[4] For convenience, values for the change in YPLL between 2004-2014 are multiplied by -1.

[5] Country records sorted by ICER estimates.

[6] Values may not sum due to rounding errors.

Appendix 4.8

eTable 12. Net Value from Cancer Drug Spending, per Neoplasm and to Society, Adjusted to Reflect a Maximum Expected Patient Population Equal to 1.5x the Yearly Number of Incident Cases, 2004-2014

Country	Net Value per Neoplasm[1,2]					Net Value to Society3				
	10%	25%	50%	75%	90%	10%	25%	50%	75%	90%
France	$6,623.23	$27,787.25	$63,060.61	$98,333.97	$119,497.99	$3.69	$15.50	$35.18	$54.85	$66.66
UK	$-57.93	$17,008.97	$45,453.80	$73,898.62	$90,965.52	-$0.03	$8.80	$23.50	$38.21	$47.04
Australia	$3,825.04	$18,546.19	$43,081.43	$67,616.67	$82,337.81	$0.74	$3.58	$8.32	$13.06	$15.90
US	$-16,418.61	$-5,698.27	$12,168.97	$30,036.21	$40,756.56	-$39.96	-$13.87	$29.61	$73.10	$99.18

Source:

Authors' analysis of data, as described Methods section.

Notes:

[1] Adjusted to reflect incidence-adjusted expenditure (cost, C) or YPLLs (effect, E).

[2] Figures given in terms of constant 2014 US dollars.

[3] Figures given in terms of billion, constant 2014 US dollars.

[4] Country records sorted by estimates of the net value generated per neoplasm, where the assumed percentage of health gains observed owing to cancer drug care equaled 50%.

[5] Values may not sum due to rounding errors.

Appendix 4.9

eTable 13. Net Value from Cancer Drug Spending, per Neoplasm and to Society, Assuming 10%-90% of Survival Gains are Attributable to Drug Development, 2004-2014

Country	Net Value per Neoplasm[1,2]					Net Value to Society[3]				
	10%	25%	50%	75%	90%	10%	25%	50%	75%	90%
France	$9,305.05	$40,106.37	$91,441.91	$142,777.46	$173,578.78	$3.46	$14.91	$34.01	$53.10	$64.55
UK	-$748.65	$23,859.06	$64,871.91	$105,884.76	$130,492.47	-$0.26	$8.22	$22.36	$36.50	$44.98
Australia	$5,737.56	$27,819.28	$64,622.14	$101,425.00	$123,506.71	$0.74	$3.58	$8.32	$13.06	$15.90
US	-$24,253.95	-$7,612.42	$20,123.46	$47,859.34	$64,500.87	-$39.35	-$12.35	$32.65	$77.65	$104.65

Source:

Authors' analysis of data, as described Methods section.

Notes:

[1] Adjusted to reflect incidence-adjusted expenditure (cost, C) or YPLLs (effect, E).

[2] Figures given in terms of constant 2014 US dollars.

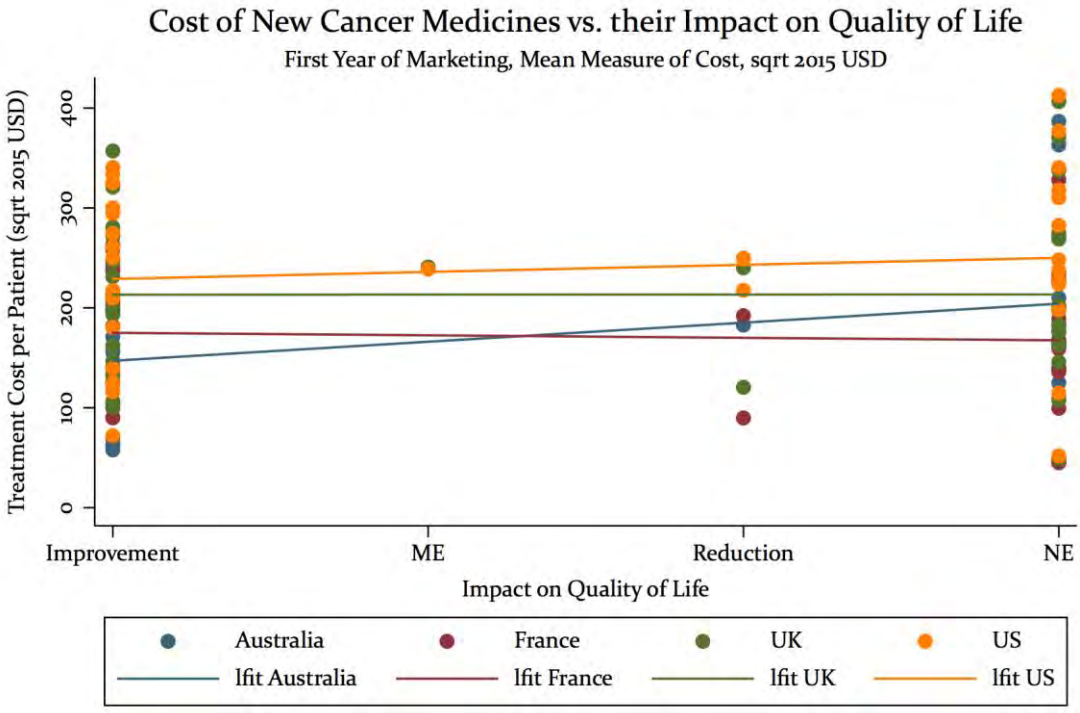
[3] Figures given in terms of billion, constant 2014 US dollars.

[4] Country records sorted by estimates of the net value generated per neoplasm when the percentage of long-term gains in YPLLs attributed to cancer drug innovation equals 50%.

[5] Values may not sum due to rounding errors.

Appendix 5.1

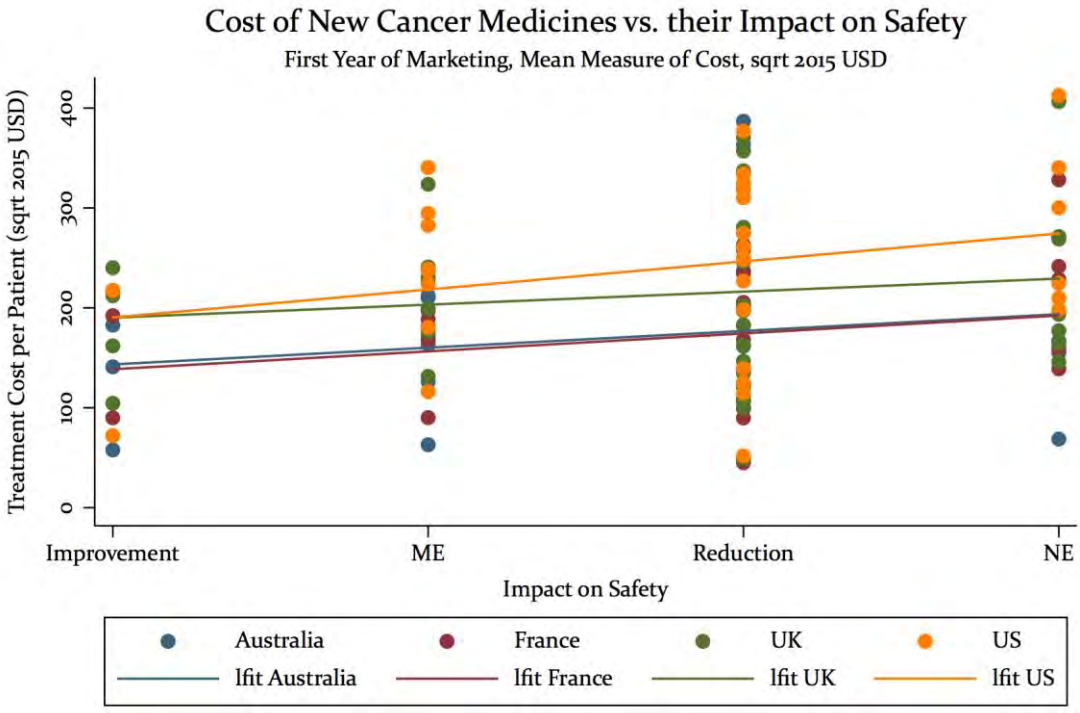
eFigure 4. Cost of New Cancer Medicines vs. their Impact on Quality of Life



Source: Authors' analysis of data, as described in Methods section
Note: ME = 'Mixed Evidence' NE = 'None Established'

Appendix 5.2

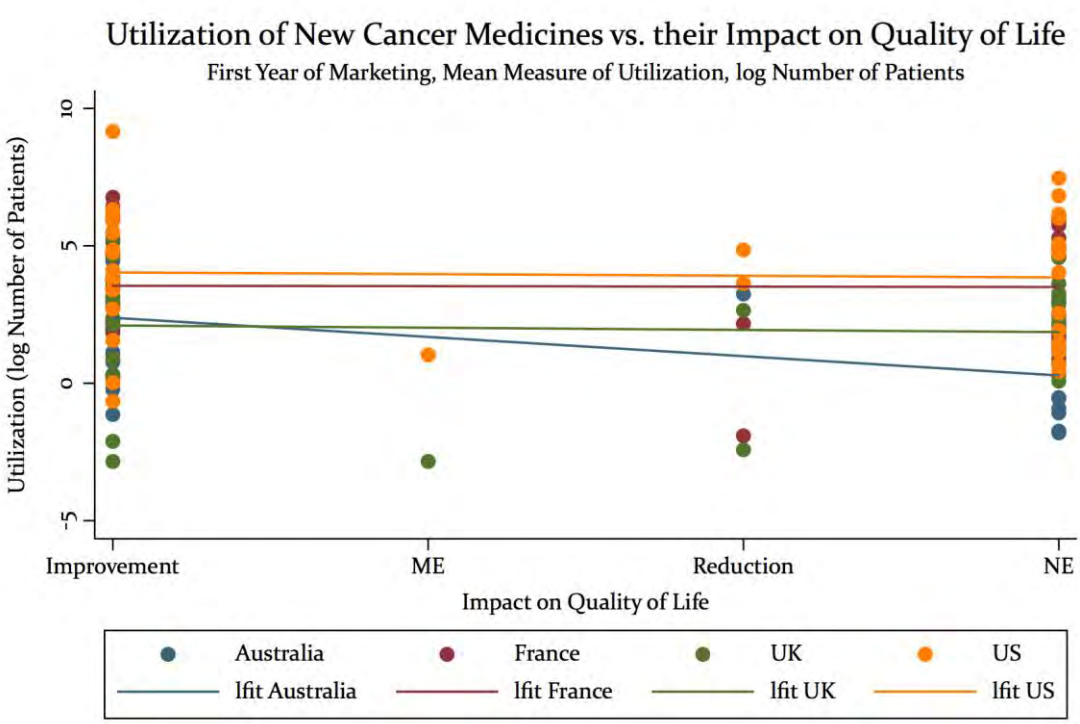
eFigure 5. Cost of New Cancer Medicines vs. their Impact on Safety



Source: Authors' analysis of data, as described in Methods section
Note: ME = 'Mixed Evidence' NE = 'None Established'

Appendix 5.3

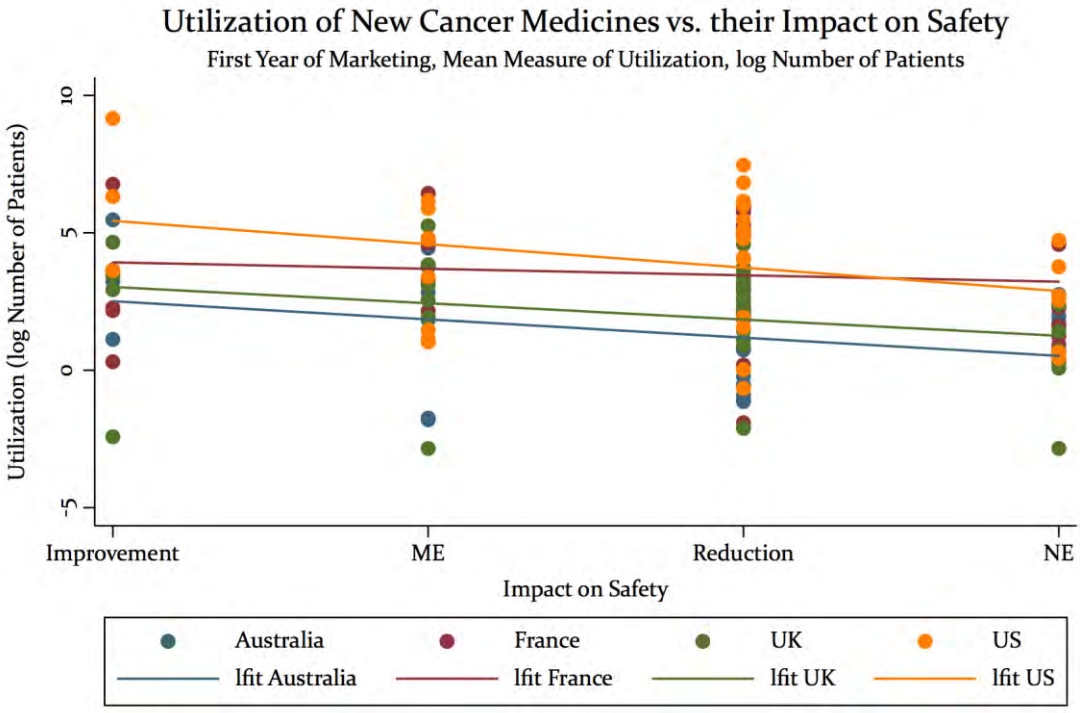
eFigure 6. Utilization of New Cancer Medicines vs. their Impact on Quality of Life



Source: Authors' analysis of data, as described in Methods section
Note: ME = 'Mixed Evidence' NE = 'None Established'

Appendix 5.4

eFigure 7. Utilization of New Cancer Medicines vs. their Impact on Safety



Source: Authors' analysis of data, as described in Methods section
Note: ME = 'Mixed Evidence' NE = 'None Established'

Appendix 5.5

eTable 14. Multivariate Linear Regression Analysis, Total Cost per Patient per (b) (4) Treatment with New Medicines and their Beneficial Impact to Health in the First Year of Drug Marketing in Australia, France, the UK, and the US

Variable	Model[1]									
	(A)	(B)	(C)	(D)	(E)	(F)	(G)	(H)	(I)	(J)
Dep. Var.	sqrt_TCp	sqrt_TCp	sqrt_TCp	sqrt_TCp	sqrt_TCp	sqrt_TCp	sqrt_TCp	sqrt_TCp	sqrt_TCp	sqrt_TCp
Ind. Var[2]	1	2	3	4	1, 2	1, 3	1, 4	1, 2, 3	1, 2, 4	1, 2, 3, 4
orphan	-3.135 [22.09]				40.88 [25.15]	25.76 [21.27]	24.78 [18.56]	38.34 [25.75]	43.45 [26.16]	46.15 [33.00]
breast	68.72* [26.83]				111.0* [50.51]	98.92** [36.17]	122.5* [49.88]	108.2 [55.48]	137.9* [62.34]	132.1 [69.16]
gi	55.13 [28.51]				130.2* [55.42]	81.68** [30.69]	113.9* [47.78]	111.6 [59.50]	150.8* [65.77]	133.6 [72.48]
hematologic al	99.45*** [14.23]				87.00* [43.75]	105.3*** [29.51]	110.9* [42.84]	94.23 [49.62]	102.9 [54.29]	104.1 [60.18]
lung	21.49 [27.67]				64.21 [49.62]	57.67 [38.31]	78.75 [46.57]	84.5 [56.62]	94.18 [59.42]	108.8 [66.79]
prostate	27.08 [33.97]				37.32 [55.55]	61.47 [43.36]	93.89 [54.52]	35.32 [59.12]	73.91 [66.72]	68.4 [72.63]
renal	14.23 [12.89]				-86.11 [44.63]	23.07 [26.21]	53.89 [43.63]	-78.28 [50.86]	-51.36 [60.45]	-58.48 [66.08
skin	89.16** [30.79]				124.3* [52.69]	144.1*** [42.32]	154.4** [50.30]	134.7* [58.01]	156.2* [65.33]	156.1* [72.91]
thyroid	188.1*** [22.09]				232.1*** [25.15]	217.0*** [21.27]	245.4*** [51.27]	229.6*** [25.75]	269.4*** [48.35]	265.6*** [53.62]
OS_>/=3 mo, unc		-11.55 [41.64]			156.0** [47.25]			105 [58.10]	151.8* [57.93]	113.3 [59.59]
OS_<3 mo		19.95 [70.49]			9.501 [71.53]			-36.56 [74.49]	6.25 [72.68]	-34.8 [74.39]
OS_inc, unc		-12.06 [38.29]			-50.5 [45.93]			-66.03 [58.13]	-58.59 [48.89]	-70.47 [62.10]
NE		-34.34 [62.78]			-9.267 [52.45]			-50.74 [58.25]	-19.77 [62.77]	-58.41 [64.97]
FR		19.9 [40.72]	29.49 [25.01]	13.91 [50.48]	67.04 [43.24]	47.83 [25.58]	14.65 [25.41]	73.85 [39.03]	63.3 [45.08]	73.59 [54.41]
UK		74.45 [43.12]	66.32* [26.64]	52.49 [42.54]	118.4** [43.58]	83.04** [27.17]	68.34* [27.54]	122.2** [40.10]	111.1* [46.58]	105.9* [52.49]
US		96.37* [42.40]	82.16** [28.27]	41.85 [53.37]	130.3** [47.45]	96.75** [30.38]	50.11 [39.90]	127.1** [46.74]	75.46 [57.99]	62.52 [61.87]
OS_>/=3 mo, unc # FR		-25.49 [49.54]			-86.25 [53.13]			-41.74 [63.47]	-91.7 [61.34]	-48.49 [71.42]
OS_>/=3 mo, unc # UK		-60.91 [54.13]			-118.5* [55.92]			-77.01 [65.58]	-126.9 [64.48]	-88.99 [73.17]
OS_>/=3 mo, unc # US		-46.83 [60.68]			-67.13 [68.41]			-37.36 [72.92]	-72.15 [81.95]	-42.46 [85.33]
OS_<3 mo # FR		-98.72 [73.98]			-139.5 [72.68]			-87.81 [77.21]	-133.5 [73.98]	-85.48 [77.22]
OS_<3 mo # UK		-122.3 [75.58]			-159.9* [73.49]			-111.3 [78.42]	-154.9* [75.07]	-112.6 [78.10]
OS_<3 mo # US		-105.1 [78.16]			-132.8 [76.54]			-94.07 [82.95]	-133.7 [77.53]	-98.48 [82.95]
OS_inc, unc # FR		8.479 [43.85]			-19 [44.18]			16.65 [60.84]	4.44 [49.22]	26.67 [65.43]

OS_inc, unc # UK		-8.09 [48.22]			-31.81 [47.50]			-9.862 [63.05]	-21.38 [53.49]	-7.969 [71.99]
OS_inc, unc # US		-14.09 [48.38]			-27.81 [50.83]			-6.974 [63.08]	-11.49 [56.14]	-1.269 [72.22]
OS_NE # FR		12.73 [77.99]			-46.14 [64.61]			-3.345 [68.96]	-45.54 [75.25]	-1.881 [76.87]
OS_NE # UK		-11.12 [78.69]			-72.46 [67.19]			-37.63 [72.92]	-65.06 [76.45]	-35.12 [79.26]
OS_NE # US		-3.359 [81.33]			-54.3 [73.51]			-32.11 [82.81]	-45.91 [79.94]	-27.54 [86.13]
QoL_ME			9.484 [22.97]			-38.78 [25.60]		-7.048 [29.43]		-6.929 [55.21]
QoL_reduce			35.62* [16.49]			-36.85 [36.65]		16.64 [37.23]		11.03 [73.62]
QoL_NE			57.31 [41.98]			75.2 [42.96]		81.38 [43.00]		79.57 [45.31]
QoL_ME # UK			17.99 [31.07]			15.86 [29.30]		10.01 [39.35]		13.22 [69.07]
QoL_reduce # FR			-71.25 [45.95]			-44.44 [40.39]		-71.34 [56.18]		-55.96 [91.63]
QoL_reduce # UK			-68.77 [52.32]			-40.33 [46.35]		-49.94 [59.38]		-25.03 [92.56]
QoL_reduce # US			-31.28 [30.76]			-13.59 [38.05]		-24.96 [56.22]		12.95 [83.68]
QoL_NE # FR			-63.39 [49.98]			-89.77 [49.27]		-75.7 [48.55]		-80.55 [50.76]
QoL_NE # UK			-55.16 [52.94]			-87.67 [51.49]		-66.58 [50.78]		-68.88 [53.68]
QoL_NE # US			-35.64 [54.04]			-61.51 [53.66]		-41.17 [55.93]		-49.72 [59.52]
safety_ME				30.37 [39.36]			41.36 [38.02]		-12.05 [55.40]	-28.79 [75.59]
safety_reduce				67.54 [47.77]			71.38 [42.39]		40.77 [39.98]	18.7 [50.64]
safety_NE				38.24 [50.22]			22.42 [44.37]		-5.905 [59.99]	-33.7 [76.55]
safety_ME # FR				5.82 [58.66]			17.47 [40.92]		30.97 [61.22]	26.47 [93.09]
safety_ME # UK				8.447 [53.18]			-0.984 [44.84]		37.22 [62.89]	45.73 [88.22]
safety_ME # US				39.88 [63.04]			36.65 [57.64]		77.83 [70.83]	93.52 [93.28]
safety_reduce # FR				-51.76 [64.06]			-47.71 [46.21]		-36.97 [39.78]	-30.06 [59.01]
safety_reduce # UK				-35.98 [60.62]			-57.77 [49.77]		-29.89 [47.32]	-10.08 [59.36]
safety_reduce # US				1.121 [68.20]			-5.198 [56.80]		26.49 [55.82]	47.02 [64.73]
safety_NE # FR				39.98 [71.21]			52.37 [59.51]		59 [71.32]	61.81 [91.41]
safety_NE # UK				14.65 [66.83]			20.61 [62.02]		51.56 [73.24]	70.5 [90.16]
safety_NE # US				73.7 [74.15]			72.83 [67.61]		106.4 [78.15]	127.9 [92.51]
Constant	149.2*** [22.09]	177.2*** [35.15]	147.1*** [16.49]	127.1*** [32.23]	68.49 [72.01]	49.68 [42.16]	9.865 [52.39]	59.09 [72.27]	30.69 [76.02]	39.95 [79.19]
Observations	131	119	119	119	119	119	119	119	119	119
R^2	0.161	0.244	0.147	0.188	0.485	0.308	0.306	0.527	0.535	0.564
Adj R^2	0.099	0.099	0.041	0.07	0.325	0.149	0.129	0.303	0.296	0.244

Source:

Authors' analysis of data, as described in Methods section.

Notes:

[1] Sensitivity analysis with a sqrt transformation of the dependent variable, total cost per patient per (b) (4) treatment in the first year of marketing (mean estimate (b) (4) from Chapter 3), assuming treatment duration (b) (4) Overall survival is coded as a categorical variable, as described in Methods section.

[2] 1: Treatment descriptors (treated condition, rarity); 2: OS; 3: QoL; 4: safety.

[3] Reference categories: ascites; AU; OS: >/=3 months improvement, certain; QoL: improve; safety: improve.

[4] Standard errors (SE) are provided in brackets. ***: p ≤ 0.01, **: p ≤ 0.05, *: p ≤ 0.10

Appendix 5.6

eTable 15. Multivariate Linear Regression Analysis, Total Number of Patients Completing [redacted] Therapy with New Medicines per 100,000 Incident Cases of Neoplasm and their Beneficial Impact to Health in the First Year of Drug Marketing in Australia, France, the UK, and the US

Variable	Model[1]									
	(A)	(B)	(C)	(D)	(E)	(F)	(G)	(H)	(I)	(J)
Dep. Var.	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi
Ind. Var[2]	1	2	3	4	1, 2	1, 3	1, 4	1, 2, 3	1, 2, 4	1, 2, 3, 4
orphan	-0.17 [0.624]				-0.0287 [0.576]	-0.516 [0.621]	0.487 [0.633]	-0.708 [0.610]	0.156 [0.644]	-0.622 [0.593]
breast	1.973** [0.726]				0.443 [0.870]	0.748 [0.750]	0.0682 [0.958]	-0.0584 [0.967]	-0.469 [0.967]	-1.208 [0.904]
gi	2.039* [0.849]				0.98 [0.926]	1.244 [0.785]	0.551 [0.971]	0.544 [0.944]	0.479 [1.027]	-0.321 [0.957]
hematological	0.42 [0.366]				-0.494 [0.513]	-0.329 [0.476]	-1.628** [0.556]	-0.38 [0.554]	-1.253** [0.520]	-1.098* [0.520]
lung	1.527* [0.727]				0.634 [0.764]	0.00962 [0.857]	-0.384 [0.821]	0.0209 [0.885]	-0.516 [0.842]	-1.154 [0.864]
prostate	1.844* [0.773]				0.37 [0.932]	0.748 [0.753]	-0.159 [0.954]	-0.148 [0.861]	-0.826 [1.015]	-1.63 [0.884]
renal	0.909 [0.591]				0.44 [0.904]	0.0258 [0.541]	-1.545 [0.861]	0.308 [1.063]	-0.777 [1.095]	-0.807 [1.129]
skin	0.476 [0.937]				-0.253 [1.011]	-0.405 [0.963]	-1.38 [1.025]	-0.901 [1.039]	-1.012 [1.028]	-1.661 [0.987]
thyroid	-0.138 [0.624]				0.00406 [0.576]	-0.483 [0.621]	-1.376 [0.954]	-0.675 [0.610]	-1.641 [0.917]	-2.794** [0.925]
OS_>/=3 mo, unc		-3.466*** [0.721]			-3.644*** [0.966]			-2.867* [1.212]	-3.642* [1.721]	-3.394** [1.211]
OS_<3 mo		-1.435 [1.017]			-1.945 [1.112]			-0.899 [0.959]	-1.773* [0.848]	-1.126 [0.776]
OS_inc, unc		-0.641 [1.051]			-0.372 [1.160]			-0.791 [1.411]	-0.5 [0.887]	-0.797 [1.389]
OS_NE		-0.291 [1.250]			-0.32 [1.244]			0.248 [1.132]	-0.0333 [0.894]	0.385 [0.994]
OS_FR		1.695* [0.822]	1.367 [0.755]	-0.492 [1.518]	1.674 [0.948]	1.104 [0.906]	-0.492 [1.603]	0.825 [1.012]	-0.0142 [1.708]	0.97 [2.103]
OS_UK		1.141 [0.663]	0.0493 [0.765]	-1.215 [1.674]	1.12 [0.763]	-0.185 [0.870]	-1.215 [1.458]	0.275 [0.822]	-0.214 [1.298]	0.302 [1.578]
OS_US		3.014*** [0.706]	1.818* [0.833]	2.999 [1.623]	3.006*** [0.823]	1.549 [0.941]	2.895* [1.384]	2.123* [0.849]	4.273* [1.720]	4.608* [2.216]
OS_>/=3 mo, unc # FR		3.082* [1.221]			3.113* [1.378]			2.486 [1.516]	2.909 [1.967]	2.651 [1.864]
OS_>/=3 mo, unc # UK		2.317** [0.824]			2.347* [0.964]			1.727 [0.964]	2.119 [1.629]	1.479 [1.200]
OS_>/=3 mo, unc # US		0.341 [1.518]			0.339 [1.600]			-0.709 [1.479]	0.689 [2.143]	-0.316 [1.413]
OS_<3 mo # FR		2.845* [1.218]			2.875* [1.332]			1.656 [1.280]	2.558* [1.158]	1.905 [1.137]
OS_<3 mo # UK		0.187 [1.451]			0.217 [1.597]			-0.996 [1.644]	0.0333 [1.548]	-0.658 [1.565]
OS_<3 mo # US		0.722 [1.279]			0.739 [1.364]			-0.448 [1.271]	0.735 [1.197]	-0.0726 [1.211]
OS_inc, unc # FR		0.0595 [1.670]			-0.014 [1.482]			1.267 [1.815]	-0.124 [1.391]	0.992 [1.898]

OS_inc, unc # UK		-3.211 [1.729]			-3.102 [1.684]			-2.023 [2.075]	-3.040* [1.727]	-1.49 [1.727]
OS_inc, unc # US		-1.796 [1.620]			-1.701 [1.519]			-1.338 [1.967]	-2.038 [1.514]	-1.464 [2.219]
OS_NE # FR		-2.17 [1.646]			-1.816 [1.644]			-2.169 [1.507]	-1.787 [1.636]	-1.935 [1.631]
OS_NE # UK		-1.67 [1.347]			-1.327 [1.330]			-1.972 [1.240]	-0.966 [1.075]	-1.211 [1.214]
OS_NE # US		-1.756 [1.710]			-1.355 [1.714]			-2.203 [1.910]	-1.528 [1.326]	-2.215 [1.520]
QoL_ME			-3.120*** [0.670]			-2.218** [0.834]		-1.135 [1.594]		-1.388 [2.062]
QoL_reduce			0.911 [0.495]			1.621 [0.936]		2.384 [1.325]		1.842 [1.778]
QoL_NE			-2.187** [0.697]			-2.852*** [0.758]		-2.233** [0.740]		-1.814* [0.740]
QoL_ME # UK			-2.109* [0.888]			-2.143* [0.920]		-1.345 [2.139]		-2.884 [2.361]
QoL_reduce # FR			-4.484** [1.707]			-4.775* [1.875]		-4.979* [1.875]		-4.906* [1.875]
QoL_reduce # UK			-3.181 [2.050]			-3.5 [2.137]		-2.897 [2.215]		-3.366 [2.492]
QoL_reduce # US			-0.822 [0.950]			-0.849 [1.128]		-0.491 [1.875]		-1.468 [2.894]
QoL_NE # FR			2.310* [1.039]			2.738* [1.069]		2.553* [1.079]		2.417* [1.129]
QoL_NE # UK			1.920* [0.962]			2.418* [0.995]		2.538* [1.076]		2.514* [1.096]
QoL_NE # US			1.922 [1.148]			2.362* [1.123]		2.557* [1.203]		2.587* [1.027]
safety_ME				-1.819 [1.366]			-2.105 [1.308]		-0.547 [1.252]	0.629 [1.450]
safety_reduce				-2.739** [0.958]			-3.223*** [0.812]		-2.484* [0.996]	-1.007 [1.421]
safety_NE				-1.587 [0.918]			-1.987* [0.813]		-1.428 [0.959]	0.119 [1.450]
safety_ME # FR				3.109 [1.956]			3.352 [2.017]		1.313 [1.857]	-0.671 [2.261]
safety_ME # UK				2.176 [2.219]			2.482 [2.073]		0.986 [1.746]	0.0197 [1.789]
safety_ME # US				-0.969 [2.094]			-0.451 [1.946]		-2.18 [1.979]	-3.32 [2.525]
safety_reduce # FR				3.747* [1.711]			3.841* [1.768]		2.865 [1.705]	0.599 [2.221]
safety_reduce # UK				2.985 [1.783]			3.139 [1.614]		2.531 [1.340]	0.586 [1.702]
safety_reduce # US				0.586 [1.798]			0.784 [1.578]		-0.307 [1.812]	-1.97 [2.370]
safety_NE # FR				0.824 [1.690]			1.13 [1.706]		0.911 [1.665]	-1.836 [2.354]
safety_NE # UK				-0.24 [1.823]			0.00782 [1.611]		-0.354 [1.323]	-2.746 [1.683]
safety_NE # US				-2.309 [1.801]			-1.778 [1.552]		-2.518 [1.933]	-4.377 [2.623]
Constant	1.579* [0.624]	2.207*** [0.555]	2.333*** [0.495]	3.371*** [0.828]	1.964 [1.149]	2.544* [1.119]	4.116*** [1.140]	3.260** [1.439]	4.248** [1.439]	4.482** [1.633]
Observations	137	125	125	125	125	125	125	125	125	125
R^2	0.101	0.445	0.33	0.325	0.478	0.418	0.409	0.555	0.577	0.647
Adj R^2	0.037	0.345	0.251	0.232	0.326	0.292	0.268	0.359	0.375	0.409

Source:

Authors' analysis of data, as described in Methods section.

Notes:

[1] Sensitivity analysis with a natural log transformation of the dependent variable, total number of patients completing [redacted] therapy in the first year of marketing per 100,000 incident cases of neoplasm (TPi)(mean estimate of distribution from Chapter 3), assuming treatment duration [redacted] Overall survival is coded as a categorical variable, as described in Methods section.

[2] 1: Treatment descriptors (treated condition, rarity); 2: OS; 3: QoL; 4: safety.

[3] Reference categories: ascites; AU; OS: >/=3 months improvement, certain; QoL: improve; safety: improve.

[4] Standard errors (SE) are provided in brackets. ***: p ≤ 0.01, **: p ≤ 0.05, *: p ≤ 0.10

Appendix 5.7

eTable 16. Multivariate Linear Regression Analysis, Total Cost per Patient per (b) (4) Treatment with New Medicines and their Beneficial Impact to Health in the Second Year of Drug Marketing in Australia, France, the UK, and the US

Variable	Model[1]									
	(A)	(B)	(C)	(D)	(E)	(F)	(G)	(H)	(I)	(J)
Dep. Var.	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp
Ind. Var[2]	1	2	3	4	1, 2	1, 3	1, 4	1, 2, 3	1, 2, 4	1, 2, 3, 4
orphan	-9.578 [22.33]				60.28 [33.46]	17.36 [20.99]	10.09 [21.84]	88.32** [29.05]	27.6 [35.57]	79.38* [36.04]
breast	108.7*** [27.80]				88.18* [43.80]	96.22** [32.86]	121.7* [47.24]	106.5* [40.42]	104.8 [55.76]	143.8* [54.97]
gi	80.61** [25.91]				94.83* [44.84]	65.13* [31.34]	95.06* [43.83]	101.7* [39.62]	88.89 [55.17]	118.4* [52.59]
hematologic al	146.2*** [15.08]				104.7*** [30.25]	124.2*** [25.18]	135.5*** [36.80]	109.7** [32.35]	121.3** [40.24]	125.7** [41.86]
lung	77.72** [26.07]				89.22* [43.06]	72.48* [34.78]	98.41* [42.77]	132.2** [45.97]	114.2* [46.73]	141.8* [56.52]
prostate	102.0* [40.38]				118.4* [44.68]	94.25* [45.06]	132.9* [56.20]	144.0** [49.28]	148.6** [54.16]	185.8** [61.23]
renal	73.36*** [14.30]				-37.07 [22.55]	42.94 [24.51]	84.47* [40.30]	-48.2 [32.69]	22.71 [47.85]	-11.37 [51.94]
skin	150.5*** [29.72]				218.2*** [44.01]	182.8*** [35.18]	186.1*** [50.01]	243.0*** [40.16]	235.6*** [54.45]	297.6*** [58.07]
OS		0.741 [3.991]			-2.099 [4.116]			5.744 [6.052]	-0.307 [5.037]	5.554 [7.764]
FR		-38.1 [45.10]	32.06 [23.54]	17.7 [55.89]	-29.75 [46.38]	50.71* [22.53]	19.88 [24.15]	90.40* [41.55]	24.49 [44.27]	62.46 [44.96]
UK		-4.359 [47.48]	65.63* [25.56]	47.41 [42.43]	1.65 [47.64]	85.00*** [24.73]	61.92** [23.00]	105.6* [43.67]	43.35 [35.91]	66.86 [35.18]
US		46.1 [51.02]	87.52** [26.95]	46.8 [56.38]	41.94 [50.67]	96.90** [28.71]	50.16 [37.49]	134.8* [58.82]	27.27 [47.22]	47.6 [47.56]
FR # OS		7.829 [4.986]			10.94* [4.597]			2.201 [5.331]	11.22 [5.689]	2.353 [7.024]
UK # OS		10.02 [5.786]			13.54** [4.942]			6.23 [5.684]	14.03* [6.167]	5.819 [7.653]
US # OS		6.621 [6.031]			9.27 [6.432]			2.571 [7.625]	9.445 [7.279]	-0.12 [8.980]
QoL_ME			1.393 [24.44]			-39.92 [27.16]				
QoL_reduce			29.68* [11.34]			-60.78 [35.50]		-29.52 [44.77]		-32.02 [61.58]
QoL_NE			50.41 [46.68]			79.32 [51.28]		152.1 [83.53]		150.3 [101.7]
QoL_ME # UK			20.07 [33.50]			10.08 [32.58]				
QoL_reduce # FR			-66.9 [51.97]			-38.91 [40.03]		-17.91 [35.72]		-12.95 [53.19]
QoL_reduce # UK			-68.83 [51.97]			-41.57 [41.34]		0 [.]		0 [.]
QoL_reduce # US			-41.8 [26.95]			-33.82 [33.65]		0 [.]		0 [.]
QoL_NE # FR			-65.86 [54.69]			-98.18 [56.02]		-172.2* [78.73]		-202.4* [97.43]

QoL_NE # UK			-55.74 [58.52]			-94.71 [57.30]		-152.3 [79.45]		-190.6 [100.5]
QoL_NE # US			-35.38 [59.06]			-64.82 [60.35]		-143.2 [86.92]		-207.9 [106.7]
safety_ME				34.18 [34.90]			58.68* [28.00]		42.45 [45.82]	-9.705 [43.30]
safety_reduce				52.56 [50.92]			77.9 [51.34]		102.6 [83.70]	-22.04 [64.48]
safety_NE				67.11 [54.41]			73.27 [52.23]		109.1 [70.35]	-13.5 [70.42]
safety_ME # FR				-5.483 [59.70]			-0.867 [33.88]		-49.58 [63.87]	1.857 [64.27]
safety_ME # UK				4.494 [50.16]			-9.634 [35.95]		-35.71 [66.71]	23.25 [70.04]
safety_ME # US				28.91 [63.00]			23.68 [49.43]		18.39 [69.39]	79.11 [77.58]
safety_reduce # FR				-31.43 [71.53]			-39.45 [54.95]		-103.3 [86.35]	35.29 [69.53]
safety_reduce # UK				-22.09 [64.33]			-42.44 [53.77]		-92.48 [82.83]	51.01 [74.39]
safety_reduce # US				18.24 [74.64]			10 [60.89]		-20.6 [92.36]	139.6 [94.18]
safety_NE # FR				-27.01 [78.91]			0.401 [64.14]		-43.65 [81.61]	86.09 [83.85]
safety_NE # UK				7.004 [72.69]			2.764 [65.30]		-21.62 [79.83]	112.4 [88.64]
safety_NE # US				40.15 [79.10]			37.06 [71.90]		45.81 [83.49]	198.5 [99.96]
Constant	102.9*** [22.33]	179.7*** [39.58]	153.8*** [11.34]	132.2*** [31.95]	62.84 [67.63]	44.15 [36.91]	-10.27 [50.63]	-65.29 [65.24]	-24.16 [53.32]	-69.01 [64.28]
Observation	119	85	111	111	85	111	111	85	85	85
R^2	0.12	0.2	0.144	0.174	0.361	0.299	0.279	0.441	0.458	0.518
Adj R^2	0.056	0.127	0.029	0.043	0.222	0.133	0.088	0.255	0.201	0.205

Source:

Authors' analysis of data, as described Methods section.

Notes:

[1] Sensitivity analysis with a sqrt transformation of the dependent variable, total cost per patient per (b) (4) treatment in the second year of marketing (mean estimate (b) (4) from Chapter 3), assuming treatment duration (b) (4)

[2] 1: Treatment descriptors (treated condition, rarity); 2: OS; 3: QoL; 4: safety.

[3] Reference categories: ascites; AU; QoL: improve; safety: improve.

[4] Standard errors (SE) are provided in brackets. ***: p ≤ 0.01, **: p ≤ 0.05, *: p ≤ 0.10

Appendix 5.8

eTable 17. Multivariate Linear Regression Analysis, Total Number of Patients Completing (b) (4) Therapy with New Medicines per 100,000 Incident Cases of Neoplasm and their Beneficial Impact to Health in the Second Year of Drug Marketing in Australia, France, the UK, and the US

Variable	Model[1]									
	(A)	(B)	(C)	(D)	(E)	(F)	(G)	(H)	(I)	(J)
Dep. Var.	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi
Ind. Var[2]	1	2	3	4	1, 2	1, 3	1, 4	1, 2, 3	1, 2, 4	1, 2, 3, 4
orphan	-0.508 [0.566]				-1.061 [0.854]	-0.417 [0.679]	0.0856 [0.513]	-0.756 [1.183]	-0.268 [0.836]	0.118 [1.320]
breast	4.424*** [0.567]				4.114*** [0.967]	5.065*** [0.732]	4.327*** [0.629]	4.427*** [1.125]	3.682*** [0.848]	3.955** [1.212]
gi	4.278*** [0.746]				4.254*** [1.105]	5.303*** [0.770]	4.757*** [0.704]	4.649*** [1.239]	4.403*** [0.959]	4.834*** [1.338]
hematological	2.718*** [0.359]				3.163*** [0.545]	3.308*** [0.437]	2.721*** [0.390]	2.989*** [0.490]	2.756*** [0.449]	2.672*** [0.439]
lung	4.052*** [0.680]				4.441*** [0.993]	4.306*** [0.878]	4.067*** [0.685]	3.834** [1.232]	3.726*** [0.830]	4.331** [1.305]
prostate	4.162*** [0.700]				4.197*** [1.140]	4.861*** [0.842]	3.992*** [0.709]	4.310** [1.295]	3.428*** [0.892]	3.830**
renal	3.692*** [0.511]				4.411*** [1.052]	4.386*** [0.453]	2.961*** [0.595]	3.830** [1.192]	3.253* [1.297]	3.471* [1.393]
skin	4.397*** [0.592]				3.666*** [0.990]	4.683*** [0.792]	4.276*** [0.847]	4.344** [1.316]	3.307*** [0.921]	3.457** [1.288]
OS		0.0584 [0.105]			0.149 [0.127]			0.025 [0.145]	0.0652 [0.123]	0.0875 [0.174]
FR		1.229 [0.963]	1.582* [0.746]	-0.219 [1.967]	1.958* [0.877]	1.463 [0.928]	-0.145 [2.062]	1.244 [1.629]	0.622 [3.124]	0.423 [3.200]
UK		0.238 [0.862]	0.79 [0.646]	0.261 [1.553]	0.522 [0.822]	0.597 [0.753]	0.261 [1.380]	0.236 [1.399]	1.48 [1.854]	1.266 [1.894]
US		1.306 [1.024]	1.496* [0.711]	1.837 [1.556]	1.639 [0.891]	1.281 [0.802]	1.571 [1.381]	1.074 [1.494]	3.009 [1.726]	2.869 [1.768]
FR # OS		0.0501 [0.146]			-0.101 [0.164]			-0.0122 [0.184]	-0.0838 [0.145]	-0.0647 [0.195]
UK # OS		0.0596 [0.124]			-0.0359 [0.141]			0.0117 [0.153]	-0.0245	0.00841 [0.172]
US # OS		0.0778 [0.151]			-0.0135 [0.169]			0.0464 [0.186]	0.0171 [0.152]	0.0433 [0.203]
QoL_ME			-1.388** [0.422]			-0.0139 [0.555]				
QoL_reduce			2.507*** [0.572]			2.291** [0.772]		0.66 [1.133]		2.073 [1.449]
QoL_NE			-0.816 [0.853]			-1.449 [0.904]		-1.593 [1.272]		0.288 [2.200]
QoL_ME # UK			-1.254* [0.518]			-1.275* [0.545]				
QoL_reduce # FR			-2.602** [0.814]			-2.212 [1.291]		0.39 [1.091]		-0.494 [1.103]
QoL_reduce # UK			-3.252*** [0.739]			-2.788* [1.227]		0 [.]		0 [.]
QoL_reduce # US			-2.788*** [0.711]			-2.991*** [0.744]		0 [.]		0 [.]
QoL_NE # FR			0.204 [1.135]			0.961 [1.128]		0.979 [1.677]		-0.0165 [2.296]

QoL_NE # UK			-0.267 [0.994]			0.221 [1.005]		0.324 [1.499]		0.196 [2.211]
QoL_NE # US			0.304 [1.144]			0.86 [1.036]		0.942 [1.561]		0.41 [2.322]
safety_ME				-0.768 [1.636]			-0.499 [1.433]		0.801 [1.939]	0.56 [2.216]
safety_reduce				-1.467 [1.501]			-1.596 [1.302]		-0.965 [1.917]	-1.262 [2.742]
safety_NE				-1.366 [1.829]			-1.54 [1.440]		-1.647 [1.881]	-1.993 [2.619]
safety_ME # FR				2.437 [2.177]			2.565 [2.169]		1.46 [3.267]	1.845 [3.519]
safety_ME # UK				0.446 [1.833]			0.593 [1.600]		-1.107 [2.111]	-0.778 [2.423]
safety_ME # US				-0.633 [1.853]			-0.131 [1.646]		-2.389 [2.129]	-2.265 [2.421]
safety_reduce # FR				2.758 [2.056]			2.733 [2.124]		2.163 [3.242]	2.352 [3.822]
safety_reduce # UK				0.787 [1.648]			0.836 [1.492]		-0.384 [2.072]	-0.382 [2.853]
safety_reduce # US				0.374 [1.694]			0.596 [1.514]		-0.731 [2.019]	-0.81 [2.884]
safety_NE # FR				0.0737 [2.433]			1.131 [2.267]		1.18 [3.240]	1.534 [3.678]
safety_NE # UK				-1.681 [1.976]			-1.11 [1.640]		-1.587 [2.058]	-1.404 [2.670]
safety_NE # US				-1.69 [2.203]			-0.992 [1.797]		-1.993 [2.129]	-2.047 [2.796]
Constant	1.143* [0.566]	3.708*** [0.742]	4.128*** [0.572]	4.950*** [1.407]	-0.261 [1.443]	0.0779 [1.250]	1.105 [1.507]	0.761 [2.125]	0.749 [1.938]	0.282 [2.261]
Observation	121	87	113	113	87	113	113	87	87	87
R^2	0.231	0.15	0.191	0.357	0.394	0.432	0.512	0.437	0.573	0.585
Adj R^2	0.176	0.074	0.085	0.257	0.265	0.301	0.386	0.255	0.378	0.327

Source:

Authors' analysis of data, as described Methods section.

Notes:

[1] Sensitivity analysis with a natural log transformation of the dependent variable, total number of patients completing [redacted] therapy in the second year of marketing per 100,000 incident cases of neoplasm (mean estimate of distribution from Chapter 3), assuming treatment duration [redacted]

[2] 1: Treatment descriptors (treated condition, rarity); 2: OS; 3: QoL; 4: safety.

[3] Reference categories: ascites; AU; QoL: improve; safety: improve.

[4] Standard errors (SE) are provided in brackets. ***: p ≤ 0.01, **: p ≤ 0.05, *: p ≤ 0.10

Appendix 5.9

eTable 18. Multivariate Linear Regression Analysis, Total Cost per Patient per (b) (4) Treatment with New Medicines and their Beneficial Impact to Health in the Third Year of Drug Marketing in Australia, France, the UK, and the US

Variable	Model[1]									
	(A)	(B)	(C)	(D)	(E)	(F)	(G)	(H)	(I)	(J)
Dep. Var.	sqrt_TCp	sqrt_TCp	sqrt_TCp	sqrt_TCp	sqrt_TCp	sqrt_TCp	sqrt_TCp	sqrt_TCp	sqrt_TCp	sqrt_TCp
Ind. Var[2]	1	2	3	4	1, 2	1, 3	1, 4	1, 2, 3	1, 2, 4	1, 2, 3, 4
orphan	19.06 [26.66]				89.65** [29.88]	70.80** [22.04]	51.27* [24.29]	111.6***	62.21* [29.04]	102.2* [41.13]
gi	-31.01 [27.22]				9.624 [21.66]	-21.76 [27.11]	-38.41 [33.47]	3.917 [24.05]	-17.15 [31.50]	-28.95 [36.27]
hematological	23.76 [31.79]				-0.707 [25.93]	-11.25 [25.87]	-11.11 [32.71]	-12.86 [28.96]	-2.197 [28.79]	-33.86 [32.26]
lung	-12.83 [39.42]				18.03 [37.50]	-24.44 [38.50]	-6.438 [39.69]	44.64 [47.48]	23.69 [42.21]	8.162 [57.19]
prostate	-12.91 [37.06]				23.86 [29.77]	-9.521 [35.97]	4.252 [45.62]	26.29 [37.74]	39.03 [40.32]	34.26 [44.40]
renal	6.877 [36.26]					-17.38 [38.65]	-0.699 [41.93]			
skin	48.88 [33.07]				120.2*** [23.15]	91.08* [37.74]	70.25 [37.46]	106.6** [32.42]	112.1*** [27.63]	115.4** [41.77]
OS		4.575 [4.575]			0.222 [4.785]			6.955 [4.865]	2.362 [5.188]	9.882 [8.235]
FR		5.942 [49.09]	72.88** [22.09]	83.66* [32.78]	3.974 [45.70]	102.7*** [24.54]	53.19 [34.75]	136.4** [50.58]	7.547 [70.85]	140 [79.59]
UK		26.6 [48.73]	71.37* [30.46]	52.82 [49.71]	31.4 [44.79]	114.1*** [28.47]	69.91 [38.77]	118.3* [46.95]	27.35 [34.87]	48.73 [26.42]
US		74.5 [52.17]	93.47** [31.04]	53.23 [59.71]	73.35 [49.19]	125.5*** [32.29]	70.32 [52.20]	156.0* [62.76]	39.26 [60.55]	63.49 [61.80]
FR # OS		2.728 [5.766]			8.527 [5.457]			-0.739 [5.322]	9.238 [6.027]	0.193 [9.528]
UK # OS		6.026 [6.199]			11.16* [5.382]			5.702 [5.202]	11.08 [6.415]	1.025 [8.461]
US # OS		2.495 [6.438]			7.197 [7.076]			1.896 [7.354]	6.789 [7.810]	-4.613 [9.844]
QoL_ME			-16.06 [25.30]			-65.52* [29.66]				
QoL_reduce			18.03 [17.99]			-101.7** [37.21]		-3.222 [42.44]		-29.98 [62.13]
QoL_NE			28.45 [42.12]			52.88 [45.48]		124.6* [58.55]		137.1 [95.30]
QoL_reduce # FR			-104.5 [54.16]			-12.31 [31.52]		-51.17 [49.91]		31.77 [91.14]
QoL_reduce # UK			-74.55 [55.05]			4.677 [32.74]		0 [.]		0 [.]
QoL_reduce # US			-41.15 [31.04]			-2.368 [35.49]		0 [.]		0 [.]
QoL_NE # FR			-85.14 [49.73]			-120.9* [49.36]		-157.8** [55.14]		-157.1 [87.19]
QoL_NE # UK			-46.18 [58.11]			-94.93 [55.04]		-114.2 [59.39]		-179.3* [86.78]
QoL_NE # US			-29.94 [58.25]			-65.42 [58.12]		-113.5 [73.02]		-199.2 [101.1]

QoL_ME				29.25 [38.57]			22.32 [37.95]		7.185 [54.13]	-52.85 [56.65]
safety_reduce				60.64 [45.62]			78.93 [47.21]		66.59 [67.62]	-72.16 [87.66]
safety_NE				77.56 [68.59]			101.8 [58.79]		91.48 [69.36]	-16.76 [78.49]
safety_ME # FR				-46.35 [38.60]			16.26 [46.18]		17.78 [83.17]	-20.33 [63.92]
safety_ME # UK				5.581 [54.29]			20.63 [46.54]		2.719 [65.84]	82.51 [71.18]
safety_ME # US				35.2 [67.75]			50.21 [62.21]		51.91 [83.83]	123.2 [93.02]
safety_reduce # FR				-96.17 [52.83]			-55.16 [54.97]		-50.51 [87.13]	-13.52 [95.39]
safety_reduce # UK				-25.61 [66.81]			-26.61 [58.56]		-22.58 [69.26]	142.6 [91.25]
safety_reduce # US				15.62 [76.51]			8.595 [70.91]		12.6 [92.27]	187.3 [121.4]
safety_NE # FR				-72.14 [75.82]			-41.27 [66.40]		0 [.]	0 [.]
safety_NE # UK				-8.22 [87.33]			-24.91 [71.76]		10.96 [78.64]	141.1 [77.29]
safety_NE # US				28.27 [91.54]			2.391 [79.80]		54.2 [91.93]	199 [103.3]
Constant	207.2*** [23.85]	158.3*** [39.85]	165.4*** [17.99]	132.7*** [32.78]	118.2** [40.16]	123.3*** [28.32]	92.93* [44.96]	18.25 [57.05]	70.95 [47.27]	65.12 [57.54]
Observation	93	72	87	87	72	87	87	72	72	72
R^2	0.105	0.221	0.161	0.198	0.395	0.351	0.327	0.456	0.505	0.552
Adj R^2	0.031	0.135	0.025	0.028	0.259	0.166	0.096	0.257	0.253	0.224

Source:

Authors' analysis of data, as described Methods section.

Notes:

[1] Sensitivity analysis with a sqrt transformation of the dependent variable, total cost per patient per (b) (4) treatment (TCp) in the third year of marketing (mean estimate (b) (4) from Chapter 3), assuming treatment duration (b) (4)

[2] 1: Treatment descriptors (treated condition, rarity); 2: OS; 3: QoL; 4: safety.

[3] Reference categories: ascites; AU; QoL: improve; safety: improve.

[4] Standard errors (SE) are provided in brackets. ***: p ≤ 0.01, **: p ≤ 0.05, *: p ≤ 0.10

Appendix 5.10

eTable 19. Multivariate Linear Regression Analysis, Total Number of Patients Completing (b) (4) Therapy with New Medicines per 100,000 Incident Cases of Neoplasm and their Beneficial Impact to Health in the Third Year of Drug Marketing in Australia, France, the UK, and the US

Variable	Model[1]									
	(A)	(B)	(C)	(D)	(E)	(F)	(G)	(H)	(I)	(J)
Dep. Var.	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi
Ind. Var[2]	1	2	3	4	1, 2	1, 3	1, 4	1, 2, 3	1, 2, 4	1, 2, 3, 4
orphan	-1.132** [0.415]				-2.026** [0.599]	-1.825** [0.563]	-0.215 [0.446]	-2.129** [0.796]	-0.628 [0.638]	-0.835 [0.771]
gi	-0.45 [0.522]				0.000222 [0.589]	-0.107 [0.562]	0.682 [0.427]	0.0497 [0.571]	0.93 [0.481]	1.07 [0.536]
hematological	-1.151** [0.432]				-0.317 [0.535]	-0.762 [0.516]	-1.205* [0.474]	-0.343 [0.765]	-0.66 [0.577]	-0.799 [0.627]
lung	-0.356 [0.447]				0.415 [0.610]	-1.140* [0.531]	0.217 [0.537]	-0.47 [0.915]	0.501 [0.603]	-0.109 [0.794]
prostate	-0.503 [0.649]				-0.106 [0.788]	-0.479 [0.652]	-0.529 [0.370]	-0.0641 [0.429]	0.0196 [0.429]	-0.0611 [0.433]
renal	-0.497 [0.714]					0.49 [0.729]	-1.659* [0.651]			
skin	-0.172 [0.333]				-0.432 [0.330]	-0.265 [0.497]	0.181 [0.611]	-0.0475 [0.510]	-0.236 [0.535]	0.115 [0.535]
OS		0.0826 [0.113]			0.214 [0.114]			0.049 [0.101]	0.112 [0.0871]	-0.0864 [0.122]
FR		0.235 [1.188]	-0.533 [1.231]	-5.002 [3.058]	0.632 [1.007]	-1.492 [1.507]	-4.943 [2.980]	-3.59 [3.046]	-8.349*** [0.855]	-8.538*** [1.095]
UK		-0.255 [1.052]	0.129 [0.529]	-0.238 [0.755]	-0.117 [0.822]	-0.935 [0.567]	-0.31 [1.088]	-1.149 [0.915]	0.529 [0.843]	0.112 [0.967]
US		0.235 [1.091]	0.43 [0.514]	-0.334 [0.660]	0.477 [0.844]	-0.627 [0.554]	-0.406 [1.018]	-0.855 [0.877]	0.0808 [0.850]	-0.325 [0.978]
FR # OS		0.0213 [0.139]			-0.156 [0.150]			0.189 [0.241]	-0.125 [0.111]	-0.0439 [0.145]
UK # OS		0.0384 [0.134]			-0.108 [0.130]			-0.0293 [0.098]	-0.052 [0.144]	0.144 [0.122]
US # OS		0.0912 [0.142]			-0.0414 [0.147]			0.0516 [0.125]	0.0272 [0.111]	0.218 [0.136]
QoL_ME			-1.173** [0.399]			0.364 [0.568]				
QoL_reduce			1.363*** [0.324]			1.346* [0.563]		-0.265 [0.897]		1.227 [0.959]
QoL_NE			-1.533 [0.918]			-2.969*** [0.770]		-2.612** [0.846]		-2.820* [1.239]
QoL_reduce # FR			-0.109 [1.282]			-0.726 [1.314]		3.712 [3.034]		-2.222 [1.582]
QoL_reduce # UK			-1.627** [0.531]			-2.139** [0.785]		0 [.]		0 [.]
QoL_reduce # US			-1.710** [0.514]			-2.478*** [0.571]		0 [.]		0 [.]
QoL_NE # FR			2.023 [1.624]			3.27 [1.650]		4.7 [2.755]		1.15 [1.551]
QoL_NE # UK			0.0257 [1.134]			1.378 [0.935]		1.255 [1.048]		2.537* [1.255]
QoL_NE # US			0.414 [1.167]			1.692 [0.928]		1.793 [1.017]		2.951* [1.291]

safety_ME				-2.616** [0.976]			-1.854 [0.932]		-1.148 [0.915]	-0.36 [1.258]
safety_reduce				-1.574** [0.513]			-1.283 [0.790]		-1.449 [0.932]	0.947 [1.407]
safety_NE				-4.235** [1.519]			-4.105** [1.294]		-3.818** [1.313]	-1.95 [1.498]
safety_ME # FR				7.208* [3.193]			7.475* [3.052]		10.18*** [1.042]	9.707*** [1.429]
safety_ME # UK				1.835 [1.337]			2.232 [1.424]		0.054 [1.491]	-0.958 [1.768]
safety_ME # US				1.867 [1.224]			2.048 [1.295]		0.592 [1.178]	-0.275 [1.540]
safety_reduce # FR				6.109 [3.088]			6.068* [3.015]		10.10*** [1.003]	8.915*** [1.726]
safety_reduce # UK				0.0926 [0.824]			0.0365 [1.143]		-0.591 [1.026]	-3.228* [1.575]
safety_reduce # US				0.605 [0.820]			0.552 [1.113]		0.242 [1.073]	-2.486 [1.580]
safety_NE # FR				6.339 [3.489]			6.707* [3.193]		10.26*** [1.437]	9.600*** [1.536]
safety_NE # UK				0.173 [1.736]			0.671 [1.570]		-0.111 [1.414]	-1.798 [1.525]
safety_NE # US				1.581 [1.865]			1.937 [1.630]		1.135 [1.545]	-0.888 [1.697]
Constant	6.087*** [0.166]	4.650*** [0.902]	5.510*** [0.324]	6.891*** [0.423]	5.046*** [0.843]	7.616*** [0.493]	7.006*** [0.803]	7.184*** [0.914]	6.402*** [0.897]	7.169*** [1.167]
Observation	94	73	88	88	73	88	88	73	73	73
R^2	0.22	0.089	0.142	0.477	0.348	0.41	0.626	0.471	0.786	0.82
Adj R^2	0.156	-0.009	0.005	0.368	0.204	0.245	0.499	0.281	0.671	0.684

Source:

Authors' analysis of data, as described Methods section.

Notes:

[1] Sensitivity analysis with a natural log transformation of the dependent variable, total number of patients completing [redacted] therapy in the third year of marketing per 100,000 incident cases of neoplasm (mean estimate of distribution from Chapter 3), assuming treatment duration [redacted] (b) (4)

[2] 1: Treatment descriptors (treated condition, rarity); 2: OS; 3: QoL; 4: safety.

[3] Reference categories: ascites; AU; QoL: improve; safety: improve.

[4] Standard errors (SE) are provided in brackets. ***: $p \leq 0.01$, **: $p \leq 0.05$, *: $p \leq 0.10$

Appendix 5.11

eTable 20. Multivariate Linear Regression Analysis, Total Number of Patients Completing [redacted] Therapy with New Medicines per 100,000 Population and their Beneficial Impact to Health in the First Year of Drug Marketing in Australia, France, the UK, and the US

Variable	Model[1]									
	(A)	(B)	(C)	(D)	(E)	(F)	(G)	(H)	(I)	(J)
Dep. Var.	log_ TPp	log_ TPp	log_ TPp	log_ TPp	log_ TPp	log_ TPp	log_ TPp	log_ TPp	log_ TPp	log_ TPp
Ind. Var[2]	1	2	3	4	1, 2	1, 3	1, 4	1, 2, 3	1, 2, 4	1, 2, 3, 4
orphan	-0.142 [0.616]				0.156 [0.716]	-0.485 [0.618]	0.508 [0.628]	-0.696 [0.814]	1.22 [0.869]	0.189 [0.940]
breast	2.021** [0.719]				0.451 [0.978]	0.791 [0.747]	0.111 [0.950]	-0.231 [0.939]	0.23 [1.048]	-0.661 [0.952]
gi	2.051* [0.839]				0.925 [1.089]	1.252 [0.778]	0.554 [0.961]	0.296 [1.042]	1.235 [1.157]	0.387 [0.951]
hematological	0.421 [0.362]				-0.582 [0.559]	-0.352 [0.474]	-1.636** [0.502]	-0.732 [0.502]	-1.049*** [0.289]	-0.967** [0.309]
lung	1.551* [0.716]				0.82 [0.819]	0.017 [0.850]	-0.365 [0.811]	-0.806 [1.031]	0.0931 [0.812]	-0.2 [1.157]
prostate	1.901* [0.765]				0.968 [0.944]	0.796 [0.750]	-0.109 [0.945]	-0.0547 [0.924]	0.294 [1.033]	-0.574 [0.991]
renal	0.917 [0.588]				1.024 [0.783]	0.0209 [0.539]	-1.541 [0.854]	0.222 [0.951]	-0.252 [0.981]	0.0736 [1.179]
skin	0.545 [0.930]				0.34 [1.294]	-0.351 [0.961]	-1.314 [1.017]	0.165 [1.248]	0.651 [1.284]	-0.586 [1.161]
thyroid	-0.0604 [0.616]				0.237 [0.716]	-0.404 [0.618]	-1.307 [0.946]	-0.614 [0.814]	0.0461 [1.209]	-0.88 [1.141]
OS		0.115 [0.0960]			0.16 [0.127]			-0.0198 [0.121]	0.127 [0.0960]	0.0908 [0.108]
FR		1.952 [1.004]	1.367 [0.744]	-0.466 [1.497]	2.241* [0.994]	1.117 [0.895]	-0.466 [1.582]	0.431 [1.443]	-0.27 [2.150]	0.00336 [2.400]
UK		0.333 [0.741]	0.0299 [0.758]	-1.213 [1.656]	0.666 [0.841]	-0.193 [0.862]	-1.213 [1.443]	-1.531 [1.328]	-0.171 [1.410]	-0.286 [1.576]
US		2.482** [0.931]	1.763* [0.827]	2.964 [1.596]	2.859** [0.955]	1.506 [0.934]	2.854* [1.363]	1.069 [1.613]	4.238* [1.968]	4.312* [2.030]
FR # OS		-0.0523 [0.209]			-0.0883 [0.237]			-0.00197 [0.141]	-0.155 [0.208]	-0.128 [0.191]
UK # OS		0.1 [0.118]			0.0585 [0.146]			0.204 [0.141]	0.0173 [0.117]	0.193 [0.124]
US # OS		0.0301 [0.152]			-0.0146 [0.174]			0.0988 [0.190]	-0.013 [0.144]	0.0863 [0.164]
QoL_ME			-3.090*** [0.667]			-2.173* [0.828]				
QoL_reduce			0.956 [0.489]			1.614 [0.932]		1.228 [1.335]		1.705 [1.309]
QoL_NE			-2.198** [0.684]			-2.856*** [0.750]		-3.417** [1.188]		-1.536 [1.539]
QoL_ME # UK			-2.090* [0.884]			-2.124* [0.915]				
QoL_reduce # FR			-4.494* [1.722]			-4.729* [1.863]		-6.749*** [1.882]		-6.732** [2.045]
QoL_reduce # UK			-3.206 [2.035]			-3.467 [2.148]		-0.25 [1.821]		1.593 [2.204]
QoL_reduce # US			-0.856 [0.938]			-0.841 [1.124]		0 [.]		0 [.]

QoL_NE # FR			2.300* [1.025]			2.716* [1.056]		3.276* [1.387]		2.581 [1.595]
QoL_NE # UK			1.918* [0.951]			2.401* [0.985]		3.108* [1.306]		3.577* [1.523]
QoL_NE # US			1.923 [1.139]			2.358* [1.114]		2.485 [1.573]		2.219 [1.758]
safety_ME				-1.797 [1.349]			-2.078 [1.287]		-1.266 [1.515]	-0.181 [1.492]
safety_reduce				-2.724** [0.938]			-3.196*** [0.788]		-3.576* [1.365]	-1.677 [1.755]
safety_NE				-1.549 [0.906]			-1.945* [0.793]		-2.441 [1.403]	-0.674 [1.812]
safety_ME # FR				3.075 [1.930]			3.329 [1.991]		3.677 [2.352]	2.487 [2.400]
safety_ME # UK				2.153 [2.200]			2.472 [2.053]		1.743 [1.754]	0.153 [1.721]
safety_ME # US				-0.991 [2.069]			-0.452 [1.925]		-2.437 [2.299]	-3.583 [2.246]
safety_reduce # FR				3.721* [1.687]			3.820* [1.746]		4.306 [2.158]	2.394 [2.627]
safety_reduce # UK				2.965 [1.763]			3.121 [1.597]		2.167 [1.616]	-1.104 [2.028]
safety_reduce # US				0.568 [1.771]			0.776 [1.557]		0.17 [2.071]	-2.144 [2.497]
safety_NE # FR				0.75 [1.673]			1.08 [1.687]		1.47 [2.201]	-0.97 [2.583]
safety_NE # UK				-0.289 [1.807]			-0.0268 [1.596]		-0.223 [1.474]	-3.257 [1.901]
safety_NE # US				-2.354 [1.781]			-1.803 [1.535]		-3.157 [2.076]	-5.198* [2.417]
Constant	-3.743*** [0.616]	-3.887*** [0.631]	-2.930*** [0.489]	-1.913* [0.808]	-4.707*** [1.233]	-2.752* [1.113]	-1.208 [1.115]	-1.348 [1.609]	-2.27 [1.502]	-1.897 [1.880]
Observations	137	96	125	125	96	125	125	96	96	96
R^2	0.102	0.248	0.329	0.326	0.313	0.419	0.411	0.447	0.534	0.634
Adj R^2	0.039	0.189	0.25	0.233	0.174	0.293	0.27	0.27	0.339	0.421

Source:

Authors' analysis of data, as described in Methods section.

Notes:

[1] Sensitivity analysis with a natural log transformation of the dependent variable, total number of patients completing [redacted] therapy in the first year of marketing per 100,000 population (mean estimate of distribution from Chapter 3), assuming treatment duration [redacted]

[2] 1: Treatment descriptors (treated condition, rarity); 2: OS; 3: QoL; 4: safety.

[3] Reference categories: ascites; AU; QoL: improve; safety: improve.

[4] Standard errors (SE) are provided in brackets. ***: p ≤ 0.01, **: p ≤ 0.05, *: p ≤ 0.10

Appendix 5.12

eTable 21. Multivariate Linear Regression Analysis, Total Cost per Patient per (b) (4) Treatment with New Medicines and their Beneficial Impact to Health in the First Year of Drug Marketing in Australia, France, the UK, and the US

Variable	Model[1]									
	(A)	(B)	(C)	(D)	(E)	(F)	(G)	(H)	(I)	(J)
Dep. Var.	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp
Ind. Var[2]	1	2	3	4	1, 2	1, 3	1, 4	1, 2, 3	1, 2, 4	1, 2, 3, 4
orphan	-6.114 [21.50]				55.36* [26.70]	21.49 [20.38]	21.56 [17.44]	71.22* [28.11]	35.38 [24.07]	75.58* [34.03]
breast	41.25 [26.14]				60.02 [41.08]	72.70* [35.05]	98.93* [47.24]	70.1 [42.03]	103.5 [57.83]	135.4* [59.49]
gi	22.61 [26.86]				71.52 [36.89]	49.85 [28.83]	84.73 [44.95]	73.66 [39.74]	102.2 [56.65]	129.6* [61.43]
hematological	77.61*** [13.38]				58.26 [32.37]	85.79** [27.75]	92.80* [40.28]	63.14 [38.22]	92.22 [49.24]	94.24 [52.16]
lung	2.058 [27.38]				44.5 [39.95]	41.16 [37.16]	62.08 [44.28]	68.56 [48.60]	89.04 [52.66]	108.5 [61.83]
prostate	4.987 [32.23]				50 [44.31]	40.57 [40.71]	75.91 [51.17]	67.21 [47.07]	105.7 [59.95]	139.4* [64.20]
renal	-2.629 [12.50]				-69.50** [24.37]	9.014 [24.60]	41.36 [41.09]	-74.25* [35.02]	-1.03 [50.10]	-19.94 [56.53]
skin	73.49* [29.89]				207.3*** [36.70]	128.7** [40.58]	142.2** [49.04]	226.0*** [37.74]	256.3*** [56.65]	314.0*** [59.70]
thyroid	145.0*** [21.50]				206.4*** [26.70]	172.6*** [20.38]	206.3*** [48.40]	222.3*** [28.11]	272.3*** [56.59]	311.5***
OS		1.426 [4.682]			-1.742 [5.083]			4.423 [4.604]	-1.248 [5.346]	3.296 [5.992]
FR		-16.02 [41.89]	25.91 [23.75]	11.91 [53.78]	-9.803 [41.74]	43.49 [25.14]	9.933 [25.79]	79.44 [44.18]	13.75 [42.80]	36.44 [42.25]
UK		19.91 [42.46]	61.47* [25.05]	46.44 [43.78]	17.01 [42.62]	76.73** [26.23]	61.25* [26.60]	101.4* [42.83]	41.17 [37.82]	58.65 [32.08]
US		56.11 [44.62]	77.12** [27.12]	39.97 [53.31]	53.35 [44.22]	90.40** [29.95]	47.15 [38.16]	134.3* [57.63]	26.46 [52.11]	43.88 [49.44]
FR # OS		4.376 [5.541]			8.566 [5.590]			1.408 [5.271]	10.05 [5.745]	3.365 [6.667]
UK # OS		7.011 [5.897]			11.17 [5.636]			4.495 [5.170]	12.68* [5.893]	5.823 [6.740]
US # OS		3.589 [6.266]			6.898 [6.930]			0.557 [7.237]	7.636 [6.886]	-0.563 [7.965]
QoL_ME			25.08 [21.89]			-20.13 [24.33]				
QoL_reduce			41.23* [16.01]			-33.56 [35.67]		-18.65 [49.26]		-34.26 [66.09
QoL_NE			49.46 [38.22]			71.37 [40.38]		122.4 [61.96]		118.9 [83.56]
QoL_ME # UK			17.84 [29.16]			15.86 [28.32]				
QoL_reduce # FR			-69.52 [46.42]			-44.17 [39.90]		-32.58 [63.44]		13.71 [94.26]
QoL_reduce # UK			-65.11 [52.03]			-37.45 [44.99]		-22.17 [62.25]		19.1 [97.60]
QoL_reduce # US			-28.82 [29.03]			-9.926 [38.41]		0 [.]		0 [.]

QoL_NE # FR			-54.25 [46.16]			-80.6 [46.23]		-135.2* [64.90]		-156.1 [84.32]
QoL_NE # UK			-45.28 [48.88]			-77.82 [48.24]		-131.8* [64.64]		-160.8 [86.00
QoL_NE # US			-28.14 [50.37]			-54.77 [50.69]		-130.3 [72.97]		-182.1 [95.39]
safety_ME				26.67 [38.85]			40.55 [36.33]		17.66 [48.99]	-22.13 [52.26]
safety_reduce				58.7 [45.65]			68.96 [40.26]		88.66 [68.78]	-5.685 [64.94]
safety_NE				35.42 [48.96]			24.39 [42.62]		45.67 [63.05]	-49.87 [71.88]
safety_ME # FR				7.697 [60.65]			20.45 [39.92]		-7.278 [63.17]	35.69 [73.63]
safety_ME # UK				14.9 [52.96]			5.378 [42.52]		-5.673 [63.03]	43.41 [69.07]
safety_ME # US				41.45 [61.75]			38.13 [54.31]		42.23 [73.10]	95.14 [81.70]
safety_reduce # FR				-48.04 [64.53]			-42.21 [44.22]		-90.58 [74.76]	18.03 [72.28]
safety_reduce # UK				-29.63 [58.98]			-50.9 [46.93]		-93.11 [74.19]	22.79 [74.56]
safety_reduce # US				1.556 [66.18]			-5.256 [54.04]		-26.71 [85.13]	107.4 [97.44]
safety_NE # FR				43.98 [71.87]			59.6 [56.75]		30.14 [75.53]	137 [79.42]
safety_NE # UK				23.87 [65.26]			27.3 [59.29]		35.75 [78.35]	151.8 [81.97]
safety_NE # US				75.21 [72.38]			74.3 [64.90]		93.03 [82.63]	227.9* [95.90]
Constant	162.6*** [21.50]	155.3*** [35.15]	140.1*** [16.01]	122.6*** [32.69]	84.15 [57.77]	64.76 [40.27]	22.03 [49.71]	-6.597 [61.36]	-1.442 [62.48]	-37.72 [64.63]
Observation	131	90	119	119	90	119	119	90	90	90
R^2	0.162	0.166	0.151	0.206	0.379	0.309	0.321	0.439	0.493	0.543
Adj R^2	0.1	0.095	0.045	0.09	0.243	0.15	0.147	0.243	0.26	0.246

Source:

Authors' analysis of data, as described in Methods section.

Notes:

[1] Sensitivity analysis with a sqrt transformation of the dependent variable, total cost per patient per (b) (4) treatment (TCp) in the first year of marketing (median estimate (b) (4) from Chapter 3), assuming treatment duration (b) (4)

[2] 1: Treatment descriptors (treated condition, rarity); 2: OS; 3: QoL; 4: safety.

[3] Reference categories: ascites; AU; QoL: improve; safety: improve.

[4] Standard errors (SE) are provided in brackets. ***: p ≤ 0.01, **: p ≤ 0.05, *: p ≤ 0.10

Appendix 5.13

eTable 22. Multivariate Linear Regression Analysis, Total Number of Patients Completing [redacted] Therapy with New Medicines per 100,000 Incident Cases of Neoplasm and their Beneficial Impact to Health in the First Year of Drug Marketing in Australia, France, the UK, and the US

Variable	Model[1]									
	(A)	(B)	(C)	(D)	(E)	(F)	(G)	(H)	(I)	(J)
Dep. Var.	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi
Ind. Var[2]	1	2	3	4	1, 2	1, 3	1, 4	1, 2, 3	1, 2, 4	1, 2, 3, 4
orphan	-0.147 [0.616]				0.154 [0.737]	-0.455 [0.608]	0.505 [0.647]	-0.744 [0.829]	1.132 [0.905]	-0.000534 [0.908]
breast	1.989** [0.721]				0.491 [0.984]	0.87 [0.731]	0.105 [1.017]	-0.217 [0.935]	0.339 [1.079]	-0.638 [0.919]
gi	1.924* [0.836]				0.812 [1.114]	1.199 [0.761]	0.439 [1.032]	0.15 [1.042]	1.143 [1.202]	0.207 [0.917]
hematologic al	0.553 [0.354]				-0.409 [0.544]	-0.132 [0.455]	-1.480* [0.622]	-0.516 [0.476]	-0.814** [0.299]	-0.727* [0.292]
lung	1.465* [0.697]				0.767 [0.825]	0.107 [0.824]	-0.387 [0.876]	-0.709 [1.024]	0.153 [0.856]	-0.183 [1.121]
prostate	1.967* [0.767]				1.084 [0.970]	0.981 [0.741]	0.0346 [1.026]	0.0779 [0.939]	0.539 [1.087]	-0.416 [0.973]
renal	0.973 [0.557]				0.909 [0.755]	0.18 [0.508]	-1.409 [0.907]	0.24 [0.930]	-0.128 [0.992]	0.216 [1.172]
skin	0.607 [0.937]				0.469 [1.299]	-0.217 [0.969]	-1.178 [1.119]	0.172 [1.231]	0.828 [1.316]	-0.523 [1.120]
thyroid	-0.701 [0.616]				-0.401 [0.737]	-1.01 [0.608]	-1.958 [1.014]	-1.299 [0.829]	-0.52 [1.247]	-1.554 [1.116]
OS		0.114 [0.0933]			0.151 [0.121]			-0.012 [0.115]	0.124 [0.0911	0.0854 [0.102]
FR		1.998* [0.984]	1.348 [0.726]	-0.496 [1.498]	2.257* [0.980]	1.119 [0.871]	-0.496 [1.574]	0.429 [1.429]	-0.263 [2.189]	0.0346 [2.454]
UK		0.363 [0.720]	0.0375 [0.768]	-1.175 [1.577]	0.711 [0.819]	-0.164 [0.858]	-1.175 [1.365]	-1.531 [1.303]	-0.162 [1.471]	-0.267 [1.651]
US		2.576** [0.887]	1.842* [0.794]	3.073* [1.526]	2.907** [0.919]	1.609 [0.905]	2.974* [1.343]	1.167 [1.554]	4.322* [2.001]	4.405* [2.068]
FR # OS		-0.0608 [0.200]			-0.0912 [0.225]			-0.00719 [0.215]	-0.159 [0.198]	-0.128 [0.177]
UK # OS		0.105 [0.114]			0.0622 [0.138]			0.209 [0.131]	0.0186 [0.113]	0.203 [0.121]
US # OS		0.0225 [0.144]			-0.0153 [0.164]			0.0919 [0.177]	-0.0175 [0.135]	0.0894 [0.148]
QoL_ME			-2.811*** [0.631]			-2.007* [0.802]				
QoL_reduce			1.143* [0.482]			1.799 [0.950]		1.399 [1.276]		1.961 [1.180]
QoL_NE			-2.089** [0.658]			-2.675*** [0.744]		-3.238** [1.195]		-1.652 [1.398]
QoL_ME # UK			-2.001* [0.869]			-2.032* [0.899]				
QoL_reduce # FR			-4.634* [1.810]			-4.903* [1.983]		-7.094*** [1.839]		-7.326*** [1.906]
QoL_reduce # UK			-3.086 [1.989]			-3.381 [2.068]		-0.241 [1.761]		1.383 [2.165]
QoL_reduce # US			-0.853 [0.914]			-0.89 [1.091]		0 [.]		0 [.]

QoL_NE # FR			2.306* [0.992]			2.679* [1.038]		3.346* [1.397]		2.806 [1.434]
QoL_NE # UK			1.882* [0.940]			2.373* [0.971]		3.177* [1.293]		3.822** [1.406]
QoL_NE # US			1.822 [1.079]			2.205* [1.075]		2.408 [1.523]		2.368 [1.561]
safety_ME				-1.605 [1.340]			-1.877 [1.304]		-1.067 [1.603]	0.116 [1.547]
safety_reduce				-2.590** [0.961]			-3.006*** [0.830]		-3.321* [1.418]	-1.269 [1.658]
safety_NE				-1.393 [0.921]			-1.729* [0.818]		-2.05 [1.458]	-0.134 [1.767]
safety_ME # FR				2.97 [1.900]			3.222 [1.977]		3.62 [2.409]	2.311 [2.427]
safety_ME # UK				2.102 [2.100]			2.41 [1.976]		1.752 [1.849]	0.0275 [1.767]
safety_ME # US				-1.095 [1.986]			-0.584 [1.900]		-2.434 [2.358]	-3.678 [2.266]
safety_reduce # FR				3.739* [1.682]			3.837* [1.732]		4.288 [2.194]	2.196 [2.530]
safety_reduce # UK				2.933 [1.687]			3.129* [1.519]		2.179 [1.666]	-1.318 [1.957]
safety_reduce # US				0.472 [1.688]			0.669 [1.515]		0.0859 [2.091]	-2.413 [2.349]
safety_NE # FR				0.888 [1.652]			1.19 [1.675]		1.485 [2.249]	-1.176 [2.542]
safety_NE # UK				-0.29 [1.745]			-0.0566 [1.557]		-0.189 [1.542]	-3.451 [1.860]
safety_NE # US				-2.339 [1.690]			-1.838 [1.495]		-3.185 [2.107]	-5.376* [2.336]
Constant	1.169 [0.616]	0.972 [0.609]	1.928*** [0.482]	2.869*** [0.846]	0.157 [1.242]	1.944 [1.092]	3.478** [1.235]	3.357* [1.640]	2.29 [1.574]	2.705 [1.938]
Observation	137	96	125	125	96	125	125	96	96	96
R^2	0.091	0.263	0.335	0.333	0.316	0.414	0.407	0.458	0.519	0.638
Adj R^2	0.027	0.204	0.258	0.242	0.177	0.288	0.265	0.285	0.318	0.427

Source:

Authors' analysis of data, as described in Methods section.

Notes:

[1] Sensitivity analysis with a natural log transformation of the dependent variable, total number of patients completing [redacted] therapy in the first year of marketing per 100,000 incident cases of neoplasm (TPi)(median estimate of distribution from Chapter 3), assuming treatment duration [redacted]

[2] 1: Treatment descriptors (treated condition, rarity); 2: OS; 3: QoL; 4: safety.

[3] Reference categories: ascites; AU; QoL: improve; safety: improve.

[4] Standard errors (SE) are provided in brackets. ***: p ≤ 0.01, **: p ≤ 0.05, *: p ≤ 0.10

Appendix 5.14

eTable 23. Multivariate Linear Regression Analysis, Total Cost per Patient per (b) (4) Treatment with New Medicines and their Beneficial Impact to Health in the First Year of Drug Marketing in Australia, France, the UK, and the US

Variable	Model[1]									
	(A)	(B)	(C)	(D)	(E)	(F)	(G)	(H)	(I)	(J)
Dep. Var.	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp
Ind. Var[2]	1	2	3	4	1, 2	1, 3	1, 4	1, 2, 3	1, 2, 4	1, 2, 3, 4
orphan	2.977 [22.27]				77.04* [35.47]	27.01 [22.51]	24.99 [22.33]	86.12* [34.30]	62.61 [39.16]	124.3** [44.56]
breast	55.89* [24.39]				89.8 [51.50]	92.10* [38.52]	111.2 [65.67]	94.42 [54.67]	123.1 [85.48]	159.1 [87.30]
gi	57.17 [32.04]				120.1* [49.21]	83.83* [36.54]	112 [67.46]	114.6* [53.26]	138.8 [85.89]	175.2 [90.27]
hematological	104.7*** [17.60]				106.2* [43.05]	126.2** [38.92]	127.2* [61.09]	115.2* [52.48]	136.1 [76.48]	142.2 [80.85]
lung	-19.86 [28.48]				36.5 [51.85]	30.09 [43.23]	32.92 [61.69]	79.73 [60.81]	57.03 [80.56]	125.2 [91.64]
prostate	20.74 [36.35]				81.57 [57.79]	60.59 [50.23]	84.23 [71.59]	99.23 [62.73]	121.9 [89.05]	167.3 [93.22]
renal	5.133 [10.46]				-40.28 [32.41]	22.94 [29.05]	52.56 [60.33]	-31.77 [47.16]	-2.624 [76.92]	-9.807 [82.73]
skin	94.75** [31.32]				248.3*** [48.11]	160.6*** [43.92]	148.5* [62.67]	252.5*** [50.63]	277.1** [84.79]	329.3*** [88.96]
thyroid	198.1*** [22.27]				272.2*** [35.47]	222.2*** [22.51]	250.9*** [68.05]	281.3*** [34.30]	322.6*** [81.57]	365.9*** [84.10]
OS		1.18 [5.159]			-4.639 [5.647]			5.071 [5.544]	-3.993 [6.508]	6.17 [7.262]
FR		-16.88 [56.34]	33.74 [26.81]	15.94 [49.28]	-26.11 [51.31]	50.63 [27.34]	-0.197 [23.00]	78.38 [46.85]	-17.09 [37.46]	7.796 [38.42]
UK		22.14 [57.53]	69.35* [28.59]	54.98 [42.50]	7.065 [52.47]	85.67** [28.66]	66.06** [19.54]	109.7* [43.85]	34.73 [26.52]	56.86* [22.65]
US		48.56 [58.73]	79.53** [26.60]	42.19 [53.70]	31.45 [52.49]	93.60** [28.88]	50.52 [30.19]	132.2* [50.76]	19.79 [30.44]	46.25 [40.89]
FR # OS		5.094 [6.824]			12.2 [6.260]			3.259 [5.570]	13.13 [7.323]	2.666 [6.805]
UK # OS		7.264 [7.648]			13.95* [6.790]			5.232 [5.867]	15.44 [7.934]	5.356 [7.151]
US # OS		4.824 [7.132]			10.87 [7.266]			2.397 [6.468]	12.26 [7.698]	-0.191 [7.620]
QoL_ME			30.37 [20.88]			-39.12 [28.84]				
QoL_reduce			54.42** [16.48]			-35.39 [34.11]		-21.77 [55.81]		-73.35 [64.33]
QoL_NE			77.53 [49.80]			93.02 [48.50]		163.1 [82.54]		218.3* [107.7]
QoL_ME # UK			12.34 [31.34]			10.09 [27.58]				
QoL_reduce # FR			-75.49 [47.04]			-48.17 [41.20]		-20.72 [60.28]		67.47 [77.95]
QoL_reduce # UK			-71.68 [53.46]			-43.8 [47.38]		-21.24 [56.95]		76.67 [75.37]
QoL_reduce # US			-28.26 [29.33]			-11.63 [34.07]		0 [.]		0 [.]

QoL_NE # FR			-66.6 [59.77]			-93.47 [56.72]		-151.5 [84.45]		-221.1* [99.35]
QoL_NE # UK			-55.7 [62.62]			-90.31 [59.16]		-151.7 [84.04]		-218.3* [100.6]
QoL_NE # US			-39.23 [62.80]			-68.29 [59.44]		-152.7 [87.60]		-261.8* [107.1]
safety_ME				11.13 [40.11]			2.453 [41.76]		-40.64 [52.74]	-97.8 [68.67]
safety_reduce				58.2 [52.65]			46.81 [45.16]		57.35 [79.37]	-99.49 [64.92]
safety_NE				33.19 [64.09]			6.164 [49.67]		-0.97 [63.87]	-167.4 [89.70]
safety_ME # FR				11.81 [56.72]			37.95 [42.76]		25.42 [71.15]	108.8 [95.15]
safety_ME # UK				10.77 [53.25]			0.244 [44.63]		-3.29 [77.36]	80.45 [95.90]
safety_ME # US				30.52 [62.92]			19.57 [57.75]		0.158 [80.25]	76.83 [101.4]
safety_reduce # FR				-49.4 [67.65]			-29.66 [49.62]		-66.67 [85.01]	104.6 [71.03]
safety_reduce # UK				-34.75 [65.50]			-53.41 [50.55]		-92.5 [83.10]	77.11 [69.42]
safety_reduce # US				1.645 [72.57]			-5.821 [54.30]		-33.85 [86.44]	169.9 [85.93]
safety_NE # FR				38.03 [89.02]			57.76 [75.18]		44.05 [88.42]	204.9* [101.5]
safety_NE # UK				15.94 [85.38]			18.05 [76.24]		30.64 [95.82]	191.5 [103.6]
safety_NE # US				71.72 [92.96]			62.28 [77.17]		80.69 [92.01]	275.0* [105.5]
Constant	143.4*** [22.27]	161.2** [48.17]	128.8*** [16.48]	128.0*** [32.35]	62.27 [71.06]	30.98 [49.42]	31.11 [65.87]	-60.86 [78.25]	19.37 [83.28]	-58.98 [93.60]
Observation	127	86	115	115	86	115	115	86	86	86
R^2	0.213	0.112	0.128	0.136	0.372	0.331	0.299	0.434	0.442	0.499
Adj R^2	0.153	0.032	0.016	0.005	0.226	0.171	0.112	0.224	0.168	0.149

Source:

Authors' analysis of data, as described in Methods section.

Notes:

[1] Sensitivity analysis with a sqrt transformation of the dependent variable, total cost per patient per (b) (4) treatment in the first year of marketing (mean estimate (b) (4) from Chapter 3), assuming treatment duration (b) (4)

[2] 1: Treatment descriptors (treated condition, rarity); 2: OS; 3: QoL; 4: safety.

[3] Reference categories: ascites; AU; QoL: improve; safety: improve.

[4] Standard errors (SE) are provided in brackets. ***: $p \leq 0.01$, **: $p \leq 0.05$, *: $p \leq 0.10$

Appendix 5.15

eTable 24. Multivariate Linear Regression Analysis, Total Number of Patients Completing (b) (4) Therapy with New Medicines per 100,000 Incident Cases of Neoplasm and their Beneficial Impact to Health in the First Year of Drug Marketing in Australia, France, the UK, and the US

Variable	Model[1]									
	(A)	(B)	(C)	(D)	(E)	(F)	(G)	(H)	(I)	(J)
Dep. Var.	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi
Ind. Var[2]	1	2	3	4	1, 2	1, 3	1, 4	1, 2, 3	1, 2, 4	1, 2, 3, 4
orphan	-0.0487 [0.613]				0.325 [0.721]	-0.33 [0.610]	0.633 [0.640	-0.477 [0.790]	1.313 [0.899]	0.223 [0.917]
breast	2.135** [0.714]				0.532 [0.991]	0.937 [0.745]	0.0767 [1.049]	-0.126 [0.936]	0.273 [1.134]	-0.642 [0.998
gi	2.548** [0.857]				1.334 [1.125]	1.779* [0.811]	1.031 [1.122]	0.742 [1.075]	1.673 [1.304]	0.817 [1.065]
hematological	0.487 [0.360]				-0.573 [0.569]	-0.271 [0.484]	-1.684* [0.687]	-0.744 [0.496]	-1.080* [0.531]	-1.029* [0.424]
lung	2.830*** [0.709]				2.113* [0.887]	1.347 [0.883]	0.983 [0.943]	0.543 [1.091]	1.515 [1.001]	1.181 [1.188]
prostate	2.265** [0.783]				1.346 [0.951]	1.204 [0.759]	0.304 [1.053]	0.367 [0.907]	0.82 [1.131]	-0.0657 [1.057]
renal	0.951 [0.562]				0.738 [0.769]	0.059 [0.545]	-1.616 [0.983]	-0.0456 [0.932]	0.0359 [1.146]	0.399 [1.286]
skin	0.602 [0.923]				0.443 [1.288]	-0.259 [0.957]	-1.004 [1.093]	0.287 [1.246]	0.835 [1.340]	-0.409 [1.185]
thyroid	-0.635 [0.613]				-0.261 [0.721]	-0.916 [0.610]	-1.92 [1.069]	-1.063 [0.790]	-0.457 [1.390]	-1.375 [1.336]
OS		0.0732 [0.0933]			0.166 [0.120]			-0.0133 [0.110]	0.125 [0.094	0.0738 [0.102]
FR		1.77 [1.101]	1.318 [0.794]	-0.49 [1.496]	2.242* [1.004]	1.117 [0.894]	-0.49 [1.719]	0.41 [1.505]	-0.332 [2.219]	-0.0892 [2.500]
UK		0.0745 [0.849]	-0.0243 [0.810]	-1.202 [1.615]	0.677 [0.822]	-0.17 [0.858]	-1.202 [1.306]	-1.535 [1.286]	-0.226 [1.239]	-0.368 [1.443]
US		2.477* [0.957]	1.790* [0.812]	3.062 [1.555]	3.035*** [0.829]	1.589 [0.847]	2.792** [0.939]	1.224 [1.208]	4.132** [1.438]	4.164** [1.528]
FR # OS		-0.0338 [0.199]			-0.079 [0.227]			0.0122 [0.224]	-0.153 [0.189]	-0.107 [0.166]
UK # OS		0.132 [0.115]			0.0687 [0.136]			0.218 [0.127]	0.0203 [0.122]	0.213 [0.156]
US # OS		0.0341 [0.138]			-0.0235 [0.150]			0.093 [0.139]	-0.0327 [0.116]	0.0929 [0.112]
QoL_ME			-3.451*** [0.626]			-2.239** [0.784]				
QoL_reduce			0.492 [0.516]			1.492 [0.915]		1.142 [1.145]		1.963 [1.010]
QoL_NE			-2.408** [0.765]			-2.821*** [0.758]		-3.413** [1.208]		-1.884 [1.541]
QoL_ME # UK			-2.059* [0.884]			-2.114* [0.897]				
QoL_reduce # FR			-4.403* [1.704]			-4.527* [1.855]		-6.350** [1.881]		-6.700*** [1.511]
QoL_reduce # UK			-3.08 [2.042]			-3.258 [2.159]		0.0833 [1.696]		1.55 [2.496]
QoL_reduce # US			-0.8 [0.929]			-0.758 [1.035]		0 [.]		0 [.]

QoL_NE # FR			2.300* [1.127]			2.696* [1.087]		3.294* [1.473]		2.921 [1.573]
QoL_NE # UK			1.874 [1.049]			2.372* [1.008]		3.123* [1.326]		3.909* [1.783]
QoL_NE # US			1.99 [1.165]			2.424* [1.060]		2.548 [1.347]		2.744 [1.570]
safety_ME				-0.937 [1.485]			-1.048 [1.243]		0.0365 [1.375]	1.227 [1.359]
safety_reduce				-2.182* [1.019]			-2.472*** [0.664]		-2.679* [1.180]	-0.487 [1.557]
safety_NE				-0.963 [1.019]			-1.445* [0.579]		-1.558 [1.214]	0.491 [1.918]
safety_ME # FR				3.055 [2.089]			3.372 [2.152]		3.797 [2.444]	2.493 [2.533]
safety_ME # UK				2.037 [2.297]			2.449 [2.015]		1.864 [1.684]	0.163 [1.660]
safety_ME # US				-0.988 [2.118]			-0.156 [1.661]		-1.856 [1.806]	-3.144 [1.758]
safety_reduce # FR				3.658* [1.711]			3.823* [1.873]		4.338 [2.243]	2.108 [2.654]
safety_reduce # UK				2.826 [1.758]			3.102* [1.502]		2.203 [1.533]	-1.374 [2.115]
safety_reduce # US				0.414 [1.749]			0.849 [1.191]		0.364 [1.605]	-2.382 [1.918]
safety_NE # FR				0.735 [1.847]			1.269 [1.891]		1.587 [2.379]	-1.086 [2.844]
safety_NE # UK				-0.415 [1.866]			0.107 [1.525]		-0.102 [1.475]	-3.364 [2.134]
safety_NE # US				-2.516 [1.869]			-1.583 [1.206]		-2.922 [1.736]	-5.343* [2.175]
Constant	1.376* [0.613]	1.828* [0.718]	2.687*** [0.516]	3.059*** [0.847]	0.325 [1.180]	2.277* [1.082]	3.234** [1.081]	3.629* [1.490]	1.901 [1.374]	2.321 [1.733]
Observation	137	96	125	125	96	125	125	96	96	96
R^2	0.159	0.224	0.33	0.299	0.35	0.453	0.448	0.469	0.559	0.653
Adj R^2	0.1	0.162	0.252	0.202	0.219	0.335	0.315	0.3	0.375	0.451

Source:

Authors' analysis of data, as described in Methods section.

Notes:

[1] Sensitivity analysis with a natural log transformation of the dependent variable, total number of patients completing [redacted] therapy in the first year of marketing per 100,000 incident cases of neoplasm (TPi)(mean estimate of distribution from Chapter 3), assuming treatment duration [redacted]

[2] 1: Treatment descriptors (treated condition, rarity); 2: OS; 3: QoL; 4: safety.

[3] Reference categories: ascites; AU; QoL: improve; safety: improve.

[4] Standard errors (SE) are provided in brackets. ***: p ≤ 0.01, **: p ≤ 0.05, *: p ≤ 0.10

Appendix 5.16

eTable 25. Multivariate Linear Regression Analysis, Total Cost per Patient per (b) (4) Treatment with New Medicines and their Beneficial Impact to Health in the First Year of Drug Marketing in Australia, France, the UK, and the US

Variable	Model[1]									
	(A)	(B)	(C)	(D)	(E)	(F)	(G)	(H)	(I)	(J)
Dep. Var.	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp	sqrt_ TCp
Ind. Var[2]	1	2	3	4	1, 2	1, 3	1, 4	1, 2, 3	1, 2, 4	1, 2, 3, 4
orphan	3.356 [17.85]				59.47 [30.43]	24.21 [19.58]	19.7 [19.57]	74.26* [31.67]	56.89 [35.00]	112.2** [37.79]
breast	71.24*** [19.52]				105.8* [43.93]	105.1** [32.04]	119.3* [55.37]	114.0* [47.08]	130.1 [71.71]	167.2* [73.55]
gi	63.03* [28.63]				124.3** [42.49]	87.81** [32.53]	108.5 [58.88]	125.9* [48.29]	139 [74.24]	175.4* [78.19]
hematological	98.07*** [15.90]				105.2** [34.77]	112.3*** [33.00]	117.0* [50.56]	109.1* [43.16]	125.2* [62.29]	130.8* [65.24]
lung	-22.22 [20.37]				23.15 [41.77]	23.55 [35.58]	20.95 [52.72]	56.24 [51.75]	46.72 [68.37]	100.2 [74.79]
prostate	39.42 [31.84]				90.67 [50.89]	75.81 [44.48]	89.6 [61.19]	109.1 [56.60]	117.9 [75.97]	163.1* [79.27]
renal	20.25* [8.825]				2.731 [27.12]	38.17 [25.24]	61.98 [50.94]	6.543 [40.92]	19.13 [65.12]	13.58 [71.39]
skin	113.4*** [27.01]				252.1*** [40.88]	165.9*** [37.64]	151.0** [53.14]	264.5*** [45.75]	271.0*** [71.24]	324.1*** [75.93]
thyroid	229.4*** [17.85]				285.5*** [30.43]	250.3*** [19.58]	273.1*** [57.61]	300.3*** [31.67]	325.1*** [70.05]	369.6*** [74.17]
OS		1.198 [4.548]			-4.718 [4.780]			2.01 [5.058]	-4.716 [5.989]	3.641 [6.651]
FR		-12.01 [48.79]	21.12 [22.93]	12.54 [43.69]	-22.23 [45.43]	36.35 [22.84]	-10.06 [20.80]	51.75 [42.59]	-32.46 [33.03]	-15.36 [35.86]
UK		24.51 [50.19]	56.77* [24.89]	51.88 [37.77]	8.446 [46.32]	70.08** [24.41]	59.82** [18.26]	86.73* [41.44]	30.72 [22.09]	47.57* [19.01]
US		39.21 [52.08]	62.29* [24.92]	39.84 [48.60]	24.36 [47.38]	74.42** [25.56]	46.41 [26.60]	98.91* [46.83]	20.85 [26.72]	43.43 [32.69]
FR # OS		3.635 [5.949]			9.432 [5.298]			3.569 [5.038]	10.73 [6.586]	2.443 [6.543]
UK # OS		5.552 [6.854]			10.86 [5.948]			4.619 [5.544]	12.71 [7.238]	4.645 [7.027]
US # OS		4.404 [6.554]			8.919 [6.342]			3.085 [5.972]	10.83 [7.415]	0.202 [8.521]
QoL_ME			59.67** [20.31]			4.493 [27.32]				
QoL_reduce			65.84*** [14.44]			-30.86 [28.61]		10.87 [50.92]		-45.91 [75.21]
QoL_NE			72.99 [46.60]			78.28 [45.14]		123.6 [77.00]		184 [95.08]
QoL_ME # UK			7.534 [28.70]			6.351 [24.76]				
QoL_reduce # FR			-57.64 [41.01]			-21.84 [29.91]		-30.53 [54.07]		54.72 [88.66]
QoL_reduce # UK			-56.8 [46.67]			-19.08 [34.85]		-36.31 [52.26]		64.25 [87.84]
QoL_reduce # US			-11.26 [28.82]			15.54 [37.46]		0 [.]		0 [.]

QoL_NE # FR			-48.9 [54.44]			-71.92 [52.48]		-113.8 [79.40]		-188.8 [94.21]
QoL_NE # UK			-42.83 [57.44]			-73.47 [54.61]		-121.9 [79.65]		-186 [96.43]
QoL_NE # US			-32.61 [58.60]			-56.67 [55.21]		-121.2 [83.05]		-231.1* [108.0]
safety_ME				-11.62 [34.69]			-12.73 [31.84]		-51.99 [37.54]	-106.1* [50.11]
safety_reduce				32.64 [49.90]			21.48 [43.50]		30.22 [74.01]	-105.4 [63.26]
safety_NE				8.857 [55.46]			-11.51 [43.80]		-32.68 [54.65]	-174.3* [81.85]
safety_ME # FR				-0.643 [50.74]			31.8 [34.38]		39.05 [54.65]	107.4 [69.54]
safety_ME # UK				-2.64 [48.36]			-8.111 [35.65]		-4.042 [53.55]	63.38 [64.95]
safety_ME # US				7.343 [59.07]			0.177 [48.67]		-20.12 [63.79]	46.06 [75.46]
safety_reduce # FR				-38.88 [62.37]			-14.4 [46.91]		-37.44 [78.23]	109.5 [66.71]
safety_reduce # UK				-28.76 [61.16]			-47.64 [48.00]		-77.12 [76.65]	66.21 [68.38]
safety_reduce # US				0.804 [67.89]			-6.876 [51.15]		-31.48 [80.54]	145.2 [91.31]
safety_NE # FR				33.67 [77.51]			62.51 [66.76]		62.16 [76.93]	203.0* [93.23]
safety_NE # UK				7.959 [73.30]			12.69 [65.63]		27.89 [81.17]	166.5 [95.00]
safety_NE # US				57.25 [81.56]			49.74 [67.82]		65.41 [81.08]	237.6* [99.86]
Constant	103.4*** [17.85]	130.7** [42.10]	101.1*** [14.44]	119.8*** [28.81]	38.86 [64.39]	7.668 [42.24]	26.07 [56.23]	-55.91 [71.85]	23.97 [71.14]	-43.12 [78.06]
Observation	131	90	119	119	90	119	119	90	90	90
R^2	0.244	0.096	0.136	0.117	0.373	0.34	0.324	0.415	0.443	0.494
Adj R^2	0.188	0.019	0.029	-0.012	0.236	0.189	0.151	0.212	0.188	0.166

Source:

Authors' analysis of data, as described in Methods section.

Notes:

[1] Sensitivity analysis with a sqrt transformation of the dependent variable, total cost per patient per (b) (4) treatment in the first year of marketing (mean estimate (b) (4) from Chapter 3), assuming treatment duration (b) (4)

[2] 1: Treatment descriptors (treated condition, rarity); 2: OS; 3: QoL; 4: safety.

[3] Reference categories: ascites; AU; QoL: improve; safety: improve.

[4] Standard errors (SE) are provided in brackets. ***: $p \leq 0.01$, **: $p \leq 0.05$, *: $p \leq 0.10$

Appendix 5.17

eTable 26. Multivariate Linear Regression Analysis, Total Number of Patients Completing (b) (4) Therapy with New Medicines per 100,000 Incident Cases of Neoplasm and their Beneficial Impact to Health in the First Year of Drug Marketing in Australia, France, the UK, and the US

Variable	Model[1]									
	(A)	(B)	(C)	(D)	(E)	(F)	(G)	(H)	(I)	(J)
Dep. Var.	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi	log_ TPi
Ind. Var[2]	1	2	3	4	1, 2	1, 3	1, 4	1, 2, 3	1, 2, 4	1, 2, 3, 4
orphan	0.0467 [0.624]				0.394 [0.754]	-0.155 [0.613]	0.802 [0.687]	-0.483 [0.841]	1.275 [0.992]	-0.254 [0.940
breast	1.01 [0.722]				-0.679 [1.027]	-0.268 [0.766]	-0.822 [1.077]	-1.371 [0.977]	-0.72 [1.184]	-1.856 [1.048]
gi	1.185 [0.870]				-0.0419 [1.166]	0.446 [0.833]	-0.146 [1.149]	-0.69 [1.144]	0.439 [1.346]	-0.766 [1.130]
hematologic al	-0.413 [0.369]				-1.562** [0.577]	-1.147* [0.498]	-2.365** [0.702]	-1.720** [0.537]	-1.901**	-1.875** [0.564]
lung	2.203** [0.682]				1.45 [0.908]	0.531 [0.869]	0.536 [0.979]	-0.51 [1.094]	1.036 [1.103]	-0.22 [1.305]
prostate	1.457 [0.825]				0.484 [1.014]	0.344 [0.793]	-0.279 [1.112]	-0.649 [0.975]	0.178 [1.194]	-1.094 [1.135]
renal	0.605 [0.534]				-0.123 [0.738]	-0.409 [0.548]	-1.753 [0.966]	-1.15 [0.924]	-0.576 [1.128]	-0.593 [1.340]
skin	-0.0827 [0.931]				-0.822 [1.346]	-1.02 [0.950]	-1.542 [1.123]	-0.848 [1.303]	-0.245 [1.418]	-1.435 [1.250]
thyroid	-1.055 [0.624]				-0.708 [0.754]	-1.256* [0.613]	-2.12 [1.099]	-1.584 [0.841]	-0.645 [1.430]	-1.874 [1.447]
OS		0.0701 [0.109]			0.179 [0.122]			-0.0373 [0.108]	0.15 [0.109]	0.0059 [0.124]
FR		1.828 [1.170]	1.292 [0.736]	-0.488 [1.483]	2.348* [1.018]	1.16 [0.828]	-0.488 [1.603]	0.449 [1.475]	-0.309 [2.219]	0.0178 [2.565]
UK		0.224 [0.957]	-0.0551 [0.798]	-1.223 [1.633]	0.775 [0.854]	-0.135 [0.846]	-1.223 [1.270]	-1.507 [1.333]	-0.204 [1.425]	-0.262 [1.659]
US		2.633* [1.040]	1.813* [0.735]	3.221* [1.544]	3.243*** [0.849]	1.711* [0.792]	3.090**	1.33 [1.206]	4.357** [1.437]	4.339* [1.684]
FR # OS		-0.036 [0.206]			-0.0838 [0.227]			0.00909 [0.214]	-0.156 [0.199]	-0.0859 [0.176]
UK # OS		0.117 [0.130]			0.0652 [0.141]			0.216 [0.128]	0.0189 [0.138]	0.236 [0.188]
US # OS		0.0214 [0.149]			-0.0384 [0.153]			0.0824 [0.133]	-0.0553 [0.130]	0.116 [0.128]
QoL_ME			-4.358*** [0.548]			-3.267*** [0.692]				
QoL_reduce			0.822 [0.491]			1.683 [0.878]		0.373 [1.118]		1.387 [1.045]
QoL_NE			-2.908*** [0.707]			-3.108*** [0.744]		-3.882** [1.268]		-3.407* [1.625]
QoL_ME # UK			-1.876* [0.834]			-1.898* [0.850]				
QoL_reduce # FR			-4.829* [1.986]			-4.788* [2.102]		-6.254*** [1.818]		-7.442*** [1.610]
QoL_reduce # UK			-3.568* [1.754]			-3.58 [1.902]		0.156 [1.685]		0.793 [2.912]
QoL_reduce # US			-1.29 [0.742]			-1.202 [0.806]		0 [.]		0 [.]

QoL_NE # FR			2.422* [1.030]			2.735** [1.040]		3.390* [1.490]		3.537* [1.569]
QoL_NE # UK			2.106* [1.002]			2.419* [1.004]		3.226* [1.386]		4.538* [1.946]
QoL_NE # US			2.168* [1.058]			2.497* [1.010]		2.709 [1.383]		3.822* [1.601]
safety_ME				-1.055 [1.436]			-1.21 [1.349]		-0.17 [1.637]	1.426 [1.596]
safety_reduce				-2.472* [1.138]			-2.455** [0.825]		-2.737* [1.321]	0.543 [1.662]
safety_NE				-1.112 [1.216]			-1.394 [0.751]		-1.419 [1.313]	1.758 [1.918]
safety_ME # FR				3.074 [1.899]			3.475 [2.056]		3.79 [2.486]	1.945 [2.573]
safety_ME # UK				1.984 [2.243]			2.493 [2.065]		1.844 [2.030]	-0.398 [1.920]
safety_ME # US				-1.09 [2.014]			-0.269 [1.708]		-1.651 [1.903]	-3.317 [1.950]
safety_reduce # FR				3.644* [1.719]			3.817* [1.776]		4.368 [2.244]	1.373 [2.644]
safety_reduce # UK				2.86 [1.800]			3.114* [1.482]		2.221 [1.698]	-2.128 [2.336]
safety_reduce # US				0.255 [1.731]			0.559 [1.162]		0.282 [1.612]	-3.483 [2.014]
safety_NE # FR				0.802 [1.874]			1.385 [1.805]		1.778 [2.360]	-1.569 [2.793]
safety_NE # UK				-0.209 [1.945]			0.233 [1.521]		0.0844 [1.620]	-3.861 [2.184]
safety_NE # US				-2.553 [1.912]			-1.726 [1.235]		-2.911 [1.712]	-6.267** [2.169]
Constant	3.135*** [0.624]	2.613** [0.833]	3.847*** [0.491]	4.205*** [0.958]	2.013 [1.245]	4.162*** [1.104]	4.764*** [1.227]	5.827*** [1.598]	3.445* [1.467]	4.670* [1.963]
Observation	137	96	125	125	96	125	125	96	96	96
R^2	0.135	0.22	0.397	0.31	0.369	0.473	0.426	0.501	0.545	0.638
Adj R^2	0.073	0.158	0.326	0.215	0.241	0.36	0.289	0.341	0.355	0.428

Source:

Authors' analysis of data, as described in Methods section.

Notes:

[1] Sensitivity analysis with a natural log transformation of the dependent variable, total number of patients completing [redacted] treatment in the first year of marketing per 100,000 incident cases of neoplasm (TPi)(mean estimate of distribution from Chapter 3), assuming treatment duration [redacted]

[2] 1: Treatment descriptors (treated condition, rarity); 2: OS; 3: QoL; 4: safety.

[3] Reference categories: ascites; AU; QoL: improve; safety: improve.

[4] Standard errors (SE) are provided in brackets. ***: p ≤ 0.01, **: p ≤ 0.05, *: p ≤ 0.10

Appendix 7.1

Stata code. Print-out starts on following page.

```
1
2   ///
3   /*
4   Code by:    Sebastian Salas-Vega
5               London School of Economics and Political Science
6   Version:    v4_Final
7   Date:       31 Jan 2017
8   */
9   ///
10
11
12  * Mac
13  cd "/Users/salasveg/Desktop/Project Files/Cancer/Cancer Paper 1_FINAL/Comparative Study of Spending Value/Value Data/YLL
    Analysis/YLL Relationship with Generic Use"
14
15
16  * Prepare Stata:
17  set more off
18  set trace off
19  set maxvar 32767
20  set segmentsize 256m
21
22  * Load data:
23  use "/Users/salasveg/Desktop/Project Files/Cancer/Cancer Paper 1_FINAL/Comparative Study of Spending Value/Value Data/YLL
    Analysis/YLL Relationship with Generic Use/YLL_IHMEtotal_RelationshipwithGenericUtilization_DerivedYLLvalues.dta"
24
25
26  /// Dataset preparation
27
28  drop if (age_group_name != "Age-standardized" | sex_name !="Both sexes" | unit !="Rate per 100,000" | cause_name != "Neoplasms")
29  drop if (location_name == "Canada" | location_name == "Germany" | location_name == "Italy" | location_name == "Japan" |
    location_name == "Sweden")
30
31  gen location_id=.
32      replace location_id = 1 if location_name=="Australia"
33      replace location_id = 3 if location_name=="France"
34      replace location_id = 8 if location_name=="United Kingdom"
35      replace location_id = 9 if location_name=="United States"
36
37  drop if location_id == .
38
39  sort location_id year case_id
40
41  * Bring in utilization and expenditure data from "/Descriptives/UpdatedHADataset_expendConsumption_FINAL.dta" for years 2005,
    2010, and 2013.
42  * Look at association between YLLs in each year for each indication with three variables (taking advantage of previous command
    duplicating observations by 3. These variables include: 1) country-wide utilization of cancer medicines per year per capita (given
    e.g. off-label use, we can't link drugs by ATC to YLLs by cause_name), ///
43  * 2) country-wide proportion use of generic medicines per capita (i.e. out of all medicines used in each country in each year, what
    percentage are generics); 3) country-wide expenditure on cancer medicines per year per capita; and 4) country-wide proportion
    expenditure of generic medicines per capita (i.e. out of total expenditure for all cancer medicines ///
44  * used in each country in each year, what percentage is spent on generics).
45
46  * For volume derivations, see "Figure_VolumeConsumption_AllYears.xlsx", "UpdatedHA_Descriptives_AllYears.do",
    "Figure_VolumeConsumption_AllYears.xlsx", and "Figure_VolumeConsumption_AllYears.xlsx"
47
48  gen double totalPerCapitaSalesSU = .
49      replace totalPerCapitaSalesSU = 2.005030357 if location_name == "Australia" & year == 2004
50      replace totalPerCapitaSalesSU = 2.551342059 if location_name == "France" & year == 2004
51      replace totalPerCapitaSalesSU = 2.848168927 if location_name == "United Kingdom" & year == 2004
52      replace totalPerCapitaSalesSU = 2.545064441 if location_name == "United States" & year == 2004
53
54      replace totalPerCapitaSalesSU = 2.531855571 if location_name == "Australia" & year == 2005
55      replace totalPerCapitaSalesSU = 2.556388039 if location_name == "France" & year == 2005
56      replace totalPerCapitaSalesSU = 2.907302745 if location_name == "United Kingdom" & year == 2005
57      replace totalPerCapitaSalesSU = 2.513759391 if location_name == "United States" & year == 2005
```

```
58
59          replace totalPerCapitaSalesSU = 1.945269617 if location_name == "Australia" & year == 2006
60          replace totalPerCapitaSalesSU = 2.709957861 if location_name == "France" & year == 2006
61          replace totalPerCapitaSalesSU = 2.684843694 if location_name == "United Kingdom" & year == 2006
62          replace totalPerCapitaSalesSU = 2.502073678 if location_name == "United States" & year == 2006
63
64          replace totalPerCapitaSalesSU = 2.145730233 if location_name == "Australia" & year == 2007
65          replace totalPerCapitaSalesSU = 2.796150660 if location_name == "France" & year == 2007
66          replace totalPerCapitaSalesSU = 2.805177199 if location_name == "United Kingdom" & year == 2007
67          replace totalPerCapitaSalesSU = 2.519407778 if location_name == "United States" & year == 2007
68
69          replace totalPerCapitaSalesSU = 2.208080257 if location_name == "Australia" & year == 2008
70          replace totalPerCapitaSalesSU = 2.748605910 if location_name == "France" & year == 2008
71          replace totalPerCapitaSalesSU = 2.940797526 if location_name == "United Kingdom" & year == 2008
72          replace totalPerCapitaSalesSU = 2.507241153 if location_name == "United States" & year == 2008
73
74          replace totalPerCapitaSalesSU = 2.288237621 if location_name == "Australia" & year == 2009
75          replace totalPerCapitaSalesSU = 2.673152231 if location_name == "France" & year == 2009
76          replace totalPerCapitaSalesSU = 3.085537669 if location_name == "United Kingdom" & year == 2009
77          replace totalPerCapitaSalesSU = 2.515365710 if location_name == "United States" & year == 2009
78
79          replace totalPerCapitaSalesSU = 2.383934458 if location_name == "Australia" & year == 2010
80          replace totalPerCapitaSalesSU = 2.624139441 if location_name == "France" & year == 2010
81          replace totalPerCapitaSalesSU = 3.273018997 if location_name == "United Kingdom" & year == 2010
82          replace totalPerCapitaSalesSU = 2.552452765 if location_name == "United States" & year == 2010
83
84          replace totalPerCapitaSalesSU = 2.386668430 if location_name == "Australia" & year == 2011
85          replace totalPerCapitaSalesSU = 2.581171865 if location_name == "France" & year == 2011
86          replace totalPerCapitaSalesSU = 3.305106720 if location_name == "United Kingdom" & year == 2011
87          replace totalPerCapitaSalesSU = 2.621787826 if location_name == "United States" & year == 2011
88
89          replace totalPerCapitaSalesSU = 2.356708747 if location_name == "Australia" & year == 2012
90          replace totalPerCapitaSalesSU = 2.602557862 if location_name == "France" & year == 2012
91          replace totalPerCapitaSalesSU = 3.413042607 if location_name == "United Kingdom" & year == 2012
92          replace totalPerCapitaSalesSU = 2.595261256 if location_name == "United States" & year == 2012
93
94          replace totalPerCapitaSalesSU = 2.374399093 if location_name == "Australia" & year == 2013
95          replace totalPerCapitaSalesSU = 2.635270332 if location_name == "France" & year == 2013
96          replace totalPerCapitaSalesSU = 3.544536452 if location_name == "United Kingdom" & year == 2013
97          replace totalPerCapitaSalesSU = 2.643948123 if location_name == "United States" & year == 2013
98
99          replace totalPerCapitaSalesSU = 2.529025783 if location_name == "Australia" & year == 2014
100         replace totalPerCapitaSalesSU = 2.680253291 if location_name == "France" & year == 2014
101         replace totalPerCapitaSalesSU = 3.761700707 if location_name == "United Kingdom" & year == 2014
102         replace totalPerCapitaSalesSU = 2.690603629 if location_name == "United States" & year == 2014
103
104     label variable totalPerCapitaSalesSU "Total drug sales (SU) per capita, by location_name in each year"
105     format totalPerCapitaSalesSU %12.0g
106
107     gen double prop_Sales_generic = .
108         replace prop_Sales_generic = 0.318938467 if location_name == "Australia" & year == 2004
109         replace prop_Sales_generic = 0.151408400 if location_name == "France" & year == 2004
110         replace prop_Sales_generic = 0.349434545 if location_name == "United Kingdom" & year == 2004
111         replace prop_Sales_generic = 0.488183604 if location_name == "United States" & year == 2004
112
113         replace prop_Sales_generic = 0.416042970 if location_name == "Australia" & year == 2005
114         replace prop_Sales_generic = 0.145246739 if location_name == "France" & year == 2005
115         replace prop_Sales_generic = 0.349914158 if location_name == "United Kingdom" & year == 2005
116         replace prop_Sales_generic = 0.524453324 if location_name == "United States" & year == 2005
117
118         replace prop_Sales_generic = 0.337018569 if location_name == "Australia" & year == 2006
119         replace prop_Sales_generic = 0.144576308 if location_name == "France" & year == 2006
120         replace prop_Sales_generic = 0.352311133 if location_name == "United Kingdom" & year == 2006
121         replace prop_Sales_generic = 0.527513273 if location_name == "United States" & year == 2006
122
123         replace prop_Sales_generic = 0.343799431 if location_name == "Australia" & year == 2007
124         replace prop_Sales_generic = 0.154081218 if location_name == "France" & year == 2007
```

```
        replace prop_Sales_generic = 0.399629905 if location_name == "United Kingdom" & year == 2007
        replace prop_Sales_generic = 0.531156961 if location_name == "United States" & year == 2007

        replace prop_Sales_generic = 0.344337842 if location_name == "Australia" & year == 2008
        replace prop_Sales_generic = 0.176172289 if location_name == "France" & year == 2008
        replace prop_Sales_generic = 0.435169081 if location_name == "United Kingdom" & year == 2008
        replace prop_Sales_generic = 0.546965005 if location_name == "United States" & year == 2008

        replace prop_Sales_generic = 0.344555320 if location_name == "Australia" & year == 2009
        replace prop_Sales_generic = 0.197950464 if location_name == "France" & year == 2009
        replace prop_Sales_generic = 0.440116812 if location_name == "United Kingdom" & year == 2009
        replace prop_Sales_generic = 0.566830950 if location_name == "United States" & year == 2009

        replace prop_Sales_generic = 0.350587298 if location_name == "Australia" & year == 2010
        replace prop_Sales_generic = 0.214908438 if location_name == "France" & year == 2010
        replace prop_Sales_generic = 0.462174331 if location_name == "United Kingdom" & year == 2010
        replace prop_Sales_generic = 0.611057497 if location_name == "United States" & year == 2010

        replace prop_Sales_generic = 0.358383295 if location_name == "Australia" & year == 2011
        replace prop_Sales_generic = 0.243114008 if location_name == "France" & year == 2011
        replace prop_Sales_generic = 0.531450226 if location_name == "United Kingdom" & year == 2011
        replace prop_Sales_generic = 0.632835289 if location_name == "United States" & year == 2011

        replace prop_Sales_generic = 0.369021091 if location_name == "Australia" & year == 2012
        replace prop_Sales_generic = 0.260276730 if location_name == "France" & year == 2012
        replace prop_Sales_generic = 0.551391407 if location_name == "United Kingdom" & year == 2012
        replace prop_Sales_generic = 0.661197142 if location_name == "United States" & year == 2012

        replace prop_Sales_generic = 0.371904669 if location_name == "Australia" & year == 2013
        replace prop_Sales_generic = 0.270129408 if location_name == "France" & year == 2013
        replace prop_Sales_generic = 0.557098470 if location_name == "United Kingdom" & year == 2013
        replace prop_Sales_generic = 0.689145529 if location_name == "United States" & year == 2013

        replace prop_Sales_generic = 0.415767745 if location_name == "Australia" & year == 2014
        replace prop_Sales_generic = 0.288525472 if location_name == "France" & year == 2014
        replace prop_Sales_generic = 0.574276997 if location_name == "United Kingdom" & year == 2014
        replace prop_Sales_generic = 0.711754930 if location_name == "United States" & year == 2014
label variable prop_Sales_generic "Proportion of total drug sales sold as generics, by location_name in each year"
format prop_Sales_generic %12.0g

gen double prop_Sales_genericMG = .
    replace prop_Sales_genericMG = 0.298928202 if location_name == "Australia" & year == 2004
    replace prop_Sales_genericMG = 0.166081296 if location_name == "France" & year == 2004
    replace prop_Sales_genericMG = 0.322215670 if location_name == "United Kingdom" & year == 2004
    replace prop_Sales_genericMG = 0.499346964 if location_name == "United States" & year == 2004

    replace prop_Sales_genericMG = 0.297418662 if location_name == "Australia" & year == 2005
    replace prop_Sales_genericMG = 0.171799331 if location_name == "France" & year == 2005
    replace prop_Sales_genericMG = 0.325372987 if location_name == "United Kingdom" & year == 2005
    replace prop_Sales_genericMG = 0.545300607 if location_name == "United States" & year == 2005

    replace prop_Sales_genericMG = 0.328818017 if location_name == "Australia" & year == 2006
    replace prop_Sales_genericMG = 0.175239886 if location_name == "France" & year == 2006
    replace prop_Sales_genericMG = 0.338529012 if location_name == "United Kingdom" & year == 2006
    replace prop_Sales_genericMG = 0.552920134 if location_name == "United States" & year == 2006

    replace prop_Sales_genericMG = 0.367141923 if location_name == "Australia" & year == 2007
    replace prop_Sales_genericMG = 0.187936048 if location_name == "France" & year == 2007
    replace prop_Sales_genericMG = 0.393261749 if location_name == "United Kingdom" & year == 2007
    replace prop_Sales_genericMG = 0.560345864 if location_name == "United States" & year == 2007

    replace prop_Sales_genericMG = 0.373580000 if location_name == "Australia" & year == 2008
    replace prop_Sales_genericMG = 0.229880894 if location_name == "France" & year == 2008
    replace prop_Sales_genericMG = 0.432742529 if location_name == "United Kingdom" & year == 2008
    replace prop_Sales_genericMG = 0.584150608 if location_name == "United States" & year == 2008

```

```
        replace prop_Sales_genericMG = 0.369227657 if location_name == "Australia" & year == 2009
        replace prop_Sales_genericMG = 0.258419834 if location_name == "France" & year == 2009
        replace prop_Sales_genericMG = 0.446392379 if location_name == "United Kingdom" & year == 2009
        replace prop_Sales_genericMG = 0.621300932 if location_name == "United States" & year == 2009

        replace prop_Sales_genericMG = 0.389109696 if location_name == "Australia" & year == 2010
        replace prop_Sales_genericMG = 0.297150245 if location_name == "France" & year == 2010
        replace prop_Sales_genericMG = 0.455077569 if location_name == "United Kingdom" & year == 2010
        replace prop_Sales_genericMG = 0.643511521 if location_name == "United States" & year == 2010

        replace prop_Sales_genericMG = 0.387003541 if location_name == "Australia" & year == 2011
        replace prop_Sales_genericMG = 0.322674125 if location_name == "France" & year == 2011
        replace prop_Sales_genericMG = 0.517660701 if location_name == "United Kingdom" & year == 2011
        replace prop_Sales_genericMG = 0.636476581 if location_name == "United States" & year == 2011

        replace prop_Sales_genericMG = 0.273154116 if location_name == "Australia" & year == 2012
        replace prop_Sales_genericMG = 0.318978963 if location_name == "France" & year == 2012
        replace prop_Sales_genericMG = 0.509967521 if location_name == "United Kingdom" & year == 2012
        replace prop_Sales_genericMG = 0.634116085 if location_name == "United States" & year == 2012

        replace prop_Sales_genericMG = 0.391276901 if location_name == "Australia" & year == 2013
        replace prop_Sales_genericMG = 0.318300382 if location_name == "France" & year == 2013
        replace prop_Sales_genericMG = 0.514184231 if location_name == "United Kingdom" & year == 2013
        replace prop_Sales_genericMG = 0.638734740 if location_name == "United States" & year == 2013

        replace prop_Sales_genericMG = 0.410989933 if location_name == "Australia" & year == 2014
        replace prop_Sales_genericMG = 0.343220525 if location_name == "France" & year == 2014
        replace prop_Sales_genericMG = 0.567959785 if location_name == "United Kingdom" & year == 2014
        replace prop_Sales_genericMG = 0.679999359 if location_name == "United States" & year == 2014
label variable prop_Sales_genericMG "Proportion of total drug sales sold as generics (MG), by location_name in each year"
format prop_Sales_genericMG %12.0g

gen double prop_Sales_branded = .
    replace prop_Sales_branded = 0.681061533 if location_name == "Australia" & year == 2004
    replace prop_Sales_branded = 0.848591600 if location_name == "France" & year == 2004
    replace prop_Sales_branded = 0.650565455 if location_name == "United Kingdom" & year == 2004
    replace prop_Sales_branded = 0.511816396 if location_name == "United States" & year == 2004

    replace prop_Sales_branded = 0.583957030 if location_name == "Australia" & year == 2005
    replace prop_Sales_branded = 0.854753261 if location_name == "France" & year == 2005
    replace prop_Sales_branded = 0.650085842 if location_name == "United Kingdom" & year == 2005
    replace prop_Sales_branded = 0.475546676 if location_name == "United States" & year == 2005

    replace prop_Sales_branded = 0.662981431 if location_name == "Australia" & year == 2006
    replace prop_Sales_branded = 0.855423692 if location_name == "France" & year == 2006
    replace prop_Sales_branded = 0.647688867 if location_name == "United Kingdom" & year == 2006
    replace prop_Sales_branded = 0.472486727 if location_name == "United States" & year == 2006

    replace prop_Sales_branded = 0.656200569 if location_name == "Australia" & year == 2007
    replace prop_Sales_branded = 0.845918782 if location_name == "France" & year == 2007
    replace prop_Sales_branded = 0.600370095 if location_name == "United Kingdom" & year == 2007
    replace prop_Sales_branded = 0.468843039 if location_name == "United States" & year == 2007

    replace prop_Sales_branded = 0.655662158 if location_name == "Australia" & year == 2008
    replace prop_Sales_branded = 0.823827711 if location_name == "France" & year == 2008
    replace prop_Sales_branded = 0.564830919 if location_name == "United Kingdom" & year == 2008
    replace prop_Sales_branded = 0.453034995 if location_name == "United States" & year == 2008

    replace prop_Sales_branded = 0.655444680 if location_name == "Australia" & year == 2009
    replace prop_Sales_branded = 0.802049536 if location_name == "France" & year == 2009
    replace prop_Sales_branded = 0.559883188 if location_name == "United Kingdom" & year == 2009
    replace prop_Sales_branded = 0.433169050 if location_name == "United States" & year == 2009

    replace prop_Sales_branded = 0.649412702 if location_name == "Australia" & year == 2010
    replace prop_Sales_branded = 0.785091562 if location_name == "France" & year == 2010
    replace prop_Sales_branded = 0.537825669 if location_name == "United Kingdom" & year == 2010
```

```
257         replace prop_Sales_branded = 0.388942503 if location_name == "United States" & year == 2010
258
259         replace prop_Sales_branded = 0.641616705 if location_name == "Australia" & year == 2011
260         replace prop_Sales_branded = 0.756885992 if location_name == "France" & year == 2011
261         replace prop_Sales_branded = 0.468549774 if location_name == "United Kingdom" & year == 2011
262         replace prop_Sales_branded = 0.367164711 if location_name == "United States" & year == 2011
263
264         replace prop_Sales_branded = 0.630978909 if location_name == "Australia" & year == 2012
265         replace prop_Sales_branded = 0.739723270 if location_name == "France" & year == 2012
266         replace prop_Sales_branded = 0.448608593 if location_name == "United Kingdom" & year == 2012
267         replace prop_Sales_branded = 0.338802858 if location_name == "United States" & year == 2012
268
269         replace prop_Sales_branded = 0.628095331 if location_name == "Australia" & year == 2013
270         replace prop_Sales_branded = 0.729870592 if location_name == "France" & year == 2013
271         replace prop_Sales_branded = 0.442901530 if location_name == "United Kingdom" & year == 2013
272         replace prop_Sales_branded = 0.310854471 if location_name == "United States" & year == 2013
273
274         replace prop_Sales_branded = 0.584232255 if location_name == "Australia" & year == 2014
275         replace prop_Sales_branded = 0.711474528 if location_name == "France" & year == 2014
276         replace prop_Sales_branded = 0.425723003 if location_name == "United Kingdom" & year == 2014
277         replace prop_Sales_branded = 0.288245070 if location_name == "United States" & year == 2014
278     label variable prop_Sales_branded "Proportion of total drug sales sold as generics, by location_name in each year"
279     format prop_Sales_branded %12.0g
280
281     * The following two variables adjust for cancer incidence, rather than population. Data is derived from OECD & CDC data. See
        "LinReg_CancerIncidence.xlsx", "Figures_VolumeConsumption_AllYears.xlsx", & "UpdatedHA_Descriptives_AllYears.do".
282
283     gen double totalPerNeoplasmSalesSU = .
284         replace totalPerNeoplasmSalesSU = 432.545489967 if location_name == "Australia" & year == 2004
285         replace totalPerNeoplasmSalesSU = 552.292197753 if location_name == "France" & year == 2004
286         replace totalPerNeoplasmSalesSU = 607.544978967 if location_name == "United Kingdom" & year == 2004
287         replace totalPerNeoplasmSalesSU = 539.674430777 if location_name == "United States" & year == 2004
288
289         replace totalPerNeoplasmSalesSU = 533.188659683 if location_name == "Australia" & year == 2005
290         replace totalPerNeoplasmSalesSU = 542.182826225 if location_name == "France" & year == 2005
291         replace totalPerNeoplasmSalesSU = 610.643138747 if location_name == "United Kingdom" & year == 2005
292         replace totalPerNeoplasmSalesSU = 528.723447955 if location_name == "United States" & year == 2005
293
294         replace totalPerNeoplasmSalesSU = 401.061198770 if location_name == "Australia" & year == 2006
295         replace totalPerNeoplasmSalesSU = 563.229451150 if location_name == "France" & year == 2006
296         replace totalPerNeoplasmSalesSU = 555.805621555 if location_name == "United Kingdom" & year == 2006
297         replace totalPerNeoplasmSalesSU = 522.384031076 if location_name == "United States" & year == 2006
298
299         replace totalPerNeoplasmSalesSU = 429.974944284 if location_name == "Australia" & year == 2007
300         replace totalPerNeoplasmSalesSU = 569.455505290 if location_name == "France" & year == 2007
301         replace totalPerNeoplasmSalesSU = 572.879283803 if location_name == "United Kingdom" & year == 2007
302         replace totalPerNeoplasmSalesSU = 522.203704106 if location_name == "United States" & year == 2007
303
304         replace totalPerNeoplasmSalesSU = 436.532214171 if location_name == "Australia" & year == 2008
305         replace totalPerNeoplasmSalesSU = 548.561582965 if location_name == "France" & year == 2008
306         replace totalPerNeoplasmSalesSU = 592.785315781 if location_name == "United Kingdom" & year == 2008
307         replace totalPerNeoplasmSalesSU = 516.043979601 if location_name == "United States" & year == 2008
308
309         replace totalPerNeoplasmSalesSU = 447.050520656 if location_name == "Australia" & year == 2009
310         replace totalPerNeoplasmSalesSU = 522.925530244 if location_name == "France" & year == 2009
311         replace totalPerNeoplasmSalesSU = 613.968217253 if location_name == "United Kingdom" & year == 2009
312         replace totalPerNeoplasmSalesSU = 513.873672647 if location_name == "United States" & year == 2009
313
314         replace totalPerNeoplasmSalesSU = 458.407236858 if location_name == "Australia" & year == 2010
315         replace totalPerNeoplasmSalesSU = 503.368330543 if location_name == "France" & year == 2010
316         replace totalPerNeoplasmSalesSU = 643.345887794 if location_name == "United Kingdom" & year == 2010
317         replace totalPerNeoplasmSalesSU = 517.503919511 if location_name == "United States" & year == 2010
318
319         replace totalPerNeoplasmSalesSU = 451.384201435 if location_name == "Australia" & year == 2011
320         replace totalPerNeoplasmSalesSU = 485.745877190 if location_name == "France" & year == 2011
321         replace totalPerNeoplasmSalesSU = 641.984629783 if location_name == "United Kingdom" & year == 2011
322         replace totalPerNeoplasmSalesSU = 527.294254523 if location_name == "United States" & year == 2011
```

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    replace totalPerNeoplasmSalesSU = 440.247269492 if location_name == "Australia" & year == 2012
    replace totalPerNeoplasmSalesSU = 480.617706462 if location_name == "France" & year == 2012
    replace totalPerNeoplasmSalesSU = 654.808144954 if location_name == "United Kingdom" & year == 2012
    replace totalPerNeoplasmSalesSU = 517.891014978 if location_name == "United States" & year == 2012

    replace totalPerNeoplasmSalesSU = 438.530267250 if location_name == "Australia" & year == 2013
    replace totalPerNeoplasmSalesSU = 477.725398626 if location_name == "France" & year == 2013
    replace totalPerNeoplasmSalesSU = 671.531942501 if location_name == "United Kingdom" & year == 2013
    replace totalPerNeoplasmSalesSU = 523.579084986 if location_name == "United States" & year == 2013

    replace totalPerNeoplasmSalesSU = 461.391177667 if location_name == "Australia" & year == 2014
    replace totalPerNeoplasmSalesSU = 477.166378997 if location_name == "France" & year == 2014
    replace totalPerNeoplasmSalesSU = 703.951027155 if location_name == "United Kingdom" & year == 2014
    replace totalPerNeoplasmSalesSU = 528.798691910 if location_name == "United States" & year == 2014
label variable totalPerNeoplasmSalesSU "Total drug sales (SU) per incident neoplasm, by location_name in each year"
format totalPerNeoplasmSalesSU %12.0g

gen double totalPerNeoplasmSalesMG = .
    replace totalPerNeoplasmSalesMG = 43290.939500000 if location_name == "Australia" & year == 2004
    replace totalPerNeoplasmSalesMG = 60645.190200000 if location_name == "France" & year == 2004
    replace totalPerNeoplasmSalesMG = 48189.496700000 if location_name == "United Kingdom" & year == 2004
    replace totalPerNeoplasmSalesMG = 50350.944300000 if location_name == "United States" & year == 2004

    replace totalPerNeoplasmSalesMG = 42542.180100000 if location_name == "Australia" & year == 2005
    replace totalPerNeoplasmSalesMG = 61542.810300000 if location_name == "France" & year == 2005
    replace totalPerNeoplasmSalesMG = 50049.868400000 if location_name == "United Kingdom" & year == 2005
    replace totalPerNeoplasmSalesMG = 52140.842500000 if location_name == "United States" & year == 2005

    replace totalPerNeoplasmSalesMG = 44715.095700000 if location_name == "Australia" & year == 2006
    replace totalPerNeoplasmSalesMG = 66893.834400000 if location_name == "France" & year == 2006
    replace totalPerNeoplasmSalesMG = 55014.359800000 if location_name == "United Kingdom" & year == 2006
    replace totalPerNeoplasmSalesMG = 53455.308100000 if location_name == "United States" & year == 2006

    replace totalPerNeoplasmSalesMG = 46460.727290000 if location_name == "Australia" & year == 2007
    replace totalPerNeoplasmSalesMG = 69893.887600000 if location_name == "France" & year == 2007
    replace totalPerNeoplasmSalesMG = 59409.204000000 if location_name == "United Kingdom" & year == 2007
    replace totalPerNeoplasmSalesMG = 55544.900500000 if location_name == "United States" & year == 2007

    replace totalPerNeoplasmSalesMG = 47039.849570000 if location_name == "Australia" & year == 2008
    replace totalPerNeoplasmSalesMG = 70177.100900000 if location_name == "France" & year == 2008
    replace totalPerNeoplasmSalesMG = 62102.237000000 if location_name == "United Kingdom" & year == 2008
    replace totalPerNeoplasmSalesMG = 56443.977600000 if location_name == "United States" & year == 2008

    replace totalPerNeoplasmSalesMG = 46303.039100000 if location_name == "Australia" & year == 2009
    replace totalPerNeoplasmSalesMG = 68296.751800000 if location_name == "France" & year == 2009
    replace totalPerNeoplasmSalesMG = 64235.472100000 if location_name == "United Kingdom" & year == 2009
    replace totalPerNeoplasmSalesMG = 56385.799200000 if location_name == "United States" & year == 2009

    replace totalPerNeoplasmSalesMG = 46650.453300000 if location_name == "Australia" & year == 2010
    replace totalPerNeoplasmSalesMG = 67094.633300000 if location_name == "France" & year == 2010
    replace totalPerNeoplasmSalesMG = 71357.088100000 if location_name == "United Kingdom" & year == 2010
    replace totalPerNeoplasmSalesMG = 56990.767000000 if location_name == "United States" & year == 2010

    replace totalPerNeoplasmSalesMG = 47781.264100000 if location_name == "Australia" & year == 2011
    replace totalPerNeoplasmSalesMG = 65298.560500000 if location_name == "France" & year == 2011
    replace totalPerNeoplasmSalesMG = 61604.616300000 if location_name == "United Kingdom" & year == 2011
    replace totalPerNeoplasmSalesMG = 58249.813200000 if location_name == "United States" & year == 2011

    replace totalPerNeoplasmSalesMG = 48640.680710000 if location_name == "Australia" & year == 2012
    replace totalPerNeoplasmSalesMG = 66640.926500000 if location_name == "France" & year == 2012
    replace totalPerNeoplasmSalesMG = 63248.492700000 if location_name == "United Kingdom" & year == 2012
    replace totalPerNeoplasmSalesMG = 56458.940700000 if location_name == "United States" & year == 2012

    replace totalPerNeoplasmSalesMG = 50457.698340000 if location_name == "Australia" & year == 2013
    replace totalPerNeoplasmSalesMG = 66968.418100000 if location_name == "France" & year == 2013
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```
    replace totalPerNeoplasmSalesMG = 65217.815300000 if location_name == "United Kingdom" & year == 2013
    replace totalPerNeoplasmSalesMG = 55185.835200000 if location_name == "United States" & year == 2013

    replace totalPerNeoplasmSalesMG = 53564.817600000 if location_name == "Australia" & year == 2014
    replace totalPerNeoplasmSalesMG = 67577.219600000 if location_name == "France" & year == 2014
    replace totalPerNeoplasmSalesMG = 67018.856300000 if location_name == "United Kingdom" & year == 2014
    replace totalPerNeoplasmSalesMG = 54109.046000000 if location_name == "United States" & year == 2014
label variable totalPerNeoplasmSalesMG "Total drug sales (MG) per incident neoplasm, by location_name in each year"
format totalPerNeoplasmSalesMG %12.0g

* For expenditure derivations, see "Figure_Expenditure_AllYears.xlsx" & "UpdatedHA_Descriptives_AllYears.do".

gen double totalPerCapitaExpendcUSD = .
    replace totalPerCapitaExpendcUSD = 81.187264396 if location_name == "Australia" & year == 2004
    replace totalPerCapitaExpendcUSD = 118.266379249 if location_name == "France" & year == 2004
    replace totalPerCapitaExpendcUSD = 72.480729490 if location_name == "United Kingdom" & year == 2004
    replace totalPerCapitaExpendcUSD = 181.899055074 if location_name == "United States" & year == 2004

    replace totalPerCapitaExpendcUSD = 94.071870473 if location_name == "Australia" & year == 2005
    replace totalPerCapitaExpendcUSD = 145.977897890 if location_name == "France" & year == 2005
    replace totalPerCapitaExpendcUSD = 75.246040616 if location_name == "United Kingdom" & year == 2005
    replace totalPerCapitaExpendcUSD = 205.513781898 if location_name == "United States" & year == 2005

    replace totalPerCapitaExpendcUSD = 95.913764138 if location_name == "Australia" & year == 2006
    replace totalPerCapitaExpendcUSD = 177.967278175 if location_name == "France" & year == 2006
    replace totalPerCapitaExpendcUSD = 93.289306559 if location_name == "United Kingdom" & year == 2006
    replace totalPerCapitaExpendcUSD = 251.045869234 if location_name == "United States" & year == 2006

    replace totalPerCapitaExpendcUSD = 108.818357245 if location_name == "Australia" & year == 2007
    replace totalPerCapitaExpendcUSD = 213.324404210 if location_name == "France" & year == 2007
    replace totalPerCapitaExpendcUSD = 108.030546839 if location_name == "United Kingdom" & year == 2007
    replace totalPerCapitaExpendcUSD = 280.720837981 if location_name == "United States" & year == 2007

    replace totalPerCapitaExpendcUSD = 112.397252960 if location_name == "Australia" & year == 2008
    replace totalPerCapitaExpendcUSD = 236.401051239 if location_name == "France" & year == 2008
    replace totalPerCapitaExpendcUSD = 120.207686939 if location_name == "United Kingdom" & year == 2008
    replace totalPerCapitaExpendcUSD = 285.264937292 if location_name == "United States" & year == 2008

    replace totalPerCapitaExpendcUSD = 117.411007958 if location_name == "Australia" & year == 2009
    replace totalPerCapitaExpendcUSD = 224.523634636 if location_name == "France" & year == 2009
    replace totalPerCapitaExpendcUSD = 126.739632966 if location_name == "United Kingdom" & year == 2009
    replace totalPerCapitaExpendcUSD = 304.003266190 if location_name == "United States" & year == 2009

    replace totalPerCapitaExpendcUSD = 127.315192164 if location_name == "Australia" & year == 2010
    replace totalPerCapitaExpendcUSD = 214.854515573 if location_name == "France" & year == 2010
    replace totalPerCapitaExpendcUSD = 129.519135317 if location_name == "United Kingdom" & year == 2010
    replace totalPerCapitaExpendcUSD = 305.754817357 if location_name == "United States" & year == 2010

    replace totalPerCapitaExpendcUSD = 130.062387966 if location_name == "Australia" & year == 2011
    replace totalPerCapitaExpendcUSD = 199.728687794 if location_name == "France" & year == 2011
    replace totalPerCapitaExpendcUSD = 128.045712135 if location_name == "United Kingdom" & year == 2011
    replace totalPerCapitaExpendcUSD = 300.122366184 if location_name == "United States" & year == 2011

    replace totalPerCapitaExpendcUSD = 129.984045414 if location_name == "Australia" & year == 2012
    replace totalPerCapitaExpendcUSD = 185.532529470 if location_name == "France" & year == 2012
    replace totalPerCapitaExpendcUSD = 133.859713501 if location_name == "United Kingdom" & year == 2012
    replace totalPerCapitaExpendcUSD = 310.239349280 if location_name == "United States" & year == 2012

    replace totalPerCapitaExpendcUSD = 137.852952073 if location_name == "Australia" & year == 2013
    replace totalPerCapitaExpendcUSD = 197.230431233 if location_name == "France" & year == 2013
    replace totalPerCapitaExpendcUSD = 149.664435583 if location_name == "United Kingdom" & year == 2013
    replace totalPerCapitaExpendcUSD = 324.453540512 if location_name == "United States" & year == 2013

    replace totalPerCapitaExpendcUSD = 145.244274815 if location_name == "Australia" & year == 2014
    replace totalPerCapitaExpendcUSD = 206.877344740 if location_name == "France" & year == 2014
    replace totalPerCapitaExpendcUSD = 174.283105966 if location_name == "United Kingdom" & year == 2014
```

```
455         replace totalPerCapitaExpendcUSD = 376.112972620 if location_name == "United States" & year == 2014
456     label variable totalPerCapitaExpendcUSD "Total drug expenditure (2014 USD) per capita, by location_name in each year"
457     format totalPerCapitaExpendcUSD %12.0g
458
459     gen double prop_Expend_generic = .
460         replace prop_Expend_generic = 0.179896267 if location_name == "Australia" & year == 2004
461         replace prop_Expend_generic = 0.056763393 if location_name == "France" & year == 2004
462         replace prop_Expend_generic = 0.171088554 if location_name == "United Kingdom" & year == 2004
463         replace prop_Expend_generic = 0.083603761 if location_name == "United States" & year == 2004
464
465         replace prop_Expend_generic = 0.231000016 if location_name == "Australia" & year == 2005
466         replace prop_Expend_generic = 0.055387123 if location_name == "France" & year == 2005
467         replace prop_Expend_generic = 0.168299613 if location_name == "United Kingdom" & year == 2005
468         replace prop_Expend_generic = 0.076030259 if location_name == "United States" & year == 2005
469
470         replace prop_Expend_generic = 0.196902329 if location_name == "Australia" & year == 2006
471         replace prop_Expend_generic = 0.056138275 if location_name == "France" & year == 2006
472         replace prop_Expend_generic = 0.167190426 if location_name == "United Kingdom" & year == 2006
473         replace prop_Expend_generic = 0.072563095 if location_name == "United States" & year == 2006
474
475         replace prop_Expend_generic = 0.226689500 if location_name == "Australia" & year == 2007
476         replace prop_Expend_generic = 0.067375368 if location_name == "France" & year == 2007
477         replace prop_Expend_generic = 0.215554509 if location_name == "United Kingdom" & year == 2007
478         replace prop_Expend_generic = 0.072407163 if location_name == "United States" & year == 2007
479
480         replace prop_Expend_generic = 0.243427300 if location_name == "Australia" & year == 2008
481         replace prop_Expend_generic = 0.091738002 if location_name == "France" & year == 2008
482         replace prop_Expend_generic = 0.250469230 if location_name == "United Kingdom" & year == 2008
483         replace prop_Expend_generic = 0.067727315 if location_name == "United States" & year == 2008
484
485         replace prop_Expend_generic = 0.243009314 if location_name == "Australia" & year == 2009
486         replace prop_Expend_generic = 0.103774703 if location_name == "France" & year == 2009
487         replace prop_Expend_generic = 0.273296392 if location_name == "United Kingdom" & year == 2009
488         replace prop_Expend_generic = 0.086281317 if location_name == "United States" & year == 2009
489
490         replace prop_Expend_generic = 0.247678271 if location_name == "Australia" & year == 2010
491         replace prop_Expend_generic = 0.128770452 if location_name == "France" & year == 2010
492         replace prop_Expend_generic = 0.303227431 if location_name == "United Kingdom" & year == 2010
493         replace prop_Expend_generic = 0.134388905 if location_name == "United States" & year == 2010
494
495         replace prop_Expend_generic = 0.272982512 if location_name == "Australia" & year == 2011
496         replace prop_Expend_generic = 0.211824533 if location_name == "France" & year == 2011
497         replace prop_Expend_generic = 0.365832163 if location_name == "United Kingdom" & year == 2011
498         replace prop_Expend_generic = 0.149396715 if location_name == "United States" & year == 2011
499
500         replace prop_Expend_generic = 0.326145524 if location_name == "Australia" & year == 2012
501         replace prop_Expend_generic = 0.264179997 if location_name == "France" & year == 2012
502         replace prop_Expend_generic = 0.354548110 if location_name == "United Kingdom" & year == 2012
503         replace prop_Expend_generic = 0.187615570 if location_name == "United States" & year == 2012
504
505         replace prop_Expend_generic = 0.334643073 if location_name == "Australia" & year == 2013
506         replace prop_Expend_generic = 0.257387072 if location_name == "France" & year == 2013
507         replace prop_Expend_generic = 0.330761712 if location_name == "United Kingdom" & year == 2013
508         replace prop_Expend_generic = 0.250575906 if location_name == "United States" & year == 2013
509
510         replace prop_Expend_generic = 0.342387285 if location_name == "Australia" & year == 2014
511         replace prop_Expend_generic = 0.267124006 if location_name == "France" & year == 2014
512         replace prop_Expend_generic = 0.337765726 if location_name == "United Kingdom" & year == 2014
513         replace prop_Expend_generic = 0.305568658 if location_name == "United States" & year == 2014
514     label variable prop_Expend_generic "Proportion of total drug expenditure associated with generic drug sales, by location_name in
        each year"
515     format prop_Expend_generic %12.0g
516
517     gen double prop_Expend_branded = .
518         replace prop_Expend_branded = 0.820103733 if location_name == "Australia" & year == 2004
519         replace prop_Expend_branded = 0.943236607 if location_name == "France" & year == 2004
520         replace prop_Expend_branded = 0.828911446 if location_name == "United Kingdom" & year == 2004
```

```
521         replace prop_Expend_branded = 0.916396239 if location_name == "United States" & year == 2004
522
523         replace prop_Expend_branded = 0.768999984 if location_name == "Australia" & year == 2005
524         replace prop_Expend_branded = 0.944612877 if location_name == "France" & year == 2005
525         replace prop_Expend_branded = 0.831700387 if location_name == "United Kingdom" & year == 2005
526         replace prop_Expend_branded = 0.923969741 if location_name == "United States" & year == 2005
527
528         replace prop_Expend_branded = 0.803097671 if location_name == "Australia" & year == 2006
529         replace prop_Expend_branded = 0.943861725 if location_name == "France" & year == 2006
530         replace prop_Expend_branded = 0.832809574 if location_name == "United Kingdom" & year == 2006
531         replace prop_Expend_branded = 0.927436905 if location_name == "United States" & year == 2006
532
533         replace prop_Expend_branded = 0.773310500 if location_name == "Australia" & year == 2007
534         replace prop_Expend_branded = 0.932624632 if location_name == "France" & year == 2007
535         replace prop_Expend_branded = 0.784445491 if location_name == "United Kingdom" & year == 2007
536         replace prop_Expend_branded = 0.927592750 if location_name == "United States" & year == 2007
537
538         replace prop_Expend_branded = 0.756572700 if location_name == "Australia" & year == 2008
539         replace prop_Expend_branded = 0.908261998 if location_name == "France" & year == 2008
540         replace prop_Expend_branded = 0.749530770 if location_name == "United Kingdom" & year == 2008
541         replace prop_Expend_branded = 0.932272411 if location_name == "United States" & year == 2008
542
543         replace prop_Expend_branded = 0.756990686 if location_name == "Australia" & year == 2009
544         replace prop_Expend_branded = 0.896225297 if location_name == "France" & year == 2009
545         replace prop_Expend_branded = 0.726703608 if location_name == "United Kingdom" & year == 2009
546         replace prop_Expend_branded = 0.913719226 if location_name == "United States" & year == 2009
547
548         replace prop_Expend_branded = 0.752321729 if location_name == "Australia" & year == 2010
549         replace prop_Expend_branded = 0.871229548 if location_name == "France" & year == 2010
550         replace prop_Expend_branded = 0.696772569 if location_name == "United Kingdom" & year == 2010
551         replace prop_Expend_branded = 0.865610811 if location_name == "United States" & year == 2010
552
553         replace prop_Expend_branded = 0.727017488 if location_name == "Australia" & year == 2011
554         replace prop_Expend_branded = 0.788175467 if location_name == "France" & year == 2011
555         replace prop_Expend_branded = 0.634167837 if location_name == "United Kingdom" & year == 2011
556         replace prop_Expend_branded = 0.850603413 if location_name == "United States" & year == 2011
557
558         replace prop_Expend_branded = 0.673854476 if location_name == "Australia" & year == 2012
559         replace prop_Expend_branded = 0.735820003 if location_name == "France" & year == 2012
560         replace prop_Expend_branded = 0.645451890 if location_name == "United Kingdom" & year == 2012
561         replace prop_Expend_branded = 0.812383903 if location_name == "United States" & year == 2012
562
563         replace prop_Expend_branded = 0.665356927 if location_name == "Australia" & year == 2013
564         replace prop_Expend_branded = 0.742612927 if location_name == "France" & year == 2013
565         replace prop_Expend_branded = 0.669238287 if location_name == "United Kingdom" & year == 2013
566         replace prop_Expend_branded = 0.749424267 if location_name == "United States" & year == 2013
567
568         replace prop_Expend_branded = 0.657612715 if location_name == "Australia" & year == 2014
569         replace prop_Expend_branded = 0.732875994 if location_name == "France" & year == 2014
570         replace prop_Expend_branded = 0.662234274 if location_name == "United Kingdom" & year == 2014
571         replace prop_Expend_branded = 0.694431651 if location_name == "United States" & year == 2014
572     label variable prop_Expend_branded "Proportion of total drug expenditure associated with branded drug sales, by location_name in
        each year"
573     format prop_Expend_branded %12.0g
574
575     * The following two variables adjust for cancer incidence, rather than population. Data is derived from OECD & CDC data. See
        "LinReg_CancerIncidence.xlsx", "Figures_VolumeConsumption_AllYears.xlsx", & "UpdatedHA_Descriptives_AllYears.do".
576
577     gen double totalPerNeoplasmExpendcUSD = .
578         replace totalPerNeoplasmExpendcUSD = 17514.540337860 if location_name == "Australia" & year == 2004
579         replace totalPerNeoplasmExpendcUSD = 25601.270633100 if location_name == "France" & year == 2004
580         replace totalPerNeoplasmExpendcUSD = 15460.916964400 if location_name == "United Kingdom" & year == 2004
581         replace totalPerNeoplasmExpendcUSD = 38571.210844700 if location_name == "United States" & year == 2004
582
583         replace totalPerNeoplasmExpendcUSD = 19810.788222930 if location_name == "Australia" & year == 2005
584         replace totalPerNeoplasmExpendcUSD = 30960.365970500 if location_name == "France" & year == 2005
```

```
585         replace totalPerNeoplasmExpendcUSD = 15804.504192900 if location_name == "United Kingdom" & year == 2005
586         replace totalPerNeoplasmExpendcUSD = 43226.061893700 if location_name == "United States" & year == 2005
587
588         replace totalPerNeoplasmExpendcUSD = 19774.785400670 if location_name == "Australia" & year == 2006
589         replace totalPerNeoplasmExpendcUSD = 36988.181201400 if location_name == "France" & year == 2006
590         replace totalPerNeoplasmExpendcUSD = 19312.379760300 if location_name == "United Kingdom" & year == 2006
591         replace totalPerNeoplasmExpendcUSD = 52413.454805000 if location_name == "United States" & year == 2006
592
593         replace totalPerNeoplasmExpendcUSD = 21805.708088400 if location_name == "Australia" & year == 2007
594         replace totalPerNeoplasmExpendcUSD = 43444.996759000 if location_name == "France" & year == 2007
595         replace totalPerNeoplasmExpendcUSD = 22062.229199300 if location_name == "United Kingdom" & year == 2007
596         replace totalPerNeoplasmExpendcUSD = 58185.661443000 if location_name == "United States" & year == 2007
597
598         replace totalPerNeoplasmExpendcUSD = 22220.669536000 if location_name == "Australia" & year == 2008
599         replace totalPerNeoplasmExpendcUSD = 47180.475887000 if location_name == "France" & year == 2008
600         replace totalPerNeoplasmExpendcUSD = 24230.621463300 if location_name == "United Kingdom" & year == 2008
601         replace totalPerNeoplasmExpendcUSD = 58713.643874000 if location_name == "United States" & year == 2008
602
603         replace totalPerNeoplasmExpendcUSD = 22938.462231000 if location_name == "Australia" & year == 2009
604         replace totalPerNeoplasmExpendcUSD = 43921.606613900 if location_name == "France" & year == 2009
605         replace totalPerNeoplasmExpendcUSD = 25218.977968300 if location_name == "United Kingdom" & year == 2009
606         replace totalPerNeoplasmExpendcUSD = 62106.012202900 if location_name == "United States" & year == 2009
607
608         replace totalPerNeoplasmExpendcUSD = 24481.463932600 if location_name == "Australia" & year == 2010
609         replace totalPerNeoplasmExpendcUSD = 41213.876488400 if location_name == "France" & year == 2010
610         replace totalPerNeoplasmExpendcUSD = 25458.331647600 if location_name == "United Kingdom" & year == 2010
611         replace totalPerNeoplasmExpendcUSD = 61991.061914700 if location_name == "United States" & year == 2010
612
613         replace totalPerNeoplasmExpendcUSD = 24598.350737200 if location_name == "Australia" & year == 2011
614         replace totalPerNeoplasmExpendcUSD = 37586.565999500 if location_name == "France" & year == 2011
615         replace totalPerNeoplasmExpendcUSD = 24871.626262800 if location_name == "United Kingdom" & year == 2011
616         replace totalPerNeoplasmExpendcUSD = 60360.646746900 if location_name == "United States" & year == 2011
617
618         replace totalPerNeoplasmExpendcUSD = 24281.796023000 if location_name == "Australia" & year == 2012
619         replace totalPerNeoplasmExpendcUSD = 34262.530753300 if location_name == "France" & year == 2012
620         replace totalPerNeoplasmExpendcUSD = 25681.610444600 if location_name == "United Kingdom" & year == 2012
621         replace totalPerNeoplasmExpendcUSD = 61908.976827500 if location_name == "United States" & year == 2012
622
623         replace totalPerNeoplasmExpendcUSD = 25460.206793600 if location_name == "Australia" & year == 2013
624         replace totalPerNeoplasmExpendcUSD = 35754.201464500 if location_name == "France" & year == 2013
625         replace totalPerNeoplasmExpendcUSD = 28354.751177800 if location_name == "United Kingdom" & year == 2013
626         replace totalPerNeoplasmExpendcUSD = 64251.313508800 if location_name == "United States" & year == 2013
627
628         replace totalPerNeoplasmExpendcUSD = 26498.119337700 if location_name == "Australia" & year == 2014
629         replace totalPerNeoplasmExpendcUSD = 36830.442044800 if location_name == "France" & year == 2014
630         replace totalPerNeoplasmExpendcUSD = 32614.708346900 if location_name == "United Kingdom" & year == 2014
631         replace totalPerNeoplasmExpendcUSD = 73919.508473500 if location_name == "United States" & year == 2014
632     label variable totalPerNeoplasmExpendcUSD "Total drug expenditure (2014 USD) per incident neoplasm, by location_name in each year"
633     format totalPerNeoplasmExpendcUSD %12.0g
634
635     * Incidence data was obtained from OECD and CDC (for US). YLLs (neoplasms) / 100,000 data was obtained from the IHME (above) for
        2000, 2005, 2010, and 2013. Simple linear regression against year used to derive estimates of yearly YLL (all neoplasms) / 100,000
        population (provided here). These figures, alongside population estimates from the World Bank, ///
636     * were also used to derive age-adjusted YLLs (neoplasms) / inicident neoplasm (country-level average), which are used as an
        alternative depedent variable below. Refer to "YLLtrends_Expenditure_ValueAssessment.xlsx" and "LinReg_YLLtrends.xlsx" for
        information on how these values were derived.
637
638     gen double meanYLL_per100000 = .
639         replace meanYLL_per100000 = 2922.292880000 if location_name == "Australia" & year==2004
640         replace meanYLL_per100000 = 3636.453288000 if location_name == "France" & year==2004
641         replace meanYLL_per100000 = 3389.739904000 if location_name == "United Kingdom" & year==2004
642         replace meanYLL_per100000 = 3158.622756000 if location_name == "United States" & year==2004
643
644         replace meanYLL_per100000 = 2894.928600000 if location_name == "Australia" & year==2005
645         replace meanYLL_per100000 = 3596.094110000 if location_name == "France" & year==2005
646         replace meanYLL_per100000 = 3345.951130000 if location_name == "United Kingdom" & year==2005
647
```

```
        replace meanYLL_per100000 = 3129.006445000 if location_name == "United States" & year==2005

        replace meanYLL_per100000 = 2867.564320000 if location_name == "Australia" & year==2006
        replace meanYLL_per100000 = 3555.734932000 if location_name == "France" & year==2006
        replace meanYLL_per100000 = 3302.162356000 if location_name == "United Kingdom" & year==2006
        replace meanYLL_per100000 = 3099.390134000 if location_name == "United States" & year==2006

        replace meanYLL_per100000 = 2840.200040000 if location_name == "Australia" & year==2007
        replace meanYLL_per100000 = 3515.375754000 if location_name == "France" & year==2007
        replace meanYLL_per100000 = 3258.373582000 if location_name == "United Kingdom" & year==2007
        replace meanYLL_per100000 = 3069.773823000 if location_name == "United States" & year==2007

        replace meanYLL_per100000 = 2812.835760000 if location_name == "Australia" & year==2008
        replace meanYLL_per100000 = 3475.016576000 if location_name == "France" & year==2008
        replace meanYLL_per100000 = 3214.584808000 if location_name == "United Kingdom" & year==2008
        replace meanYLL_per100000 = 3040.157512000 if location_name == "United States" & year==2008

        replace meanYLL_per100000 = 2785.471480000 if location_name == "Australia" & year==2009
        replace meanYLL_per100000 = 3434.657398000 if location_name == "France" & year==2009
        replace meanYLL_per100000 = 3170.796034000 if location_name == "United Kingdom" & year==2009
        replace meanYLL_per100000 = 3010.541201000 if location_name == "United States" & year==2009

        replace meanYLL_per100000 = 2758.107200000 if location_name == "Australia" & year==2010
        replace meanYLL_per100000 = 3394.298220000 if location_name == "France" & year==2010
        replace meanYLL_per100000 = 3127.007260000 if location_name == "United Kingdom" & year==2010
        replace meanYLL_per100000 = 2980.924890000 if location_name == "United States" & year==2010

        replace meanYLL_per100000 = 2730.742920000 if location_name == "Australia" & year==2011
        replace meanYLL_per100000 = 3353.939042000 if location_name == "France" & year==2011
        replace meanYLL_per100000 = 3083.218486000 if location_name == "United Kingdom" & year==2011
        replace meanYLL_per100000 = 2951.308579000 if location_name == "United States" & year==2011

        replace meanYLL_per100000 = 2703.378640000 if location_name == "Australia" & year==2012
        replace meanYLL_per100000 = 3313.579864000 if location_name == "France" & year==2012
        replace meanYLL_per100000 = 3039.429712000 if location_name == "United Kingdom" & year==2012
        replace meanYLL_per100000 = 2921.692268000 if location_name == "United States" & year==2012

        replace meanYLL_per100000 = 2676.014360000 if location_name == "Australia" & year==2013
        replace meanYLL_per100000 = 3273.220686000 if location_name == "France" & year==2013
        replace meanYLL_per100000 = 2995.640938000 if location_name == "United Kingdom" & year==2013
        replace meanYLL_per100000 = 2892.075957000 if location_name == "United States" & year==2013

        replace meanYLL_per100000 = 2648.650080000 if location_name == "Australia" & year==2014
        replace meanYLL_per100000 = 3232.861508000 if location_name == "France" & year==2014
        replace meanYLL_per100000 = 2951.852164000 if location_name == "United Kingdom" & year==2014
        replace meanYLL_per100000 = 2862.459646000 if location_name == "United States" & year==2014
label variable meanYLL_per100000 "Mean YLL (neoplasm) per 100,000 population, age-standard, derived from OECD & CDC data"
format meanYLL_per100000 %12.0g

gen double meanYLL_perIncNeoplasm = .
        replace meanYLL_perIncNeoplasm = 6.304266673 if location_name == "Australia" & year==2004
        replace meanYLL_perIncNeoplasm = 7.834663166 if location_name == "France" & year==2004
        replace meanYLL_perIncNeoplasm = 7.193054542 if location_name == "United Kingdom" & year==2004
        replace meanYLL_perIncNeoplasm = 6.719641297 if location_name == "United States" & year==2004

        replace meanYLL_perIncNeoplasm = 6.096489538 if location_name == "Australia" & year==2005
        replace meanYLL_perIncNeoplasm = 7.599573487 if location_name == "France" & year==2005
        replace meanYLL_perIncNeoplasm = 6.999848343 if location_name == "United Kingdom" & year==2005
        replace meanYLL_perIncNeoplasm = 6.598172373 if location_name == "United States" & year==2005

        replace meanYLL_perIncNeoplasm = 5.912130502 if location_name == "Australia" & year==2006
        replace meanYLL_perIncNeoplasm = 7.371609173 if location_name == "France" & year==2006
        replace meanYLL_perIncNeoplasm = 6.816934013 if location_name == "United Kingdom" & year==2006
        replace meanYLL_perIncNeoplasm = 6.483147197 if location_name == "United States" & year==2006

        replace meanYLL_perIncNeoplasm = 5.691371801 if location_name == "Australia" & year==2007
        replace meanYLL_perIncNeoplasm = 7.148712621 if location_name == "France" & year==2007
```

```
714         replace meanYLL_perIncNeoplasm = 6.643304414 if location_name == "United Kingdom" & year==2007
715         replace meanYLL_perIncNeoplasm = 6.370670035 if location_name == "United States" & year==2007
716
717         replace meanYLL_perIncNeoplasm = 5.560909385 if location_name == "Australia" & year==2008
718         replace meanYLL_perIncNeoplasm = 6.931880308 if location_name == "France" & year==2008
719         replace meanYLL_perIncNeoplasm = 6.476068865 if location_name == "United Kingdom" & year==2008
720         replace meanYLL_perIncNeoplasm = 6.261101902 if location_name == "United States" & year==2008
721
722         replace meanYLL_perIncNeoplasm = 5.441945645 if location_name == "Australia" & year==2009
723         replace meanYLL_perIncNeoplasm = 6.721783622 if location_name == "France" & year==2009
724         replace meanYLL_perIncNeoplasm = 6.312373084 if location_name == "United Kingdom" & year==2009
725         replace meanYLL_perIncNeoplasm = 6.150347650 if location_name == "United States" & year==2009
726
727         replace meanYLL_perIncNeoplasm = 5.303569888 if location_name == "Australia" & year==2010
728         replace meanYLL_perIncNeoplasm = 6.519561471 if location_name == "France" & year==2010
729         replace meanYLL_perIncNeoplasm = 6.155617383 if location_name == "United Kingdom" & year==2010
730         replace meanYLL_perIncNeoplasm = 6.040197224 if location_name == "United States" & year==2010
731
732         replace meanYLL_perIncNeoplasm = 5.164580873 if location_name == "Australia" & year==2011
733         replace meanYLL_perIncNeoplasm = 6.325332233 if location_name == "France" & year==2011
734         replace meanYLL_perIncNeoplasm = 6.003588757 if location_name == "United Kingdom" & year==2011
735         replace meanYLL_perIncNeoplasm = 5.928798425 if location_name == "United States" & year==2011
736
737         replace meanYLL_perIncNeoplasm = 5.050072761 if location_name == "Australia" & year==2012
738         replace meanYLL_perIncNeoplasm = 6.137375408 if location_name == "France" & year==2012
739         replace meanYLL_perIncNeoplasm = 5.851093197 if location_name == "United Kingdom" & year==2012
740         replace meanYLL_perIncNeoplasm = 5.820341635 if location_name == "United States" & year==2012
741
742         replace meanYLL_perIncNeoplasm = 4.942359084 if location_name == "Australia" & year==2013
743         replace meanYLL_perIncNeoplasm = 5.955917310 if location_name == "France" & year==2013
744         replace meanYLL_perIncNeoplasm = 5.699801675 if location_name == "United Kingdom" & year==2013
745         replace meanYLL_perIncNeoplasm = 5.714303315 if location_name == "United States" & year==2013
746
747         replace meanYLL_perIncNeoplasm = 4.832152317 if location_name == "Australia" & year==2014
748         replace meanYLL_perIncNeoplasm = 5.781241472 if location_name == "France" & year==2014
749         replace meanYLL_perIncNeoplasm = 5.552540534 if location_name == "United Kingdom" & year==2014
750         replace meanYLL_perIncNeoplasm = 5.610206117 if location_name == "United States" & year==2014
751     label variable meanYLL_perIncNeoplasm "Mean YLL (neoplasm) per incident neoplasm, age-standard, derived from OECD & CDC data"
752     format meanYLL_perIncNeoplasm %12.0g
753
754     gen totalPerNeoplasmSalesKG = totalPerNeoplasmSalesMG/1000000
755     format totalPerNeoplasmSalesKG %12.0g
756
757     * To help with interpretation, convert prop_Sales_generic to non-proportion form:
758
759     gen prop_Sales_genericNP = prop_Sales_generic * 100
760         format prop_Sales_genericNP %12.0g
761
762     gen prop_Sales_brandedNP = prop_Sales_branded * 100
763         format prop_Sales_brandedNP %12.0g
764
765     gen prop_Expend_genericNP = prop_Expend_generic * 100
766         format prop_Expend_genericNP %12.0g
767
768     gen prop_Expend_brandedNP = prop_Expend_branded * 100
769         format prop_Expend_brandedNP %12.0g
770
771     * To help with interpretation, convert prop_Sales_generic to non-proportion form (KG):
772
773     gen prop_Sales_genericNPMG = prop_Sales_genericMG * 100
774         format prop_Sales_genericNPMG %12.0g
775
776     * Generate a log transformed value of YLLs, given the large positive skew.
777
778     histogram mean
779
```

```
780  histogram meanYLL_per100000
781
782  histogram meanYLL_perIncNeoplasm
783
784  * Tests for normality of dependent variables.
785
786  swilk meanYLL_per100000
787  *  meanYLL_per100000 is normally distributed.
788
789  sfrancia meanYLL_per100000
790  * meanYLL_per100000 is normally distributed.
791
792  swilk meanYLL_perIncNeoplasm
793  * meanYLL_per100000 is normally distributed.
794
795  sfrancia meanYLL_perIncNeoplasm
796  * meanYLL_per100000 is normally distributed.
797
798  * Run specifications with and one without a log-transformed 'mean' variable. The reason for this is that there appears to be
     somewhat a rightward skew in the YLLs across neoplasm incidence profile observed in each country. We don't report these variables
     because above tests for normality indicate that dependent variables are normally distributed (p > 0.05) -- these are nevertheless
     created because there is a trend towards non normality (e.g. p = 0.2).
799
800  gen ln_YLLper10000 = ln(meanYLL_per100000)
801  histogram ln_YLLper10000
802
803  gen ln_YLLperNeoplasm = ln(meanYLL_perIncNeoplasm)
804  histogram ln_YLLperNeoplasm
805
806  * Create panel_id variable for location_id clusters
807
808  egen panel_id = group(location_id)
809
810  gen LOGtotalPerNeoplasmSalesMG = ln(totalPerNeoplasmSalesMG)
811      format LOGtotalPerNeoplasmSalesMG %12.0g
812
813  gen LOGtotalPerNeoplasmSalesKG = ln(totalPerNeoplasmSalesKG)
814      format LOGtotalPerNeoplasmSalesKG %12.0g
815
816  * Create a lag variable for independent variables.
817
818  sort location_name year
819  bysort location_name: gen prop_Sales_genericNP_1lag = .
820      replace prop_Sales_genericNP_1lag = prop_Sales_genericNP[_n-1]
821      replace prop_Sales_genericNP_1lag =. if year == 2004
822
823  sort location_name year
824  bysort location_name: gen totalPerNeoplasmSalesSU_1lag = .
825      replace totalPerNeoplasmSalesSU_1lag = totalPerNeoplasmSalesSU[_n-1]
826      replace totalPerNeoplasmSalesSU_1lag =. if year == 2004
827
828  * Create a lag variable for independent variables (KG)
829
830  sort location_name year
831  bysort location_name: gen prop_Sales_genericNPMG_1lag = .
832      replace prop_Sales_genericNPMG_1lag = prop_Sales_genericNPMG[_n-1]
833      replace prop_Sales_genericNPMG_1lag =. if year == 2004
834
835  sort location_name year
836  bysort location_name: gen totalPerNeoplasmSalesMG_1lag = .
837      replace totalPerNeoplasmSalesMG_1lag = totalPerNeoplasmSalesMG[_n-1]
838      replace totalPerNeoplasmSalesMG_1lag =. if year == 2004
839
840  sort location_name year
841  bysort location_name: gen LOGtotalPerNeoplasmSalesMG_1lag = .
842      replace LOGtotalPerNeoplasmSalesMG_1lag = LOGtotalPerNeoplasmSalesMG[_n-1]
843      replace LOGtotalPerNeoplasmSalesMG_1lag =. if year == 2004
```

```
844
845   sort location_name year
846   bysort location_name: gen totalPerNeoplasmSalesKG_1lag = .
847       replace totalPerNeoplasmSalesKG_1lag = totalPerNeoplasmSalesKG[_n-1]
848       replace totalPerNeoplasmSalesKG_1lag =. if year == 2004
849
850   sort location_name year
851   bysort location_name: gen LOGtotalPerNeoplasmSalesKG_1lag = .
852       replace LOGtotalPerNeoplasmSalesKG_1lag = LOGtotalPerNeoplasmSalesKG[_n-1]
853       replace LOGtotalPerNeoplasmSalesKG_1lag =. if year == 2004
854
855   * Create time trend variable
856   bysort panel_id (year): gen timetrend3 = 1 if year == 2004
857   bysort panel_id (year): replace timetrend3 = 2 if year == 2005
858   bysort panel_id (year): replace timetrend3 = 3 if year == 2006
859   bysort panel_id (year): replace timetrend3 = 4 if year == 2007
860   bysort panel_id (year): replace timetrend3 = 5 if year == 2008
861   bysort panel_id (year): replace timetrend3 = 6 if year == 2009
862   bysort panel_id (year): replace timetrend3 = 7 if year == 2010
863   bysort panel_id (year): replace timetrend3 = 8 if year == 2011
864   bysort panel_id (year): replace timetrend3 = 9 if year == 2012
865   bysort panel_id (year): replace timetrend3 = 10 if year == 2013
866   bysort panel_id (year): replace timetrend3 = 11 if year == 2014
867
868
869   /// Analysis:
870   * Above incidence data is derived from OECD & US CDC incidence data. Refer to "LinReg_CancerIncidence.xlsx" and
      "YLLtrends_Expenditure_ValueAssessment.xlsx" for information on how these were derived.
871
872   * Age-standardized YLL rates per 100,000 across each country in each available year
873
874   by location_id: table cause_name year, contents(mean meanYLL_per100000)
875
876   scatter meanYLL_per100000 year
877
878   separate meanYLL_per100000, by(location_id)
879   twoway (scatter meanYLL_per1000001 year) (scatter meanYLL_per1000002 year) (scatter meanYLL_per1000003 year) (scatter
      meanYLL_per1000004 year) (scatter meanYLL_per1000005 year) (scatter meanYLL_per1000006 year) (scatter meanYLL_per1000007 year) (
      scatter meanYLL_per1000008 year) (scatter meanYLL_per1000009 year), ///
880     ytitle(YLL / 100000) legend(order(1 "Australia" 2 "Canada" 3 "France" 4 "Germany" 5 "Italy" 6 "Japan" 7 "Sweden" 8 "UK" 9 "USA"))
881
882   * Age-standardized YLL rates per incident neoplasm across each country in each available year
883
884   by location_id: table cause_name year, contents(mean meanYLL_perIncNeoplasm)
885
886   scatter meanYLL_perIncNeoplasm year
887
888   separate meanYLL_perIncNeoplasm, by(location_id)
889   twoway (scatter meanYLL_perIncNeoplasm1 year) (scatter meanYLL_perIncNeoplasm2 year) (scatter meanYLL_perIncNeoplasm3 year) (
      scatter meanYLL_perIncNeoplasm4 year) (scatter meanYLL_perIncNeoplasm5 year) (scatter meanYLL_perIncNeoplasm6 year) (scatter
      meanYLL_perIncNeoplasm7 year) (scatter meanYLL_perIncNeoplasm8 year) (scatter meanYLL_perIncNeoplasm9 year), ///
890     ytitle(YLL / Inc Neoplasm) legend(order(1 "Australia" 2 "Canada" 3 "France" 4 "Germany" 5 "Italy" 6 "Japan" 7 "Sweden" 8 "UK" 9
      "USA"))
891
892   *** YLL / country
893
894   separate meanYLL_perIncNeoplasm, by(location_id)
895   separate prop_Sales_brandedNP, by(location_id)
896   twoway (scatter meanYLL_perIncNeoplasm1 prop_Sales_brandedNP1) (scatter meanYLL_perIncNeoplasm2 prop_Sales_brandedNP2) (scatter
      meanYLL_perIncNeoplasm3 prop_Sales_brandedNP3) (scatter meanYLL_perIncNeoplasm4 prop_Sales_brandedNP4) (scatter
      meanYLL_perIncNeoplasm5 prop_Sales_brandedNP5) (scatter meanYLL_perIncNeoplasm6 prop_Sales_brandedNP6) (scatter
      meanYLL_perIncNeoplasm7 prop_Sales_brandedNP7) (scatter meanYLL_perIncNeoplasm8 prop_Sales_brandedNP8) (scatter
      meanYLL_perIncNeoplasm9 prop_Sales_brandedNP9), ///
897     ytitle(meanYLL_perIncNeoplasm1) xtitle(prop_Sales_brandedNP) legend(order(1 "Australia" 2 "Canada" 3 "France" 4 "Germany" 5
      "Italy" 6 "Japan" 7 "Sweden" 8 "UK" 9 "USA"))
898
```

```
* Model specification 1 -- non-log transformed mean variable (based on swilk, sfrancia)

global id panel_id
global t year
global ylist meanYLL_perIncNeoplasm
global xlist LOGtotalPerNeoplasmSalesKG

describe $id $t $ylist $xlist
summarize $id $t $ylist $xlist

* Set data as panel data.
sort $id $t
xtset $id $t
xtdescribe
xtsum $id $t $ylist $xlist

* Fixed effects or within estimator
xtreg $ylist $xlist, fe robust
    est sto m1

* Model specification 2 -- non-log transformed mean variable (based on swilk, sfrancia)

global id panel_id
global t year
global ylist meanYLL_perIncNeoplasm
global xlist LOGtotalPerNeoplasmSalesKG prop_Sales_genericNPMG

describe $id $t $ylist $xlist
summarize $id $t $ylist $xlist

* Set data as panel data.
sort $id $t
xtset $id $t
xtdescribe
xtsum $id $t $ylist $xlist

* Fixed effects or within estimator
xtreg $ylist $xlist , fe robust
    est sto m2

* Model specification 3 -- non-log transformed mean variable (based on swilk, sfrancia)

global id panel_id
global t year
global ylist meanYLL_perIncNeoplasm
global xlist LOGtotalPerNeoplasmSalesKG

describe $id $t $ylist $xlist
summarize $id $t $ylist $xlist

* Set data as panel data.
sort $id $t
xtset $id $t
xtdescribe
xtsum $id $t $ylist $xlist

* Fixed effects or within estimator
xtreg $ylist $xlist i.year, fe robust
    est sto m3

* Model specification 4 -- non-log transformed mean variable (based on swilk, sfrancia)

global id panel_id
global t year
global ylist meanYLL_perIncNeoplasm
global xlist LOGtotalPerNeoplasmSalesKG prop_Sales_genericNPMG
```

```
965
966   describe $id $t $ylist $xlist
967   summarize $id $t $ylist $xlist
968
969   * Set data as panel data.
970   sort $id $t
971   xtset $id $t
972   xtdescribe
973   xtsum $id $t $ylist $xlist
974
975   * Fixed effects or within estimator
976   xtreg $ylist $xlist i.year, fe robust
977       est sto m4
978
979   * Model specification 5 -- non-log transformed mean variable (based on swilk, sfrancia)
980
981   global id panel_id
982   global t year
983   global ylist meanYLL_perIncNeoplasm
984   global xlist LOGtotalPerNeoplasmSalesKG
985
986   describe $id $t $ylist $xlist
987   summarize $id $t $ylist $xlist
988
989   * Set data as panel data.
990   sort $id $t
991   xtset $id $t
992   xtdescribe
993   xtsum $id $t $ylist $xlist
994
995   * Fixed effects or within estimator
996   xtreg $ylist $xlist l.LOGtotalPerNeoplasmSalesKG, fe robust
997       est sto m5
998
999   * Model specification 6 -- non-log transformed mean variable (based on swilk, sfrancia)
1000
1001  global id panel_id
1002  global t year
1003  global ylist meanYLL_perIncNeoplasm
1004  global xlist LOGtotalPerNeoplasmSalesKG prop_Sales_genericNPMG
1005
1006  describe $id $t $ylist $xlist
1007  summarize $id $t $ylist $xlist
1008
1009  * Set data as panel data.
1010  sort $id $t
1011  xtset $id $t
1012  xtdescribe
1013  xtsum $id $t $ylist $xlist
1014
1015  * Fixed effects or within estimator
1016  xtreg $ylist $xlist l.LOGtotalPerNeoplasmSalesKG, fe robust
1017      est sto m6
1018
1019  * Model specification 7 -- non-log transformed mean variable (based on swilk, sfrancia)
1020
1021  global id panel_id
1022  global t year
1023  global ylist meanYLL_perIncNeoplasm
1024  global xlist LOGtotalPerNeoplasmSalesKG prop_Sales_genericNPMG
1025
1026  describe $id $t $ylist $xlist
1027  summarize $id $t $ylist $xlist
1028
1029  * Set data as panel data.
1030  sort $id $t
1031  xtset $id $t
```

```
xtdescribe
xtsum $id $t $ylist $xlist

* Fixed effects or within estimator
xtreg $ylist $xlist l.LOGtotalPerNeoplasmSalesKG l.prop_Sales_genericNPMG, fe robust
    est sto m7

* Model specification 8 -- non-log transformed mean variable (based on swilk, sfrancia)

global id panel_id
global t year
global ylist meanYLL_perIncNeoplasm
global xlist LOGtotalPerNeoplasmSalesKG prop_Sales_genericNPMG

describe $id $t $ylist $xlist
summarize $id $t $ylist $xlist

* Set data as panel data.
sort $id $t
xtset $id $t
xtdescribe
xtsum $id $t $ylist $xlist

* Fixed effects or within estimator
xtreg $ylist $xlist l.LOGtotalPerNeoplasmSalesKG l.prop_Sales_genericNPMG i.year, fe robust
    est sto m8

    esttab m1 m2 m3 m4 m5 m6 m7 m8, ar2 r2 brackets label

    esttab m1 m2 m3 m4 m5 m6 m7 m8, p ar2 r2 brackets label

    esttab m1 m2 m3 m4 m5 m6 m7 m8, se ar2 r2 brackets label

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