THE PRICE OF INNOVATIVE ANTICANCER DRUGS

by

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ABSTRACT

Many new anticancer drugs enter the market at a relatively high price. Some healthcare authorities have made the rare decision not to fund new anticancer drugs due to their high prices. Decision-makers fear that these expensive new anticancer drugs are not generating net social benefits. The following work investigates the relationship between prices and clinical benefits of anticancer drugs that have come to market over the past decade. We show that the relationship between drug prices and clinical benefits is not linear. In fact, modern drug prices appear to rise exponentially. Drug manufacturers explain their pricing strategy with concerns towards the high cost of innovating in the pharmaceutical industry. Accordingly, a discussion of innovation in anticancer research is included. The discussion also provides insight into cancer control in the upcoming generation of personalized medicines. The aim is to gain an understanding of the social benefits received from these innovative new treatments.

Keywords: anticancer drugs, innovation, pharmaceuticals, pricing, healthcare, personalized medicines

EXECUTIVE SUMMARY

- Chapter One is an introduction to the concept of social benefits and the marketplace for new anticancer drugs. A brief discussion of the methods used to evaluate new therapeutic interventions in healthcare markets is included, as these tools commonly demonstrate the value of new anticancer drugs.
- In Chapter Two, we trace the history of cancer chemotherapy and the social benefits that anticancer drugs have provided in the past.
- In Chapter Three, we investigate the changes in clinical benefits for breast cancer drugs over time. We then correlate the clinical benefits with the prices charged for these new treatments. A similar analysis was done in Chapter Four, for drugs developed against colorectal cancer over the past decade.
- The information in Chapters Three and Four was used to establish a price-benefit relationship for anticancer drugs against breast and colorectal cancers. We find that there is a steep increase in the price of these drugs relative to their clinical benefit.
- Because the value of anticancer drugs includes both clinical and non-clinical benefits, we also discuss the non-clinical benefits of anticancer drugs in Chapter 6. The context of this concluding chapter is of future anticancer drugs in the era of personalized medicines.

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GLOSSARY

adjuvant therapy	Additional treatment to enhance the chances for a successful outcome. This might include chemotherapy after surgical removal of a tumor to ensure the complete removal of all cancerous cells.
CRC	Colorectal Cancer
DFS	Disease Free Survival. Surrogate endpoint for overall survival. Usually used in the adjuvant setting where treatments aim to prevent recurrence of the disease.
High cost drugs	A recent cohort of drugs that have an unprecedented high price associated with them
HR	Hazard Ratio. A term used to describe the relative risk reduction achieved by taking the treatment. An HR less than 1 indicates that the therapy offers some improvement over comparators
metastatic	Stage of pathological progression of cancer. The disease has spread from its primary tissue location to other sites in the body.
NICE	National Center for Health and Clinical Excellence. British authority that appraises new drugs for cost-effectiveness and makes recommendations for their use for local health authorities.
OS	Overall Survival. Clinical outcome for estimating a drugs benefit against cancer
PMPRB	Patented Medicines Pricing Review Board, a quasi-judicial organization designed to manage Canadian drug pricing and protect consumers from excessively high pricing of pharmaceuticals.
TTP	Time to progression. Surrogate endpoint for overall survival. Used commonly for drug candidates seeking "fast-track" approval.
QALY	Quality Adjusted Life Years. A way to measure the quality and quantity of live lived when evaluating therapeutic interventions.

1 Introduction

This project concerns the benefits that new anticancer drugs offer to society (i.e. their social benefits). The goal is to gain more information about the level of social benefits that these anticancer drugs have generated over time. We do so by calculating the change in prices of anticancer drugs over the past decade. We then relate the rise in drug prices to the level of clinical benefits that these drugs generate. If drug prices are much higher than the level of clinical benefits that they offer, then the level of social benefits received from these drugs may not be optimal. We also discuss non-clinical benefits, such as the social value of innovation in the pharmaceutical industry. The purpose of this project is to provide information about the value that these highly priced drugs have to society.

1.1 The Benefit of Modern Anticancer Drugs

Anticancer drugs have made significant advancements in recent years (Garattini and Betele 2002). These advancements often translate into improved health benefits for cancer patients. Recently, however, the high prices that the manufacturers charge for these new drugs has become a social concern (Rawlins 2007). Many healthcare decision-makers question whether these expensive new drugs offer net social benefits that justify their high price (McManus 2007). It is important to consider how anticancer drugs benefit society in aggregate when addressing this question.

Thirty years ago, patients with metastatic colorectal cancer had a 50% chance of surviving for five years after they were initially diagnosed with the disease (Ries et al

2006a). Today, these patients have a 65% chance of survival. Similarly, breast cancer patients now have a much greater chance of surviving the disease than they did in the 1970s (Ries et al 2006b). These improvements are directly attributable to the availability of new anticancer drugs (Schrag 2004; Chia et al 2007). Several forms of cancer are even considered curable because of these new drugs (FHCRC 2008). Clearly, cancer patients are the direct beneficiaries of anticancer drugs.

The Canadian Institute for Cancer estimates that one in three people will be stricken with some form of cancer during their life (Brodsky et al 2004). With such a high incidence rate, the disease directly or indirectly affects almost every member of society. The friends, family, or caregivers of cancer patients may also share in the benefits offered by new anticancer drugs. How do we decide which treatments offer the most benefits to society in aggregate?

One early indicator of the potential total benefits of these new drugs is their efficacy in clinical trials. Demonstration of efficacy is the first step towards establishing proof that a new drug will benefit cancer patients and society. The outcomes from clinical trials form the initial basis of most regulatory approval decisions. All new drugs must achieve regulatory approval before their release to the market. This first demonstration of clinical efficacy also contributes to the process of deciding if healthcare programs will adopt the drug.

1.2 The Net Social Benefits of Anticancer Drugs

In allocating scarce resources, healthcare decision-makers must factor in both the clinical benefits as well as the non-clinical benefits of new drugs. Indirect or non-clinical benefits may include the drug's ability to enhance a patient's quality of life or prevent disease in the long-term (Brouwer et al 2001). Other indirect benefits, such as protecting the ability of an individual to earn an income and consume goods and services, may also factor into decisions regarding the adoption of new drugs into healthcare systems (Wu 1980).

Intuitively, the greatest net social benefits occur when the costs to produce a given drug are low and the benefits received from it are high (Vining and Wiemer 2006). Figure 1 illustrates this basic point, showing a number of different levels of net social benefits (NSB_G and NSB_L) derived from a drug produced at two different cost levels (C_i and C_e). When the difference between total costs and total benefits is large, the drug provides greater net social benefit (NSB_G). Holding all else constant, the greatest difference between costs and benefits occurs when a given drug production technology is efficient and therefore follows an efficient cost curve (C_e). Lower net social benefits (NSB_L) will be realized when the drug is produced with inefficient methods that raises the whole cost curve (C_i) (Vining and Weimer 2006). It also makes sense to select the optimum output level for a drug such that net social benefits are maximized (NSB_G), rather than any other output level.

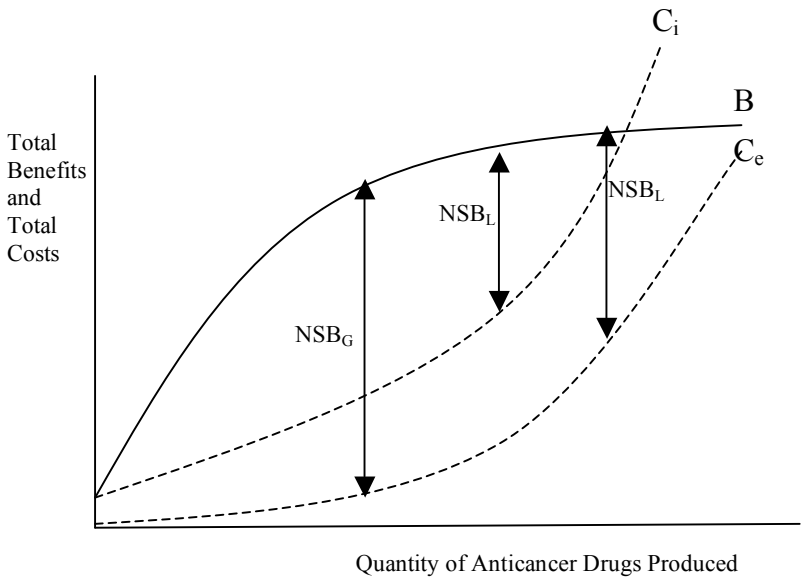


Figure 1. Maximizing Net Social Benefits
Source: Adapted from (Vining and Weimer 2006)

Given declining marginal benefits (a typical situation) and increasing marginal costs (again, a typical situation), there is a point where the total social benefits received from an anticancer drug or a portfolio of drugs will reach a maximum. Current research supports the belief that incremental gains in clinical benefits are diminishing for new anticancer drugs (Grabowski 2004). This may be a sign that the net social benefits of the anticancer drugs are nearing their maximum possible value. DiMasi and colleagues also show that the cost of innovation in the pharmaceutical industry is rising at a high rate (7.4% above inflation per year) (DiMasi et al 2003).

Recent empirical evidence has confirmed that drug prices are directly related to their therapeutic advancements (Lu and Comanor 1998; Ekelund and Persson 2003). Some fear that increased marginal costs may also serve to indicate that the high prices of new anticancer drugs are simply a way for drug companies to retain high profits (Brandes

2007). Certainly, experts now believe that the price of new anticancer drugs is about 300 times the price of anticancer drugs introduced in the 1980s (Schrag 2004).

1.3 Information Exchange in Healthcare Markets

Rising pharmaceutical prices are problematic because pharmaceutical manufacturers and healthcare decision-makers have conflicting interests. Pharmaceutical manufacturers have the main interest of earning profits from the sale of new drugs and thus favor high drug prices. Profits from sales are re-invested in research and development. This investment effectively leads to the innovation of future drugs (Grabowski 2002). In contrast, healthcare decision-makers have the interest of minimizing healthcare costs and oppose high drug prices. A conceptual understanding of healthcare markets is necessary to appreciate the impact that highly priced drugs have on healthcare systems.

Healthcare markets differ from competitive markets because of the way that information flows between supplier and consumer, as shown in Figure 2[1]. In between the primary medical suppliers (i.e. pharmaceutical manufacturers), are various regulators, such as the US Food and Drug Administration (FDA) and financial regulators, such as health insurers and agents (pharmacists or physicians). The flow of information in healthcare markets is through these intermediate regulators, with many stakeholders involved.

[1] For a discussion of market failures in healthcare, see Donaldson, C., and Gerard, K. (1989). "Countering moral hazard in public and private health care systems: a review of recent evidence." Journal of Social Policy **18**(2): 235-251.

Because the flow of information is indirect, via intermediary regulators, the rate and direction of innovation from pharmaceutical manufacturers is tightly controlled. For example, governmental regulators use the Orphan Drug Policy, to direct innovation towards the development of new drugs for rare diseases (Yin 2008). Manufacturers that develop drugs for rare diseases receive extended market exclusivity, and other monetary incentives to encourage the development of drugs for unmet medical needs. Regulators in healthcare markets may also impose policies that direct the rate of innovation of certain drugs. The FDA's accelerated approval program is one example of a policy that expedites the production of drugs that treat diseases with an unmet medical need (Fleming 2005).

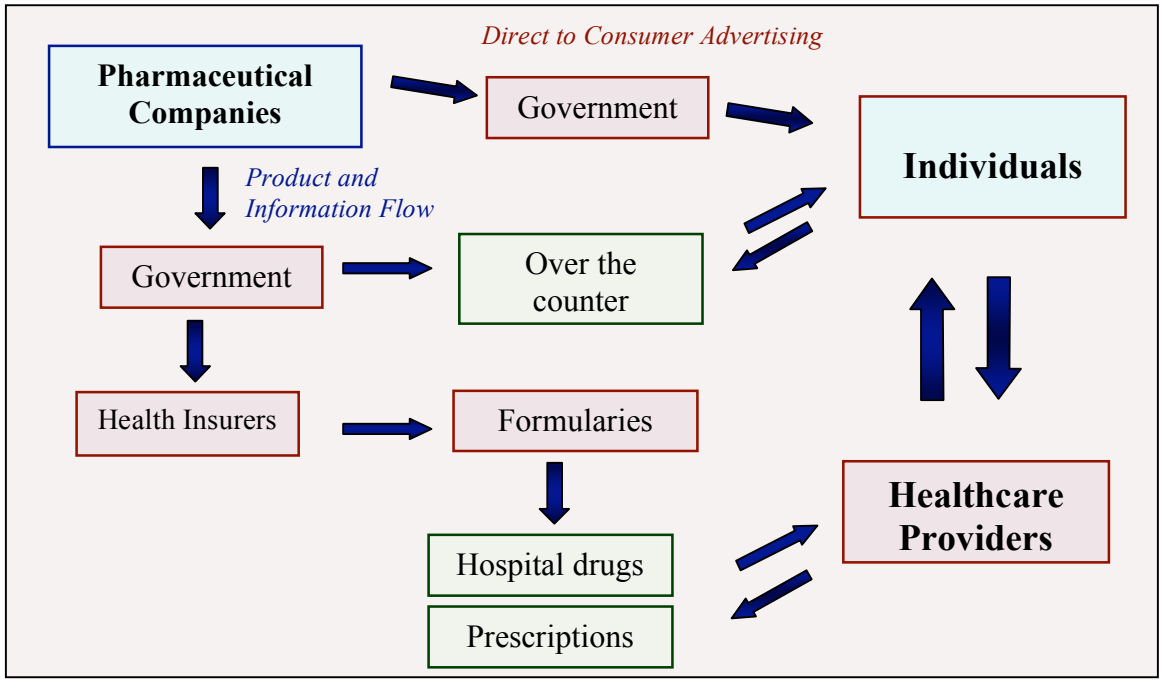


Figure 2. Information Exchange in Healthcare Markets
Information from pharmaceutical suppliers must pass through several regulators (red boxes) before healthcare consumers may receive the drug.
Source: Author's illustration, adapted from published reviews of healthcare markets (Ess et al 2003), (Drummond et al 1997).

Governmental regulators, such as the FDA, must balance the need for safe and effective therapies with the need to promote pharmaceutical innovation (Philipson et al

2008). Over the past few decades, it has become increasingly expensive to innovate in the pharmaceutical industry. In the 1960s, the FDA received criticism for their approval of a sleeping pill that contained thalidomide, a chemical later found to cause extreme birth defects. The disaster affected over 8000 infants in North America. In response to this tragedy, the FDA's approval process underwent a series of reforms. Experts now estimate that post-thalidomide clinical trials cost drug manufacturers approximately ten times more than they did before the reforms (Reviewed in Connors 1996). The high cost of conducting clinical trials is a suggested cause for the high prices of anticancer drugs.

Some Economists question whether the FDA's emphasis on safety is a social loss, since there is a great level of social benefits that result from the production of new drugs (Philipson et al 2008). Aspinall and Hamermesh (2007) note that healthcare regulators will face critical operational changes as new medicines of the future make their way into healthcare markets (Aspinall and Hamermesh 2007).

1.4 Healthcare Systems and Expensive New Therapeutics

The high prices of new anticancer drugs imposes significant strains on many healthcare budgets (Rawlins 2007). The problem of rising pharmaceutical expenditures is a global concern. Almost every developed country has experienced a sharp rise in drug spending in recent years (OECD 2005). In Canada, the amount spent on new anticancer drugs has steadily increased--at a rate of 20% per year over the past ten years (Brodsky et al 2004). The rate of drug spending is well above Canada's rate of inflation and growth in GDP

during this time (Government of Canada 2008). Efforts to control pharmaceutical expenditures have been largely unsuccessful, across the globe (Ess et al 2003).

While many factors contribute to the problem of pharmaceutical expenditures, high drug prices are one of the main problems that healthcare authorities hold accountable for the strain on healthcare budgets. For example, some healthcare authorities have chosen not to adopt Genentech's new anticancer drug, Avastin® (trade name, Bevacizumab) because of concerns about its high price (Berenson 2006). For many healthcare authorities, the clinical benefits offered by the drug do not appear to be worth the amount that Genentech charges for the drug (Unspecified Author #1 2006; McManus 2007).

In addition to concerns over healthcare budgets, governments are also concerned about the threat that expensive new drugs impose on social equity. The selective reimbursement of Avastin® by some healthcare payers is a good example of the equity concerns at hand. In Canada, six out of ten provinces have decided against the public reimbursement of Avastin®. However, the remaining four provinces will publicly reimburse the drug in their health programs (CBC 2007; CBC 2008(a); CBC 2008(b)). As a result, cancer patients in one province might not receive the same standard of care that is available in another province. In the US, even the "patient-pays" fraction of Avastin®'s co-payments are expensive for many cancer sufferers (Berenson 2006). This effectively means that some people cannot afford to extend their lives. In such cases, physicians may be inclined to withhold information about expensive treatments from their patients. Indeed, some physicians admit to having withheld information about new treatments when they felt that their patients could not afford the upfront cost of the drug (Thomson et al 2006).

The strain that expensive new drugs place on healthcare systems is likely to increase as populations in developed countries age. It is anticipated that the population demographics for developed countries will shift towards more elderly persons and persons with health needs that require drug therapy (OECD 1994). Therefore, mechanisms to value and regulate pharmaceutical expenditures are becoming increasingly important in many healthcare landscapes (Ess et al 2003).

1.5 Valuing the Health Benefits of New Drugs

Drug manufacturers must establish the value of their new drugs in order to sell them within healthcare markets. Drug manufacturers may utilize a number of different evaluation tools to demonstrate the value of new anticancer drugs. The ideal way to ascertain value of these new drugs is to demonstrate their cost-effectiveness through a cost-effectiveness analysis (CEA) (Murray et al 2000; Drummond 2004).

Before drug manufacturers prove that new drugs are cost-effective, they must prove the clinical value of the new drug. The following discussion concerns the regulation of drugs before they enter healthcare markets. The discussion refers to the diffusion of highly priced anticancer drugs into the Canadian healthcare system, specifically.

Regulatory agencies use clinical data to ascertain the clinical benefit of new drugs. In the Canadian system, Health Canada uses clinical data to ensure that new drugs are effective before they enter the Canadian market (HC 2008). Similarly, the Food and Drugs Administration (FDA) regulates the release of drugs in the US, and the European Medicines Agency (EMEA) regulates European drug approvals.

Review of the cost-effectiveness of new drugs may occur at different levels of authority in different countries. Some countries require manufacturers to provide pharmacoeconomic evaluations for the drugs that they sell[2]. Other nations have committees or review panels that investigate the cost-effectiveness of new drugs coming to market.

Canada has a quasi-judicial organization, called the Patented Medicines Pricing Review Board (PMPRB), which attempts to ensure that the price of new drugs is not "excessive". After Health Canada approves new drugs for use, the PMPB makes recommendations to the government about the cost-effectiveness of new anticancer drugs. After this regulatory screen, provincial governments are then responsible for deciding whether or not to adapt new drugs onto their provincial formularies. Other factors, such as budget constraints, political pressure and pressure from patient advocacy groups may also contribute to adoption decisions (Kapiriri et al 2007).

1.5.1 Economic Evaluation

Evaluation of new drugs through a CEA is a classic approach to economic evaluation (Drummond 1997). Healthcare decision-makers may also use a more extensive form of analysis known as cost-benefit analysis (CBA) to inform resource allocation decisions. This form of analysis estimates a monetary value for all of the resources consumed by the adoption of a new drug and for all benefits that it may provide (Boardman et al 2006). The

[2] The International Society for Pharmacoeconomic Outcomes Research is good resource which summarizes international guidelines for healthcare evaluations: http://www.ispor.org/PEguidelines/index.asp.

use of CBA is sometimes impractical for healthcare decisions, since some healthcare resources are not readily convertible into monetary values (Ackerman and Heinzerling 2002). For example, the amount of pain that patients experience is not easily quantifiable into dollar terms.

To work around this problem, health programs use measures of utility rather than dollar values to determine the health benefits of new drugs. The utility refers to a set of the preferences that individuals have for a particular state of health. This enables health outcomes to follow the established protocols of CBA (Drummond et al 1997).

Quality Adjusted Life Years (QALYs) express utility in terms of time. QALYs are calculated by multiplying the utility measure by a relevant number of life years gained (Elliot and Payne 2005). QALYs account for benefits in both the quality and length of life provided by new healthcare interventions (i.e. anticancer drugs). Utility measures in economic evaluations allow for comparison of health gains from different programs for different diseases. Thus, cost utility analyses often inform decisions towards the most efficient allocation of healthcare funds (or resources).

1.5.2 Prioritization of Healthcare Resources

Decision-makers in healthcare programs must prioritize new therapeutics in order to efficiently ration scarce healthcare resources (Millar 2002). Many members of the medical community fear that healthcare budgets are in danger of eventual depletion. One concern for healthcare capacity constraints originates from Hiatt's argument that there are diminishing healthcare resources (Hiatt 1975). If each member of society consumes these resources out of their own rational self-interest, then society (in aggregate) will have fewer

resources available. Hiatt's argument has generated widespread concern over healthcare rationing and prioritization. Authorities in many healthcare systems respond to the perceived threat of insustainability by prioritization and price regulation.

Experts in economics fear that the move to protect healthcare funds by prioritization may have adverse effects on the introduction of future breakthrough drugs (Vernon 2003b). Intuitively, pharmaceutical manufacturers oppose any program (especially price regulations) that reduces their ability to earn profits. Thus, there are conflicting interests between those interests of healthcare authorities and the interest of pharmaceutical manufacturers.

Many fear that high drug prices place a substantial strain on healthcare resources. Pharmaceutical manufacturers fear that if drug prices are too low, they will not be able to afford the high cost of innovating and the development of new drugs. These conflicting interests do not appear to complement today's healthcare operations or pharmaceutical business models. If the trend for high pricing continues, changes to these systems will be required. These changes may require larger social investments in pharmaceutical innovation (Murphy and Topel 2008). In the next chapter, we look back in time to explore the amount of social benefits received from the innovation of new anticancer drugs throughout history.

2 The History of Anticancer Drugs

Since high drug prices fuel innovation, it is worthwhile to look at how innovation has brought forward new anticancer drugs throughout history. This section discusses the development of anticancer drugs over the past century. There have been three main eras of innovation: 1) the era of early cytotoxic drugs, 2) the era of therapeutics and 3) the current era of the targeted therapies. In the next decade or so, we will enter the next era of personalized medicines.

Cancer did not become a significant social concern up until the 20th century. The lack of awareness of cancer may be a reflection of the average life expectancy at the time. Around 1900, persons living in developed countries were expected to live less than 50 years (WHO 2007). The medical gains made during the mid-1900s greatly increased life spans and enabled the detection of cancer in its early stages. Since then, scientists, clinicians and governments have made significant gains in the fight against cancer.

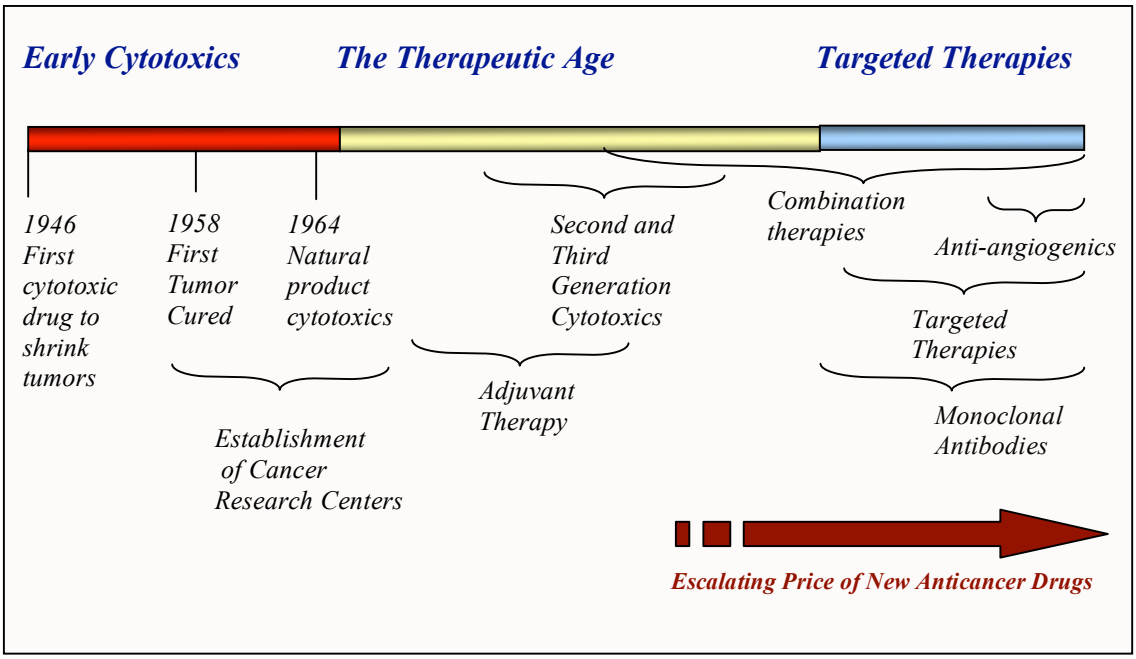


Figure 3. Timeline of Innovative Progress in Cancer Therapy
Source: Author's illustration and knowledge of anticancer drugs

2.1 Early Cytotoxics: Anticancer Drugs of the 1950s and 1960s

The therapeutic administration of nitrogen mustards was the first major breakthrough in cancer chemotherapy (Goodman et al 1946). Goodman et al (1946) used rudimentary clinical trials to show that these (otherwise toxic) compounds could reduce the size of tumor masses. The use of cytotoxic agents also established that cancer cells were highly sensitive to the toxic agents. This finding led the way to several other new anticancer drugs.

Throughout the 1950s and 1960s, other toxic agents were developed. These agents could shrink different types of tumors with differing degrees of success. During this time, society's awareness of cancer also increased. For example, in 1955 the National Cancer Chemotherapy Service Center became the first organization specifically devoted to cancer. Other establishments, such as the Montgomery Wall Research Park, Howard Hughes Medical Centre, the Memorial Sloan-Kettering Cancer Centre, soon followed (Triolo 1961).

During this time, the pharmaceutical industry went through similar organizational changes. Research groups at major pharmaceutical manufacturing companies formed cancer-specific teams (Bud 1978). The Natural Products Division at Eli Lilly Company was a notable team formed during this period. The scientists in the Natural Products Division were the first to isolate a class of cytotoxic drugs from periwinkle flowers (Pearce and Millar 2005). Many chemotherapy regimens today still use this highly effective class of drugs. The combination of scientists with clinicians formed the foundation for the next era of innovations in medical practices: the therapeutic age.

2.1.1 The Therapeutic Age: Progress against Cancer in the 1970s and 1980s

Throughout the 1970s and 1980s, innovations arising from medical practice rather than from pharmaceutical chemistry fueled the fight against cancer. The combination of different anticancer methods resulted in increased survival times (Diamandopoulus 1996). These combinations included the use of surgical, chemotherapeutic and/or radiological techniques that fought cancer (Kardinal and Yarbro 1979).

During this era, childhood acute lymphoid leukemia, Hodgkin's disease, testicular cancers and choliocarcinomas all became curable diseases (FHCRC 2008). The ability to detect the disease early on also contributed to increased chances for surviving cancer in the 1980s (Strax 1988). When detected early, breast and skin cancers also became curable diseases. In 1980, the overall probability for surviving five years with any type of cancer in the US was about 50% (Ries et al 2006c). That number increased to 9% in the following decade.

By the end of the 1970s, it was common to administer one or two cytotoxic drugs in combination with anti-inflammatory or antinauseal drugs. The addition of these drugs to chemotherapy regimens increased the quality of life for cancer patients by offering relief from the discomforting side effects of chemotherapy. The combination of several different anticancer drugs in a regimen also increased the effectiveness of the primary anticancer drug (Frei 1985).

2.1.2 Targeted Therapeutics

Scientific advancements made in the 1980s and early 1990s led to the next era of targeted therapeutics. Targeted therapeutics are technically superior to the anticancer drugs of previous eras. These new drugs are technically superior because they act specifically on one biochemical pathway in diseased cells. The ability to specifically target diseased cells with an anticancer drug prevents unintended damage to healthy cells.

Targeted anticancer drugs have also generated substantial revenues for the pharmaceutical industry. One example is the anticancer drug, Gleevac®, introduced in 2001 by Novartis. Gleevac®, works specifically on chronic myelogenous leukemias, and leaves healthy cells unharmed. Gleevac® generated more than three billion dollars in sales for Novartis in 2007 alone (Novartis 2008).

The targeted drug, Taxol® (for breast and ovarian cancers) was the first anticancer drug to cause extensive concern over its high price (Sheldon 1997; Evans et al 2002). Critics initially argued that increasing R&D expenditures were the cause for the high prices of targeted drugs by pharmaceutical manufacturers (DiMasi et al 1992; Grabowski and Vernon 1994). The high-price trend has continued through the 1990s and, indeed, into the second millennium. Now, nearly every new anticancer drug reaches market at a high price (Grabowski et al 2002). As we enter the era of personalized medicine, experts anticipate the trend to high pricing will continue (Dreyer 2006).

2.1.3 The Forthcoming Era of Personalized Medicines

Healthcare landscapes will change as we enter the era of personalized medicine. The greatest changes are expected to affect the development, marketing and uptake of future drugs into healthcare systems (Aspinall and Hamermesh 2007). The business models used by pharmaceutical manufacturers today will also need to change. This change is needed because future therapies will treat small sub-classes of disease instead of the large, generalized diseases classes of today (Unspecified Author #2 2007).

Cancer therapies of the future will offer sophisticated improvements that originate from recent accomplishments in the field of genomics (Dunham et al 1999; Venter et al 2001). Genome-based medicines will match the pathology of a specific disease with greater precision. Narrowly-focused drugs against particular disease subclasses will replace the broad-spectrum blockbuster drugs that are common today (Dreyer 2006). Diagnostic tests will be necessary to confirm that the suspected molecular target is available. Without a doubt, these advancements will come at a very high price.

3 Clinical Benefits of Drugs against Breast Cancer

The following two chapters are an analysis of the clinical benefits of new anticancer drugs in recent history. These clinical benefits are then related to the drug prices in order to gain an understanding of how the price-benefit ratio has increased over time in Chapter Four. This chapter specifically focuses on the increases in clinical benefits of breast cancer drugs over time.

Several effective treatments against breast cancer have come to market over the past decade. Herceptin® (Trastuzumab) is one of the most advanced breast cancer drugs to be developed. Herceptin® is an effective targeted therapeutic that attacks a specific subclass of breast cancer. The type of tumors that Herceptin® works on are known as the "HER2 positive" subclass of breast tumors. Until the advent of Herceptin®, patients with HER2 positive tumors had a poor prognosis for survival. Now, over 400, 000 women worldwide have received the drug since its initial approval in 1998 (Genentech 2008a). Herceptin® has allowed these breast cancer patient either to be cured or at least live longer before disease progression.

The known number of breast cancer subclasses has increased over time (see Appendix I). Clinicians today are now able to diagnose different disease subclasses with greater precision than in the past. More subclasses will emerge as our understanding of the mechanisms of disease progression further improves. The continued discovery of small differences between tumor subtypes will also bring forth new therapeutic targets for future drugs.

3.1 Assessing the Benefits of New Anticancer Drugs with Clinical Trial Endpoints

Demonstration of efficacy in a clinical trial is usually the first indication that a new drug will be of some benefit to society. Several other factors, however, may also influence the FDA's decision towards the approval of new drugs. These include the severity of disease at hand and the availability of other effective medicines (Pazdur 2008).

The primary and secondary endpoints of a clinical trial are the main outcomes that indicate a drug's clinical efficacy. The FDA publicizes all clinical outcomes that support their approval decisions on the Internet (FDA 2008d). Currently, complete electronic records are available on the FDA's website for most drugs approved after 1984. This FDA-publicized information has been the main source of clinical outcomes used in this report.

A comprehensive list of all FDA-approved breast and colorectal cancer drugs can be found in Appendix I and II, respectively. Robust records of approval decisions did not become available on the FDA website until the mid-1980s. It is for this reason that the analyses in the upcoming sections are limited to those drugs approved over the past decade.

In 1992, the FDA introduced a process known as "accelerated approvals" for new drugs that could treat serious or life-threatening diseases (Fleming 2005). The move to expedite the approval process led to the need for faster indicators of clinical benefits. Because of the need for faster indication of clinical benefits, the use of surrogate endpoints arose for rapid assessment of clinical trial outcomes.

Surrogate endpoints are early indicators of the ability of a drug to improve overall

survival (OS, the "gold standard" for cancer outcomes). Time to progression (TTP) and overall response rates (ORR) are two surrogate endpoints that are used to estimate the effectiveness of anticancer drugs (Pazdur 2008). Surrogate endpoints may also assess the benefit of treatments against diseases that progress slowly. All clinical trials submitted to the FDA use surrogate indicators to describe the clinical benefits of new breast cancer treatments.

3.2 Drugs Approved for the Treatment of Metastatic Breast Cancer

Metastatic breast cancer is an advanced stage of disease progression. At this point, the diseased tissue has spread from the breast area and axillary lymph nodes under the arm to other organs (Cotterill 2000). When breast cancer has reached the metastatic stage of progression, surgical procedures to remove the diseased tissues are often ineffective. Drugs developed against metastatic breast cancer aim to slow the progression of the disease, since a cure is not likely (Moore and Cobleigh 2007). The FDA usually uses the endpoint, time to progression (TTP) to measure the clinical efficacy of new drugs against metastatic breast cancer.

3.2.1 First-Line Treatments

"First-line treatments" are drugs used as the initial treatment of cancer. Table 1 lists some of the first-line treatments that have recently become available for metastatic breast cancer. The ability of new drugs to slow the disease has steadily increased over time.

Longer times to disease progression (TTP) indicate that a new drug is more effective at slowing disease progression. In 1998, the new drug, Herceptin® was shown to halt disease progression for 6.5 months. The expected TTP for first-line metastatic breast cancers has steadily increased over time. Currently, in 2008, Avastin® has been shown to offer 11.5 months before signs of disease progression resume (FDA 2008). This is equivalent to an expected two-year increase in overall survival for those patients who receive Avastin®.

Table 1. Drugs Approved as First-Line Treatments of Metastatic Breast Cancer

Drug	Approval date	Trial Reference	Trial Comparators	Primary endpoint	Outcome (Median months)*	Secondary endpoint(s)	Secondary outcome(s)
Nolvadex®, tamoxifen	04/01/93	(FDA 1993)	**Nolvadex®** (Single arm)	ORR	50%	N/A	N/A
Herceptin®, trastuzumab	09/25/98	(FDA 1998)	**Herceptin®** + Paclitaxel	TTP	6.7 95% CI (5.2-9.9) p<0.0001	ORR	38% (28-48) p<0.001
			Paclitaxel		2.5 (2.0-2.3) p<0.0001		15% (8-22) p<0.001
Arimidex®, anastrazole	09/01/00	(FDA 2000b)	**Arimidex®**	TTP	8.5 (HR=1.01††, lower 95% CI=0.87)	ORR	32.9% (HR=-1.01% lower 95% CI=-0.77%)
			tamoxifen		8.3		32.6%
Femara®, letrozole	01/09/01	(FDA 2001b)	**Femara®**	TTP	9.4 (HR=0.70, 95%CI 0.6-0.82) p=0.0001	ORR	30% (Odds ratio=1.71 (1.26-2.32) p=0.0006
			tamoxifen		6.0		20%
Avastin®, bevicizumab	02/22/08	(FDA 2008)	**Avastin®** + Paclitaxel	PFS**	11.3 (10.5-13.3) p<0.0001	OS	26.5 (23.7-29.2) p 0.14
			Paclitaxel		5.8 (5.4-8.2) p<0.0001		24.8 (21.4-27.4) p 0.14

*when available, 95% CI is indicated in brackets below outcomes

** Progression free survival (PFS) is comparable to TTP. PFS includes data from patients who have passed away before the disease progresses (Pazdur 2008). TTP measures do not include patients who have died.

† 95 % CI=95% confidence interval, the certainty that 95% of all data points fall within the specified limits (lower limit-higher limit)

‡ HR=Hazard ratio, the relative risk that a treatment offers a greater benefit over a comparative treatment. Hazard ratios less than one indicated that there is improvement over the comparator.

Source: Author's retrieval, comprehension and simplification of FDA web-published data. This summary (and all forthcoming summaries of FDA approvals in this project) was generated by the author, using the main clinical trial outcome that informed the FDAs approval decision. The trial reference is cited in the "Reference" column.

3.2.2 Second-Line Treatments

Patients may receive second-line treatments after a prior treatment has failed. The chances of survival are much lower for surviving breast cancer patients that are treated with second-line drugs, after the failure of first-line treatments. Second-line therapies seek to improve a patient's quality of life and delay the onset of tumor progression. The main clinical outcome used to evaluate second-line drugs is the Overall Response Rate (ORR). ORR measures the percentage of patients who experience a reduction in tumor size for a given amount of time (Pazdur 2008). TTP measures are usually the secondary (or supporting) endpoints in most second-line treatments.

Table 2 lists the drugs approved for the second-line treatment of metastatic breast cancer, since 1994. In 1994, 26% of all patients receiving Taxol® responded to it. While receiving Taxol®, the average patient could expect 3.5-months of survival without tumor progression. Ten years later, in 2004, the drug Gemzar® almost doubled the percentage of patients that responded to 43%, and delivered 5.2 months of lifetime before the disease progressed.

Table 2. Drugs Approved as Second-Line Treatments of Metastatic Breast Cancer

Drug	Approval date	Reference	Comparators	Primary endpoint	Outcome	Secondary Endpoint(s)	Outcome
Taxol®, paclitaxel	04/13/94	(FDA 1994)	**Taxol®** (single arm)	ORR	26% (22-30%)	i) TTP ii) Survival	i) 3.5 (range 0.03-17.1) ii) 11.7 (range 0-18.9
Taxotere®, docetaxel	05/14/96	(FDA 1998c)	**Taxotere®**	ORR	41%*	i) TTP ii) O/S iii) 1 yr survival	i) 4 (0.2-17.5) ii) 10 (0.2-24.6) iii) 43%
Arimidex®, anastrazole	12/27/95	(FDA 1995)	**Arimidex®**	ORR	10.3%	Duration of Response	92-512d
			Megestrol acetate		7.9%		111-427d
Fareston®, toremifene	05/29/97	(FDA 1997; GTx 2008)	**Fareston®**	RR**	a) 21.3% b) 20.4% c) 31.3%	i) TTP ii) Survival	i) a) 5.6 ii) a) 33.6 b) 4.9 b) 25.4 c) 7.3 c) 33.0
			Tamoxifen		a) 19.1% b) 20.8% c) 37.3%		i) a) 5.8 ii) a) 34 b) 5.0 b) 23.4 c) 10.2 c) 38.7
			Femara®		23.6%		i) 5.67 ii) 24.3
			Megesterol acetate		16.3%		i) 5.6 ii) 22.0
Xeloda®, capectibine	04/30/98	(FDA 1998b)	**Xeloda®** (single arm)	ORR	18.5% (12.4%-26.1%)	TTP	3.13 (2.8-3.9)
Herceptin® , trastuzumab	09/25/98	(FDA 1998)	**Herceptin®** (single arm)	ORR	14%	i) TTP ii) Survival	i) 3.1 95%CI (2.3-3.4) ii) 12.8 95%CI (9.9-ongoing)
Aromasin®, exemestane	10/21/99	(FDA 1999c)	**Aromasin®**	ORR	15%	TTP******	4.73
			Megesterol acetate		12.4%		3.87
Faslodex®, fulvestrant	05/25/02	(FDA 2002c)	**Faslodex®**	ORR i) European trial ii) US trial	i) 20.3% ii) 17%	TTP	i) 5.53 ii) 5.5
			Anastrazole		i) 14.9% ii) 17%		i) 5.2 ii) 3.43
Gemzar®, gemcitabine	05/19/04	(FDA 2004f)	**Gemzar®** + Paclitaxel	ORR	40.8% 95%CI (34.9-46.7)	TTP	5.2 95%CI (4.2-5.6)
			Paclitaxel		22.1% 95%CI (17.1-27.2)		2.9 95%CI (2.6-3.7)
Abraxane®, paclitaxel protein-bound particles	01/07/05	(FDA 2005b)	**Abraxane®**	TLRR (randomized metastatic b.c.)	21.5% 95%CI (16.2-26.7)	TLRR (failed combination chemo or relapse within 6 months)	15.5% 95%CI (9.26%-21.75%)
			Paclitaxel		11.1% 95%CI (6.9-15.1)		8.4% 95%CI (3.85%-12.94%)
Tykerb®, Lapatinib, ditosylate	03/13/07	(FDA 2007c)	**Tykerb®** + capectibine	TTP	6.3	ORR	23.7% 95%CI (18.0-30.3)
			capectabine		4.34		13.9% 95%CI (9.5-19.5)

†when available, 95% CI is indicated in brackets below outcomes

*This is for the intent to treat population. For the patients deemed evaluable (not lost to death or inability to follow-up), the overall response rate was 43%

**three trials (a, b, and c) were analyzed

Source: Author's representation, simplification and retrieval of FDA web-published data as cited in the second column

3.2.3 Improvement for Metastatic Breast Cancer: Summary of Clinical Benefits

Figure 4 shows the relationship between TTP measures (as listed in Tables 1 and 2) and the drug's approval date. New drugs against metastatic breast cancer have resulted in an overall increase in the median months to disease progression, over time. This improving trend for increasing clinical benefits is perhaps not surprising, since the FDA expects new drugs to offer improvements over pre-existing treatments.

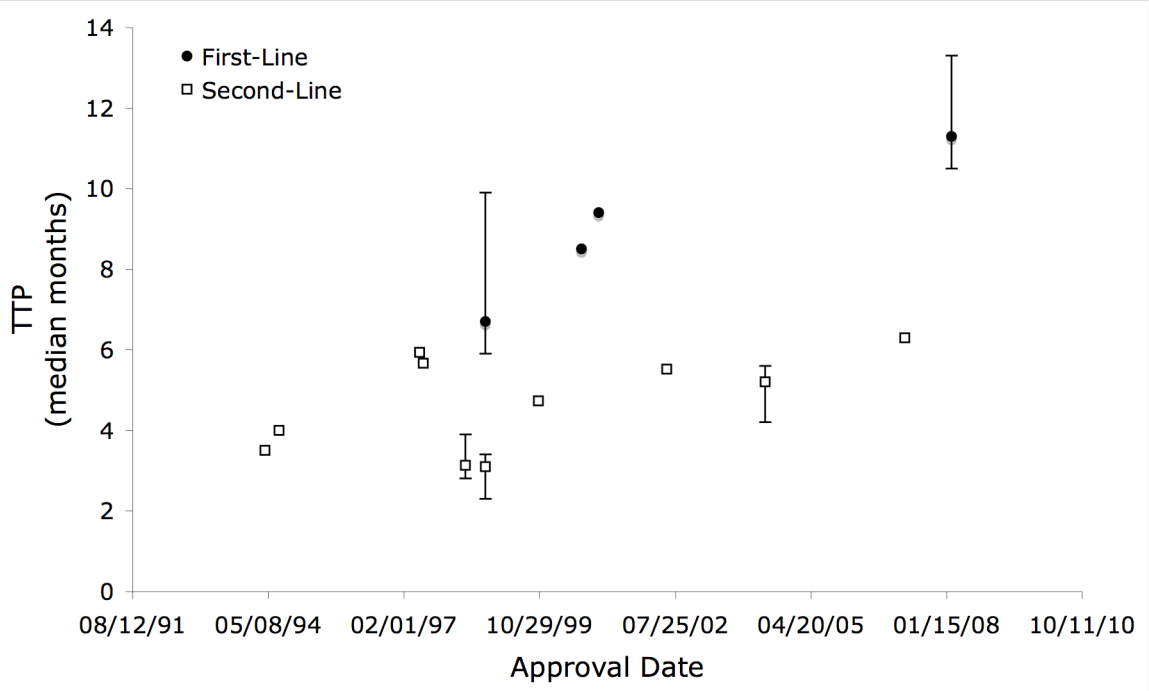


Figure 4. Clinical Benefits of First and Second-Line Treatments Approved for use against Metastatic Breast Cancer
Source: Author's representation and retrieval of clinical efficacy outcomes from FDA approval records
Error bars represent the 95% CI limits when they were included in the efficacy report. Not all FDA-published records include error estimates.

3.3 Advancement in Adjuvant Breast Cancer Treatments

Drugs used in the adjuvant setting reduce the chance that a tumor will return after some form of initial therapy. The type of initial therapy received before the administration of adjuvant treatments can vary. The selection of first-line treatment depends on the disease subclass and stage of progression. In many cases, adjuvant treatments follow the surgical removal of the primary tumor mass. Adjuvant therapy may also complement an initial round of chemotherapy.

The FDA uses the endpoint, "disease free survival (DFS)" to measure the clinical benefit of drugs that are used in the adjuvant setting. Drugs that increase DFS have a low hazard ratio, as compared to other (pre-existing) treatments (Spruance et al 2004). Table 3 summarizes the drugs approved for use as adjuvant treatments against breast cancer. The first adjuvant treatment that was approved and recorded on the FDA's website was Tamoxifen®, in 1986. The drug replaced ovarian ablation (either removal or irradiation of the ovaries) as an adjuvant treatment following surgery (FDA 1986).

Many breast cancer patients may now live their entire lives without further signs of the disease because of these new adjuvant treatments (Dinh et al 2007). Modern treatments also aim to enhance the quality of life for patients that receive adjuvant chemotherapy. The concern over quality of life is particularly important, since adjuvant therapies often last for five years. Some of these treatments are as simple as once-daily hormone pills. The use of Herceptin®-containing regimens has produced the greatest reduction in disease recurrence of all adjuvant treatments.

Table 3. Drugs Approved for Adjuvant Breast Cancer Therapy

Drug	Specific Indication	Approval date	Reference	Comparators	Primary end-point	Outcome	Other end-point	Outcome
Nolvadex®, tamoxifen	After surgery	12/03/86	(FDA 1986)	**Nolvadex®**, tamoxifen	n/a			
				Ovarian ablation				
Nolvadex®, tamoxifen	Metastatic	03/16/89	(FDA 1989)	**Nolvadex®,** tamoxifen	DFS	Equal efficacy		
				Ovarian Ablation				
Nolvadex®, tamoxifen	Node positive b.c. after surgery	06/21/90	(FDA 1990)	**Nolvadex®,** tamoxifen	DFS	Modest improvement		
				Placebo				
Ellence®, epirubicin	Axillary involvement after resection	09/15/99	(FDA 1999)	CP, **Ellence®**, Fluorouracil	RFS*	62% (HR=0.758, p=0.013)	OS	77% (HR=0.714, p=0.043)
				CP, Methotrexate, Fluorouracil		53%		70%
Taxol®, paclitaxel	Node positive after doxorubicin	10/25/99	(FDA 1999b)	CP, Dox, **Taxol®**	DFS	HR=0.78 (0.67-0.91)	OS	HR=0.74 (0.60-0.92)
				CP, Dox				
Arimidex®, anastrazole	Hormone receptor, early b. c.	09/05/02	(FDA 2002b)	**Arimidex®** (1mg/d)	RFS	HR=0.83 (0.71-0.96) p=0.0144		
				Tamoxifen				
Adriamycin®, Doxorubicin (Dox)	After resection of node positive primary bc	05/08/03	(FDA 2003)	**Adriamycin®** containing regimens†	DFS	**HR**=0.91 (0.82-1.01)	OS	HR=0.91 (0.81-1.03)
				Methotrexate, Cyclophosphamide, Fluorouracil				
Taxotere®, docetaxel	Operable, node positive b.c.	08/18/04	(FDA 2004e)	**Taxotere®,** Dox, CP	DFS	HR=0.74 (0.60-0.92)	OS	HR=0.69 (0.53-0.90)
				Fluorouracil, Dox, CP				
Femara®, letrozole	Early b.c. after 5 years of tamoxifen	10/29/04	(FDA 2004d)	**Femara®**	DFS	HR=0.62 (0.49-0.78) p=0.00003		
				Placebo				
Aromasin®, exemestane	After 2-3 years of tamoxifen	10/05/05	(FDA 2005)	**Aromasin®**	DFS	HR=0.69 (0.58-0.82) p=0.00003	OS	HR=0.86 (0.67-1.10) p=0.2296
				Tamoxifen				
Epirubicin®, epirubicin	After the treatment of axillary-node positive breast cancer	09/15/06	(FDA 2006b)	CP, **Epirubicin®,** Fluorouracil	RFS	62% HR=0.76 (0.6-0.96	OS	77% HR=0.71 (0.52-0.98)
				CP, Methotrexate, Fluorouracil		53%		70%
Herceptin®, trastuzumab	HER2+, node Positive Tumors	11/16/06	(FDA 2006c)	Dox, CP then **Herceptin®** + either paclitaxel or docetaxel	DFS	HR=0.48 (0.39-0.59) p=<0.0001	OS	HR=0.67 Not significant
				Dox, CP, then either paclitaxel or docetaxel				
Herceptin®, trastuzumab	HER2+, node positive or high risk node negative	01/18/08	(FDA 2008c)	anthracycline therapy then **Herceptin®**	DFS	HR=0.54 (0.44-0.67) p=<0.0001	OS	HR=0.75 Not significant
				anthracycline therapy				
Herceptin®, trastuzumab	As part of carboplatin and docetaxol adjuvant regimens	05/22/08	(Genentech 2008c)	Dox, CP then Docetaxol + carboplatin + **Herceptin®**	DFS	HR=0.67 (0.54-0.84) p=0.0006		
				Dox, CP then Docetaxol + **Herceptin®**		HR=0.60 (0.48-0.76) p=<0.0001		
				Dox, CP then Docetaxol				

†based on meta-analysis published by the Early Breast Cancer Trialists Collaborative Group in 1998

*5 year relapse free survival and overall survival outcomes were measured

Abbreviations used in Table 3: bc=breast cancer, OS=overall survival, DFS= disease free survival, RFS=relapse free survival, HR=hazard ratio, Dox=doxorubicin, CP=cyclophosphamide.

Source: Author's representation, comprehension and retrieval of web-published data as cited in "Reference" column

Figure 5 compares the hazard ratios of DFS for new drugs that have been used as adjuvant therapies over the past decade. One regimen of Herceptin® (approved in 2006) shows a very high level of improvement (as indicated by a low hazard ratio for DFS). Herceptin® offers substantial benefits in all four of its approved regimens.

Disease sub-classification becomes important when comparing different adjuvant treatments. Some breast cancer subclasses are more likely to return than are others. Similarly, the chance of disease recurrence is also a function of the patient's age. Therefore, the comparison of treatments in the adjuvant setting is somewhat simplified in this project.

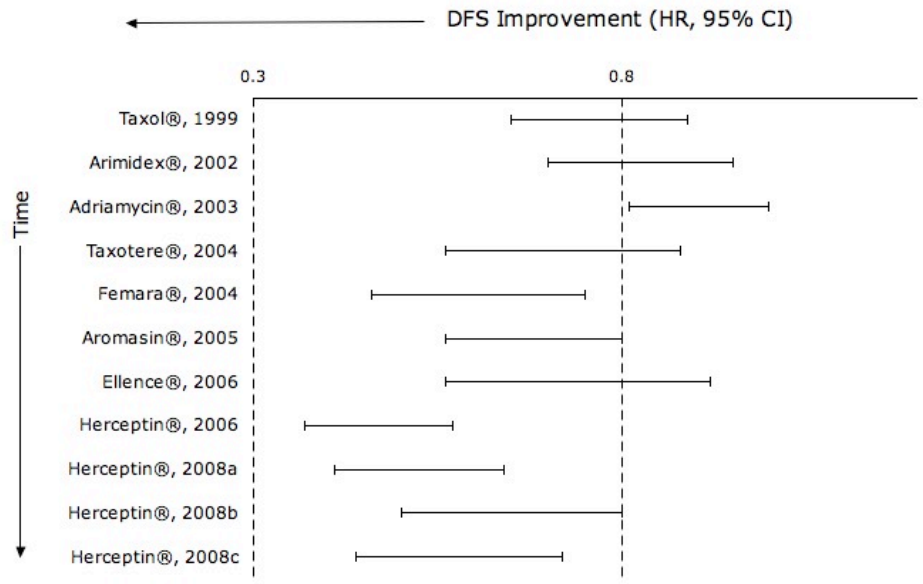


Figure 5. Clinical Benefits of New Drugs Approved as Adjuvant Therapies for Breast Cancer

Source: Author's representation of clinical efficacy outcomes retrieved from various FDA approval records listed in Table 3.

Herceptin® has proven clinical efficacy in four different adjuvant settings. The drug was initially approved in 2006 as a treatment against the "node positive" subclass of breast tumors. In 2008a, Herceptin® also received approval as an adjuvant treatment for the sub-class of patients who are "at risk of axillary node involvement". 2008b and c are adjuvant treatments that combine Herceptin® with doxorubicin (b) or oxaliplatin (c).

3.4 The Price of New Breast Cancer Treatments

This section investigates the changes in the price of new breast cancer drugs that have recently come to market in British Columbia. The author used price information provided by the BC Cancer Agency to calculate individual drug prices. All drugs in the original FDA-approved regimen were considered when calculating total treatment price. For example, if drug "A" was approved for use in combination with drug "B", the sum of the prices for drugs A and B was added to generate an estimated total treatment cost. For simplicity, the total expected price of all the drugs in the approved regimen was calculated on a "per patient" basis. These calculations are shown in Table 4[3]. The analysis is limited to those FDA-approved drugs that were also adopted into British Columbia's healthcare system due to price availability. The price of indirect and non-drug components were not included these calculations.

The duration of time that the treatment occurred for was an important contribution to the calculation of drug prices. In most cases, the drug's recommended dosage gave a reasonable indication of the expected duration of time for which the average patient would consume the drug. Metastatic treatments usually cease after visible signs of tumor progression become evident. Thus, the median months before disease progression were used to calculate the expected duration of treatment in the metastatic setting (Table 5).

[3] Out of concerns for confidentiality between the BCCA and drug manufacturers, the actual prices for the drugs remain undisclosed in this project

Table 4. Calculation of Treatment Costs for Drugs against Metastatic Breast Cancer

Drug	Trial reference	Regimen	Dosage multiplier*	Dose **	Doses /cycle	Cycles †	Remaining doses	Total mg dosed	Price per mg‡	Cumulative Drug price (per patient)	Total treatment cost
Herceptin®, trastuzumab	FDA 1998e	Herceptin®	66	4	1	1		264	[redacted]	[redacted]	[redacted]
		Herceptin®	66	2	1	29		3828	[redacted]	[redacted]	
		paclitaxel	1.6	20	1	11		352	[redacted]	[redacted]	
Arimidex®, anastrazole	FDA 2000c	Arimidex®	n/a	1	255			5508	[redacted]	[redacted]	[redacted]
Femara®, letrozole	FDA 2001c	Femara®	n/a	2.5	282			705	[redacted]	[redacted]	[redacted]
Avastin®, bevacizumab	FDA 2008	Avastin®	66	10	1	25		16500	[redacted]	[redacted]	[redacted]
		paclitaxel	1.6	90	3	13		5616	[redacted]	[redacted]	
Taxol®, paclitaxel	FDA 1994	Taxol®	1.6	175	1	5		1400	[redacted]	[redacted]	[redacted]
Taxotere®, docetaxol	FDA 1996, FDA 1998c	Taxotere®	1.6	100	1	7		1120	[redacted]	[redacted]	[redacted]
Femara®, letrozole	FDA 1997b	Femara®		2.5	170			425.25	[redacted]	[redacted]	[redacted]
Xeloda®, capectibine	FDA 1998g	Xeloda®	1.6	2510	14	5	11	325296	[redacted]	[redacted]	[redacted]
Herceptin®, trastuzumab	FDA 1998e	Herceptin®	66	4	1	1		264	[redacted]	[redacted]	[redacted]
		Herceptin®	66	2	1	14		1848	[redacted]	[redacted]	
Aromasin®, exemestane	FDA 1999d	Aromasin®	n/a	25	141.9			3547.5	[redacted]	[redacted]	[redacted]
Gemzar®, gemcitabine	FDA 2004h	Gemzar®	1.6	1250	2	9		36000	[redacted]	[redacted]	[redacted]
		paclitaxel	1.6	175	1	9		2520	[redacted]	[redacted]	[redacted]

*(average BSA (m^2) or average weight (kg)), Average BSA of a female American = 1.6mg/m^2, average weight = 66 kg

**FDA approved labels inform regimens and dosing schedules as referenced in column 2

†Calculated from TTP outcomes (Table 5)

‡Price is in Canadian dollars at approval date or closest quarter to approval date that the drug became available at the BC Cancer Agency

Source: Author's calculations and the "price per mg" of each drug (column 10) supplied by the BC Cancer Agency

Table 5. Calculation of Duration of Treatment with Metastatic Breast Cancer Drugs

Drug	Reference	TTP (Median months)	Days to progression	Weeks to progression	Weeks/ cycle	Median cycles completed	Remaining doses (mid-cycle)
Herceptin®	FDA 1998e	6.7	201	28.71	6	5	4
paclitaxel	FDA 1998e	6.7	201	28.71	1	30	
Arimidex®	FDA 2000c	8.5	255			255	
Femara®	FDA 2001c	9.4	282			282	
Avastin®	FDA 2008	11.3	339	48.43	2	25	
Taxol®	FDA 1994	3.5	105	15.00	3	5	
Taxotere®	FDA 1996, FDA 1998c	4	120	17.14	7		
Farneston®	GTx 2008	5.9	178	25.43		178	
Femara®	FDA 1997b	5.7	171	24.43		171	
Xeloda®	FDA 1998g	3.1	94	13.41	3	9	11
Herceptin®	FDA 1998e	3.1	93	13.29	1	15	
Aromasin®	FDA 1999d	4.7	141.9	20.27		141.9	
Gemzar®	FDA 2004h	5.2	156	22.2	3	9	

Source: Author's calculations

The relative prices of treatments against metastatic breast cancer are shown in Figure 6. The two targeted drugs, Herceptin® and Avastin®, are the most expensive breast cancer drugs introduced during this time.

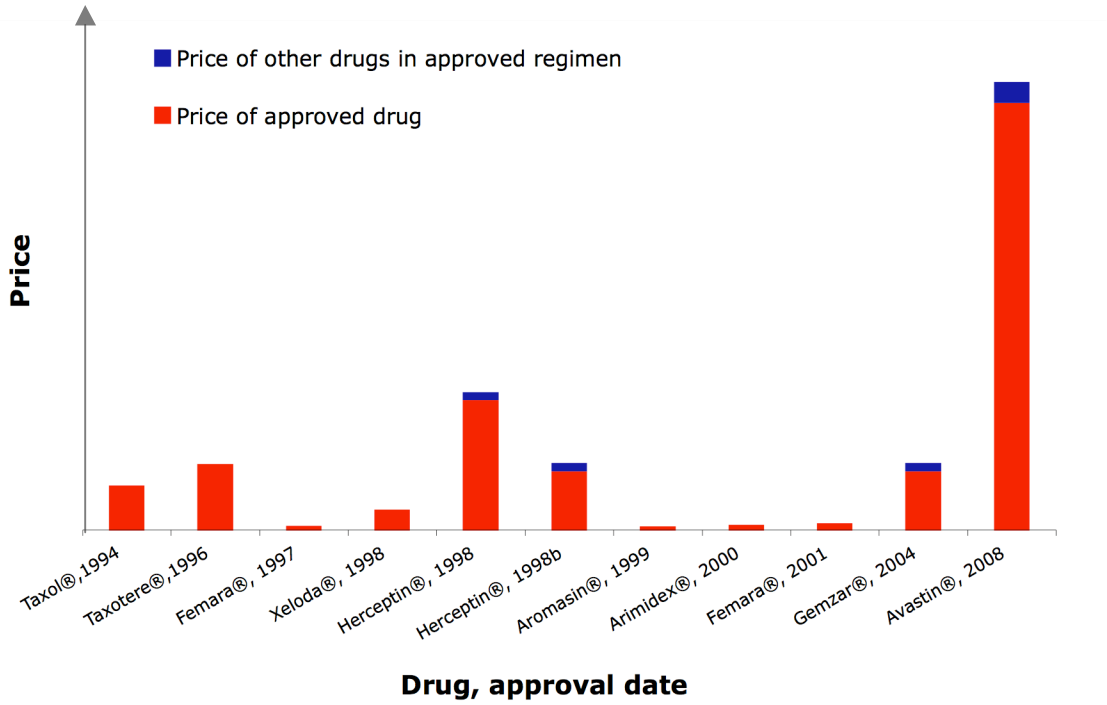


Figure 6. Prices for Metastatic Breast Cancer Treatments
Source: Author's calculations listed in Table 4 and 5

A similar calculation was used to determine the price of treatments used in the adjuvant setting against breast cancer. Table 6 shows the calculations for the prices of adjuvant breast cancer therapies. Figure 7 then illustrates how the prices for adjuvant treatments have increased over time.

Table 6. Calculation of Treatment Costs for Adjuvant Therapy of Breast Cancer

Drug	Trial reference	Regimen	Dosage multiplier*	Dose **	Doses /cycle	Cycles †	Remaining doses	Total mg dosed	Price per mg‡	Cumulative Drug Price (per patient)	Total treatment cost
Taxol®, paclitaxel	FDA 1999b	Cyclophosphamide	1.6	600	1	4		3840	[redacted]	[redacted]	[redacted]
		Doxorubicin	1.6	60	1	4		384			
		Taxol®	1.6	175	1	4		1120			
Arimidex®, anastrazole	FDA 2002d; FDA 2004g)	Arimidex®		1	1	1825		1825	[redacted]	[redacted]	[redacted]
Adriamycin®, doxorubicin	FDA 2003b	Adriamycin®	1.6	60	1	4		384	[redacted]	[redacted]	[redacted]
		Cyclophosphamide	1.6	600	1	4		3840			
Taxotere®, docetaxol	FDA 2004e	Taxotere®	1.6	75	1	6		720	[redacted]	[redacted]	[redacted]
		Adriamycin®	1.6	50	1	6		480			
		Cyclophosphamide	1.6	500	1	6		4800			
Femara®	FDA 2004d	Femara®		2.5	1	1825		4562.5	[redacted]	[redacted]	[redacted]
Aromasin®, exemestane	FDA 2005	Aromasin®		25	1	1095		27375	[redacted]	[redacted]	[redacted]
		Tamoxifen®		25	1	730		18250			
Ellence®, epirubicin	FDA 2006b	Epirubicin®	1.6	100	1	6		960	[redacted]	[redacted]	[redacted]
		5-FU®	1.6	500	1	6		4800			
		Cyclophosphamide	1.6	500	1	6		4800			
Herceptin®, trastuzumab	FDA 2006c	Herceptin®	66	4	1	1		264	[redacted]	[redacted]	[redacted]
		Herceptin®	66	2	1	51		6732			
		Adriamycin®	1.6	60	1	4		384			
		Cyclophosphamide	1.6	600	1	4		3840			
		paclitaxel	1.6	80	1	12		1536			
Herceptin®, trastuzumab	FDA 2008c FDA 2008c	Herceptin®	66	8	1	1		528	[redacted]	[redacted]	[redacted]
		Herceptin®	66	6	1	17		6732	[redacted]	[redacted]	
		Adriamycin®	1.6	60	1	4		384	[redacted]	[redacted]	
		Cyclophosphamide	1.6	600	1	4		3840	[redacted]	[redacted]	
Herceptin®, trastuzumab	Genentech 2008	Herceptin®	66	4	1	1		264	[redacted]	[redacted]	[redacted]
		Herceptin®	66	8	1	1		528	[redacted]	[redacted]	
		Herceptin®	66	2	1	11		1452	[redacted]	[redacted]	
		Herceptin®	66	6	1	13.33		5280	[redacted]	[redacted]	
		Adriamycin®	1.6	60	1	4		384	[redacted]	[redacted]	
		Cyclophosphamide	1.6	600	1	4		3840	[redacted]	[redacted]	
		docetaxel	1.6	100	1	4		640	[redacted]	[redacted]	
Herceptin®, trastuzumab	Genentech 2008	Herceptin®	66	4	1	1		264	[redacted]	[redacted]	[redacted]
		Herceptin®	66	2	1	11		1452	[redacted]	[redacted]	[redacted]
		Herceptin®	66	6	1	13		5280	[redacted]	[redacted]	
		Adriamycin®	1.6	60	1	4		384	[redacted]	[redacted]	
		Cyclophosphamide	1.6	600	1	4		3840	[redacted]	[redacted]	
		docetaxel	1.6	75	1	6		720	[redacted]	[redacted]	
		carboplatin	1.6	600	1	6		5760	[redacted]	[redacted]	

*(average BSA (m^2) or average weight (kg)), Average BSA of a female American = 1.6mg/m^2, average weight = 66 kg
**FDA approved labels inform regimens and dosing schedules as referenced in column 2
† Adjuvant therapies specify the suggested length of treatment (usually 5 years) in the trial reference and approved product label
‡Price at approval date or closest quarter to approval date that the drug became available at the BC Cancer Agency
Source: Author's calculations and the "price per mg" of each drug (column 10) supplied by the BC Cancer Agency

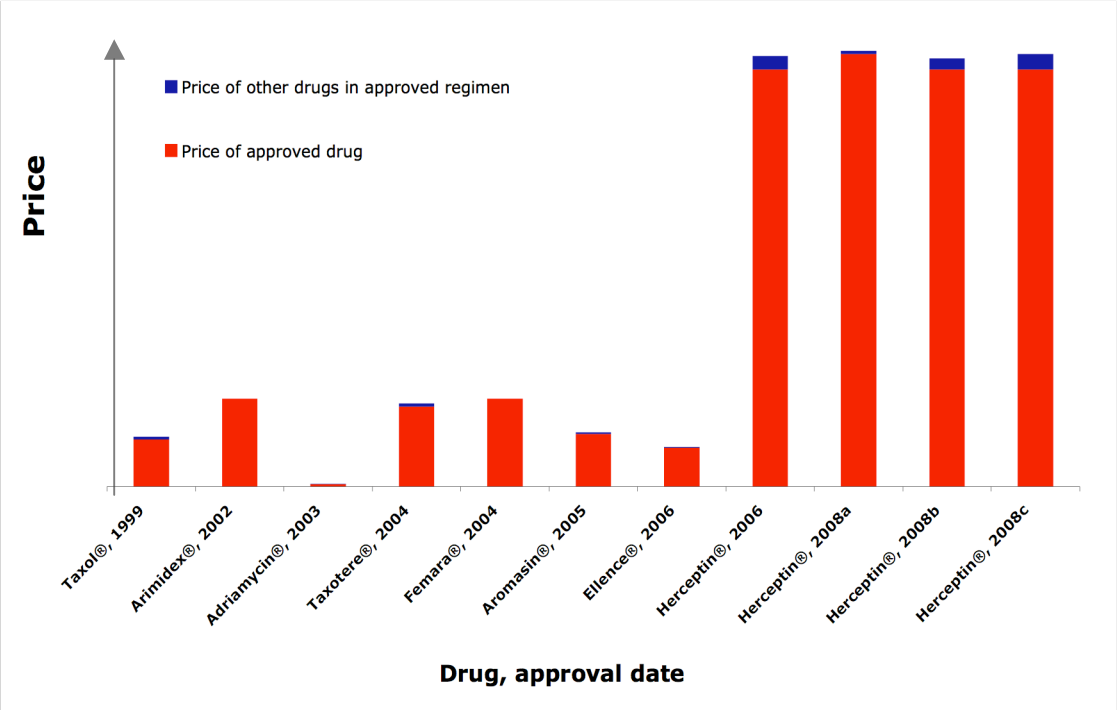


Figure 7. Prices for Adjuvant Breast Cancer Treatments
Source: Author's calculations (Table 6)

4 Clinical Benefits of Drugs against Colorectal Cancer

This chapter uses a similar framework as Chapter 3 to investigate the change in clinical benefits and prices of drugs recently developed against colorectal cancers. In the United States, cancers of the gastrointestinal tract comprise the most common form of non-skin cancer (Parkin et al 2002). These cancers often go undiagnosed, since regular screening programs for this disease are uncommon in today's medical practices (Redaelli et al 2003). The chances of survival are low for metastatic colorectal cancers (CRC) (Weitz et al 2005). Because of the relatively fast rate of progression of CRC, overall survival (OS) outcomes are the primary endpoints of clinical trials. Surrogate indicators (such as the time to progression (TTP) or disease free survival (DFS)) are the secondary endpoints for CRC trials.

Relatively few drugs that are effective against CRC have been developed over time, despite the underlying need for new treatments against this disease. For example, the drug 5-Flourouracil (5-FU) remained the most commonly-used drug against metastatic CRC for nearly twenty years (Meyerhardt and Mayer 2005). Median overall survival remained low (ten months) between 1975 and 1995 (O'Connell 1989). Over the past ten years, however, survival of up to 21 months has become possible with new anticancer drugs. Tables 7 and 8 list the FDA's newly approved drugs against metastatic CRC.

Table 7. First-Line Treatments of Metastatic Colorectal Cancer

Drug	Approval date	Reference	Comparators	Overall survival (Median months)
Camptosar®, irinotecan	4/20/00	(FDA 2000)	**Camptosar®** + 5-FU/LV	17.4
			5-FU/LV	14.1
Xeloda® , capectibine	4/30/01	(FDA 2001)	**Xeloda®**	13.07*
			5-FU/LV	13.03*
Eloxatin®, oxaliplatin	01/09/04	(FDA 2004c)	**Eloxatin®** +5-FU/LV	19.4 (17.9-21.0)
			Eloxatin® + Irinotecan	17.6 (15.8-19.6)
			5-FU/LV + Irinotecan	14.6 (12.4-16.7)
Avastin®, bevacizumab	02/26/04	(FDA 2004)	**Avastin®** + Intravenous 5-FU, leucovorin and irinotecan	20.3
			Intravenous 5-FU, leucovorin and irinotecan	15.6
Erbitux®, cetuximab	02/10/07	(FDA 2007b)	**Erbitux®**	n/a†
			Erbitux® + Irinotecan	n/a†

*Approval of Xeloda® was based on non-inferiority to 5-FU-LV using combined results of two different trials
†Overall survival data is not available for Erbitux® therefore encouraging response rates formed the basis of this approval decision
Source: Author's retrieval, comprehension and simplification of FDA web-published data as cited in "Reference" column

Table 8. Second-Line Treatments of Metastatic Colorectal Cancer

Drug	Approval date	Reference	Comparators	Overall survival (Median months)
Camptosar®, irinotecan	10/22/98	(FDA 1998d)	**Camptosar®** + Best supportive care**	9.2
			Best supportive care**	6.5
Eloxatin®, oxaliplatin	08/09/02	(FDA 2002)	**Eloxatin®** +5-FU/LV (FOLFOX4)	11
			5-FU/LV	8
Erbitux®, cetuximab	02/12/04	(FDA 2004b)	**Erbitux®** + best supportive care	6.14
			Best supportive care	4.57
Avastin®, bevacizumab	06/20/06	(FDA 2006e)	**Avastin®** + FOLFOX4*	13
			FOLFOX4*	10.8

*FOLFOX4=5-FU/LV (5-Fluorouracil/leucovorin and oxaliplatin)
** Best supportive care = this is the best supportive care that is available to patients. This may include the administration of antibiotics, analgesics, transfusions, corticosteroids, psychotherapy, radiation and any other symptomatic therapy except the class of therapeutics under clinical investigation.
Source: Author's retrieval, comprehension and simplification of FDA web-published data as cited in "Reference" column

Like breast cancer treatments, CRC drugs have provided increasing clinical benefits over time. Figure 8 shows the benefits of the six drugs against metastatic CRC that the FDA has approved over the past decade. It demonstrates that the level of clinical benefits received has steadily increased over time.

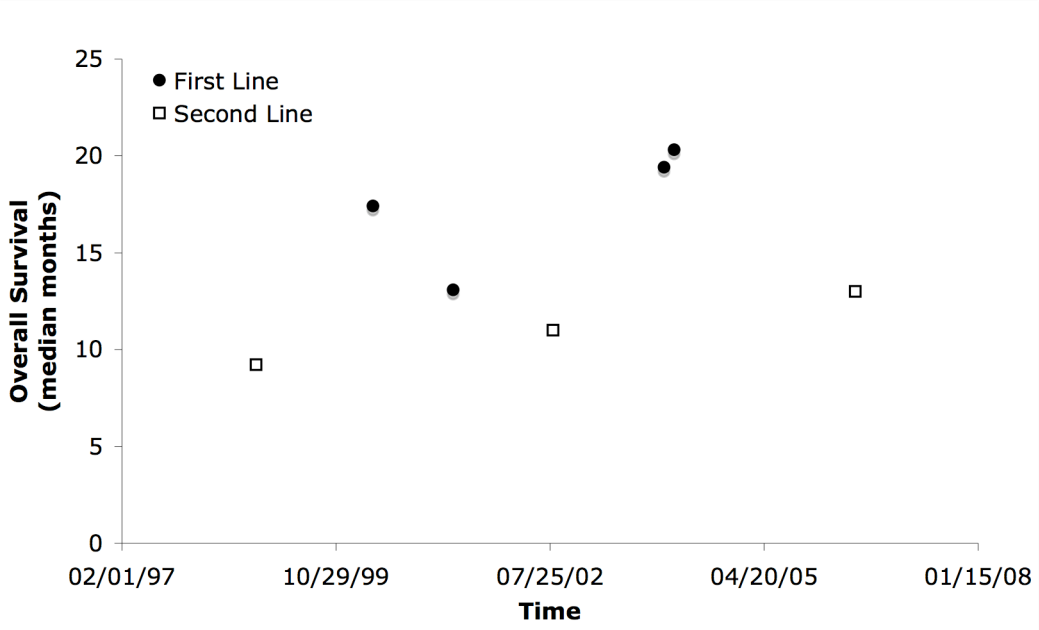


Figure 8. Improvements in the Overall Survival of Metastatic Colorectal Cancer
Source: Author's representation of data in Tables 7 and 8

4.1 The Price of New Drugs against Colorectal Cancer

New drugs against CRC work most effectively when used in combination with other drugs. Almost every new FDA approval for CRC drugs includes the use of pre-existing drugs, such as 5-FU. The calculation of CRC treatment prices was by similar methods to the calculations for breast cancer treatments described in Section 3.4. These calculations are listed in Table 9. The secondary endpoint of all CRC trials, TTP, was used to determine the expected duration of treatment for CRC patients receiving the drug (Table 10). However, the addition of other drugs to the regimen makes a significant contribution to the total price of treatment, as summarized in Figure 9.

Table 9. Calculation of Treatment Costs for Drugs against Colorectal Cancer

Drug	Trial reference	Regimen	Dosage multiplier*	Dose**	Doses /cycle	Cycles†	Remaining doses	Total mg dosed	Price per mg‡	Cumulative Drug price (per patient)	Total treatment cost
Camptosar®, irinotecan	FDA 2000d Treatment regimen 1	Camptosar®	1.7	125	4	5	4	5100	[redacted]	[redacted]	[redacted]
		LV	1.7	20				816			
		5-FU	1.7	500				20400			
Camptosar®, irinotecan	FDA 2000d, Treatment regimen 2	Camptosar®	1.7	180	3	5	3	5508			[redacted]
		LV	1.7	200				6120			
		5-FU	1.7	400				12240			
		5-FU	1.7	600				18360			
Xeloda®, capectibine	FDA 2001	Xeloda®	1.7	2500	14	8		476000			[redacted]
Eloxatin®, oxaliplatin	FDA 2004i	Eloxatin®	1.7	85	1	19		2745.5			[redacted]
		LV	1.7	200	2			12920			
		5-FU	1.7	400	2			25840			
		5-FU	1.7	600	2			38760			
Avastin®, bevicizumab	FDA 2004j	Avastin®	76.17	5	1	23	1	9140			[redacted]
		LV	1.7	20	4	6	3	918			
		5-FU	1.7	500	4	6	3	22950			
		Irinotecan	1.7	125	4	6	3	5737.5			
Camptosar®, irinotecan	FDA 1998h, Regimen 1	Camptosar®	1.7	125	4	3	1	2762.5			[redacted]
Camptosar®, irinotecan	FDA 1998h, Regimen 2	Camptosar®	1.7	350	1	9		5355			[redacted]
Eloxatin®, oxaliplatin	FDA 2002f	Eloxatin®	1.7	85	1	10		1445			[redacted]
		LV	1.7	200	2			6800			
		5-FU	1.7	400	2			13600			
		5-FU	1.7	600	2			20400			
Avastin®, bevicizumab	FDA 2006e	Avastin®	76.17	10	1	16		12187			[redacted]
		LV	1.7	200	2			10880			
		5-FU	1.7	400	2			21760			
		Oxaliplatin	1.7	85	1			2312			
		5-FU	1.7	600	2			32640			

*using the average BSA (m^2) or average weight (kg). Average BSA of a human American is 1.7mg/m^2, average weight is 76 kg
**FDA approved labels inform regimens and dosing schedules as referenced in column 2.
†Calculated from TTP outcomes (Table 10)
‡Price at approval date or closest quarter to approval date that the drug became available at the BC Cancer Agency
Source: Author's calculations and the "price per mg" of each drug (column 10) supplied by the BC Cancer Agency

Table 10. Calculation of Duration of Treatment with Drugs against Metastatic CRC

Drug	Reference	TTP (median months)	Days to progression	Weeks to progression	Weeks /cycle	Median cycles completed	Remaining doses (mid-cycle)
Camptosar®	FDA 2000	6.7	201	28.72	6	5	4
Camptosar®	FDA 2000	6.7	201	28.72	6	5	4
Xeloda®	FDA 2001	4.7	141	20.14	3	8	0
Eloxatin®	FDA 2004c	8.7	261	37.29	2	19	0
Avastin®	FDA 2004	10.6	318	45.43	2	23	1
leucovorin		10.6	318	45.43	6	6	3
irinotecan		10.6	318	45.43	6		
5-FU		10.6	318	45.43	6	6	3
Camptosar®	FDA 1998d*	5.7	171	24.43	6	10	
Eloxatin®	FDA 2002	4.6	138	19.71	2	16	
Avastin®	Giantonio, 2007	7.3	219	31.29	2	5	4

*the endpoint used for this trial was specified as time to performance status deterioration rather than time to progression, TTP
Source: Author's calculations

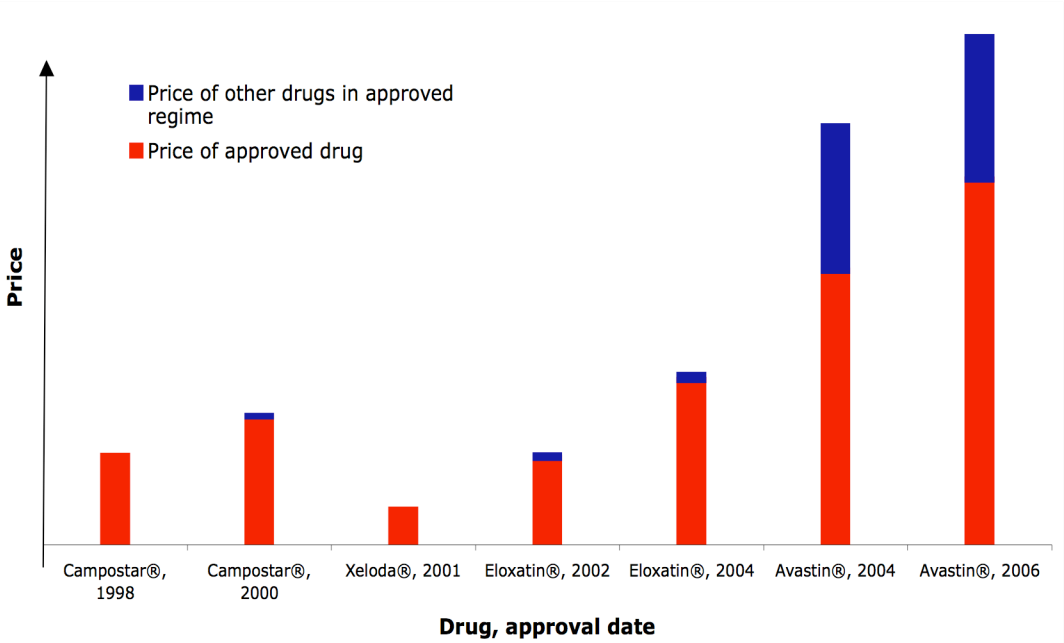


Figure 9. Prices of New Drugs against Metastatic CRC
Source: Author's calculation of regimen dosing (Tables 9 and 10)

5 Price-Benefit Relationships of New Anticancer Drugs

In this Chapter, we relate clinical benefits and drugs prices using the information presented in Chapters 3 and 4. The goal of his chapter is to see if the price of new anticancer drugs has risen faster than the level of clinical benefits received from these new drugs. In these preceding chapters, it was established that Herceptin® and Avastin® are the most expensive breast and colorectal cancer treatments. These two drugs also generate the greatest clinical benefits. Figures, 10 and 11 relate drug prices with clinical benefits for metastatic and adjuvant breast treatments, respectively. For both disease indications, increased clinical benefits come at an increased price. Figure 12 shows that the same relationship also applies to metastatic CRC drugs.

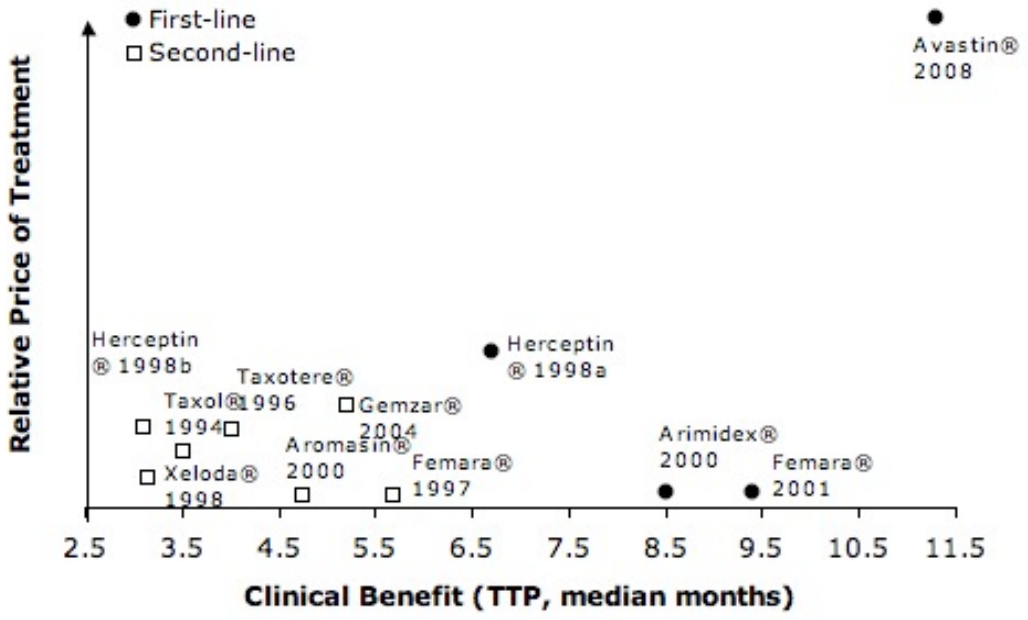


Figure 10. Price-Benefit Relationships for Drugs against Metastatic Breast Cancer
Source: Author's correlation of clinical trial outcomes and total price of drugs (Tables 4 and 5)

Four of the drugs against metastatic breast cancer do not conform to the upward trend of increased price for increased clinical benefits (see Figure 10). This apparent deviation arises from the indiscriminate grouping of all breast cancer drugs, without regard to disease sub-classifications. For example, in the metastatic setting, the Aromatase inhibitors are grouped together with HER2-targeting therapies, despite profound differences in the type of patient and tumor subclass that the drug treats (FDA 2001c; Genentech 2008c).

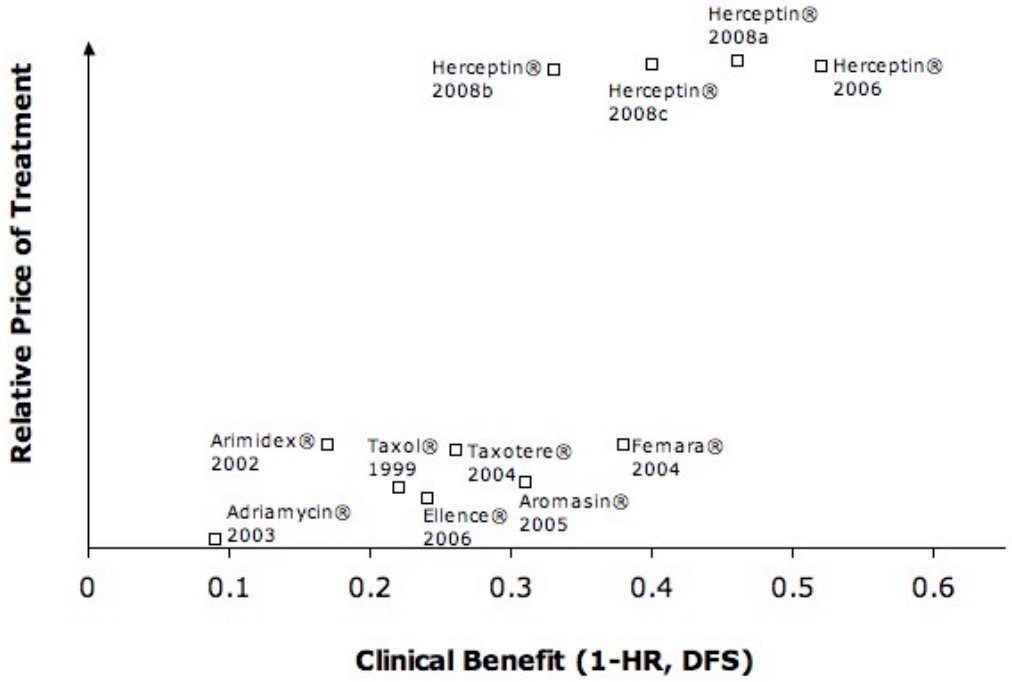


Figure 11. Price-Benefit Relationships for Drugs used as Adjuvant Therapies for Breast Cancer
Source: Author's correlation of clinical trial outcomes and total price of drugs (Table 6)

The level of benefits received from the adjuvant treatments of breast cancer appears to conform to an exponential rise in price per clinical benefit[4]. A similar relationship of steeply increasing drug prices for increased clinical benefits applies to new CRC treatments (Figure 12). In both first and second-line treatments of metastatic CRC, the greatest survival gains come at a very high price. Avastin® leads the CRC drugs in terms of price and benefits received. The exponential trend for price per benefit suggests that the value of new anticancer drugs exceeds their clinical benefit. Indeed, the clinical benefit of anticancer drugs is one component of the total value that anticancer drugs offer

[4] The data points in Figures 11 and 12 conform to exponential regression curves more closely than linear regression curves (Appendix III). The same conclusion was not possible for drugs approved against metastatic breast cancers, due to extreme variations in subclasses of the disease and the small sample size.

to society. Other non-clinical benefits such as the ability of new drugs to enhance the quality of life also contribute. One interesting non-clinical benefit under current discussion is the value of innovative new drugs against cancer, or the value of innovation (Berenson 2006). These non-clinical (or indirect) benefits are discussed in the following section.

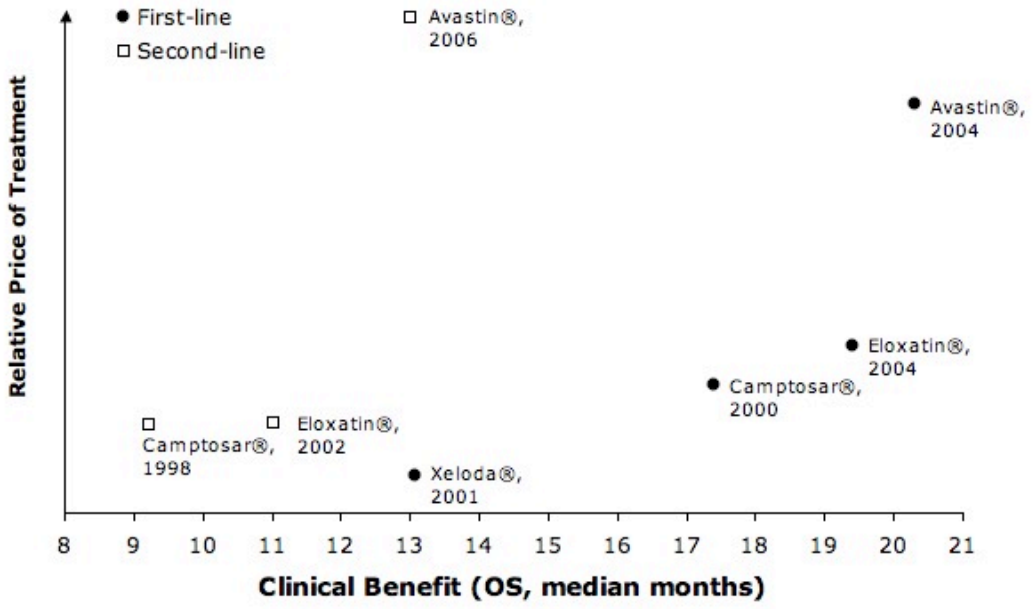


Figure 12. Price-Benefit Relationships of New CRC Drugs
Source: Author's correlation of trial outcomes and total price of drugs (Table 9)

6 Non-Clinical Benefits and Anticancer Drugs of the Future

In the previous chapters, the trend for increasingly high prices for clinically beneficial therapeutics was established. This chapter includes a discussion on innovation and future anticancer drug prices. We discuss the non-clinical benefits that new drugs offer, such as their ability to promote efficiency in healthcare budgeting, enhance the quality of life of cancer patients or promote further medical discoveries. The chapter concludes with discussions towards the large social benefits earned from the innovation of anticancer drugs.

Our findings in Chapters 3, 4 and 5 indicate that Herceptin® and Avastin® are the most effective and expensive anticancer drugs to be approved over the past decade. There are significant indicators that future anticancer treatments will also have high prices (Dreyer 2006). One example is the caliber of investment in diagnostics by the pharmaceutical manufacturer, Roche. Roche has recently acquired the small diagnostics company Ventana Medical Systems for three billion US dollars in a hostile take-over (Unspecified Author #2 2007). The acquisition is valuable for Roche as Ventana has developed a diagnostic test to determine if Roche's drugs will work. Such an acquisition may indicate that future Roche products will be co-marketed with a diagnostic test, which confirms that a drug will be effective. Anticancer treatments of the future will likely include more diagnostic testing, as the treatments become more sophisticated (Pollack 2006).

Future medicines may also benefit society by providing efficiency gains to healthcare systems. These indirect benefits may include the foregone costs of inappropriately prescribed drugs or the prevention of late-stage disease through more accurate detection methods (Aspinall and Hamermesh 2007). Thus, efficiency gains should increase the total social benefits received from new anticancer drugs.

6.1 Pharmaceutical Manufacturers: Pricing, Profits and R&D Expenses

In the past, critics have justified high drug prices with arguments concerning the manufacturer's need to recover high research and development (R&D) costs (Nagle 2007). Empirical evidence supports this argument (Grabowski et al 2002). Another argument for high drug prices is that the manufacturers need to mitigate the risk of failure during the development of new drugs (Scherer 2001).

For those drugs that manage to achieve FDA approval, the chemotherapy market promises high returns. The US chemotherapy market is now valued at $42 billion US dollars, and is rapidly expanding (Pijpers and Belsey 2006; Presswire 2006). Herceptin® and Avastin®, generate substantial revenues for their manufacturer, Genentech. These two products have now earned Genentech over $16 billion (US) in combined product sales (Genentech 2007).

Genentech appears to have earned high profits in relation to its R&D spending (see Figure 13). The high ratio of profits to R&D spending at Genentech weakens the arguments of Grabowski et al (2002) and Scherer (2001). Indeed, contemporary analyses

indicate that profit to R&D spending ratios are greater for biotech companies than for pharmaceutical companies (DiMasi et al 2007). Perhaps more importantly, the high profits that biotech companies retain may cause healthcare payers to question whether they are paying too much for these drugs.

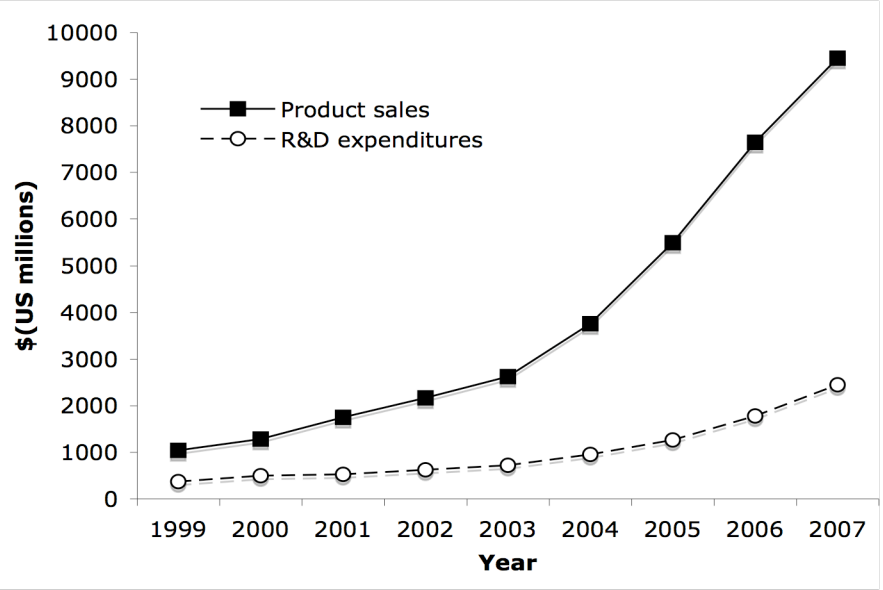


Figure 13. The Changing Ratio of R&D Expenditures to Product Sales at Genentech
Source: Author's representation of Genentech's Annual Earnings Releases (Genentech 2008b)

6.2 The Benefit of Innovation

Genentech has publicly justified its pricing strategy for Avastin® by arguing that the drug is innovative and therefore worth the extra cost to healthcare systems (Berenson 2006). Genentech's argument that innovation contributes to a drug's value is interesting when viewed in the context of historical innovation of the anticancer drugs. Figure 14 illustrates

the connectedness and degree of scientific advancements made throughout the history of the innovations of anticancer drugs.

In the 1960s, there was little reason to question the value of the early cytotoxics, which readily made their way into healthcare systems. The anticancer drugs of today have shifted from the "life-saving" drugs of the 20th century to "life-extending" drugs of the 21st century (Mason and Freemantle 1998; Rawlins 2007). The value of innovativeness and other, less tangible, benefits are now established components of the total value of new drugs (Murphy and Topel 2005).

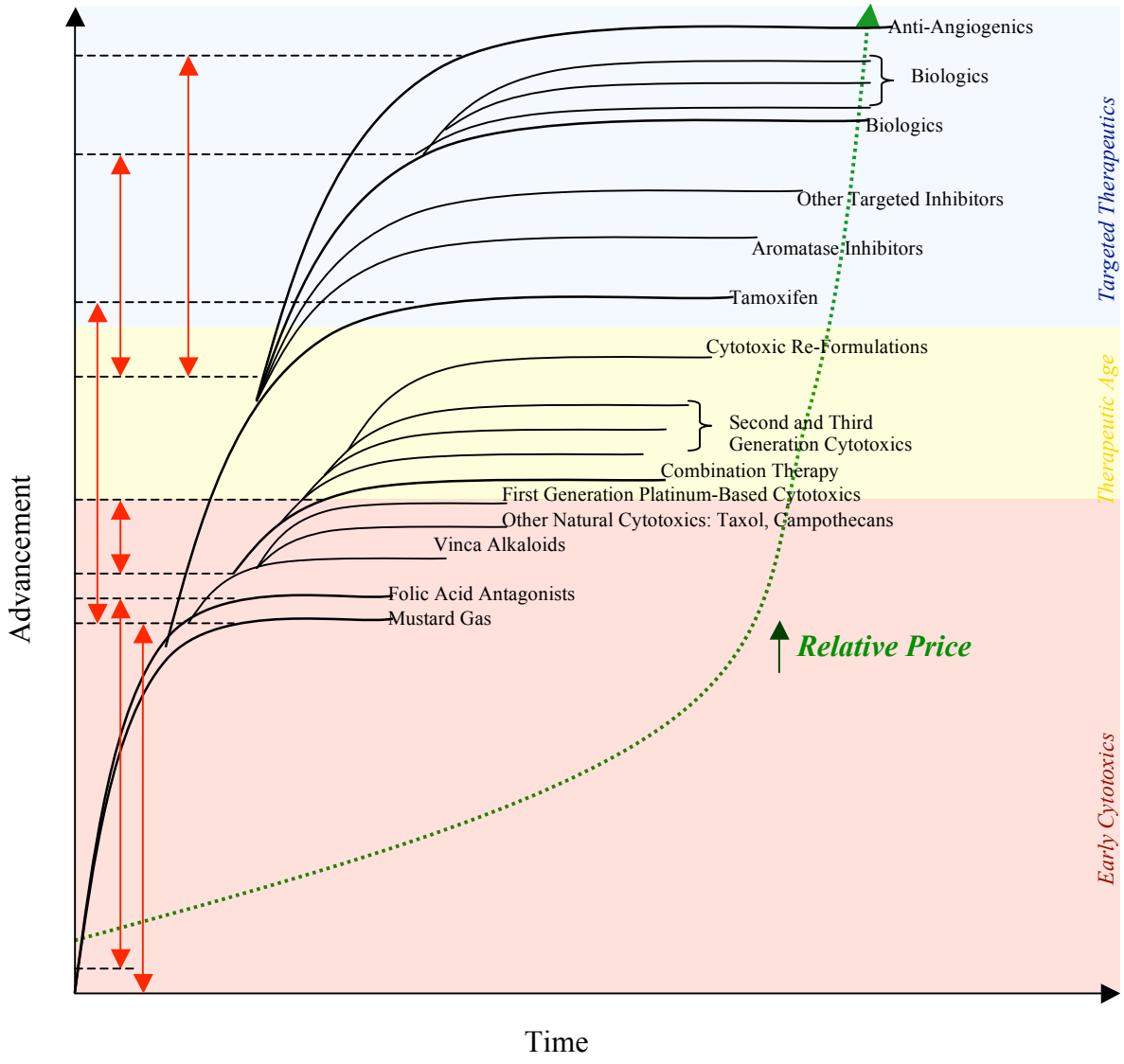


Figure 14. Tracking Innovation in the Anticancer Drugs

Big steps in innovation are represented by bold curves. Red double-ended arrows may estimate the relative size of advancement. Innovative measures are judged by their relative similarity to previous discoveries.
Source: Author's illustration and knowledge of anticancer drugs

6.3 Competition and Pharmaceutical Innovation

The development of innovative drugs gives the manufacturers a differentiation competitive advantage. For example, drugs that are manufactured by unique methods, such as the biologic drugs (Herceptin® and Avastin®), face a relatively minor threat from competition by generic drugs (Grabowski and Kyle 2007). This is because the duplication of biologic drugs is not yet technically possible (Ziegelbauer and Light 2008).

Healthcare systems encourage innovation through policies, such as reference pricing. Reference pricing policies classify all drugs according to therapeutic or molecular equivalence (Lopez-Casasnovas and Puig-Junoy 2000). Manufacturers are free to set high prices for their drugs, however, reimbursement is limited for highly priced drugs that are of low novelty. Truly novel drugs that are within their own therapeutic classification receive better reimbursement coverage. Many drug manufacturers have stopped developing "me-too products" (of low novelty) in response to the recent implementation of reference pricing in the US (Farkas and Henske 2006).

6.3.1 Marketing Strategies for New Anticancer Drugs

The market segments that an anticancer drug may access correspond with the disease indications that a new drug has been approved for. Thus, increasing the number of approved indications also increases the market potential for a new oncology drug. The strategies used by Genentech to market Herceptin® and Avastin® are two examples of strategies deployed within the chemotherapy market.

In the first strategy, the drug relies on good clinical efficacy against one particular indication to gain market share. The marketing of Herceptin® is a good example of this strategy. Herceptin® is a narrow spectrum drug that works on a unique biomarker, specific for breast cancers. Herceptin® is also very effective because of this specificity. The drug now dominates the HER2-positive segment of the breast cancer market. The potential profits from Herceptin® sales are, however, limited because the drug is only effective on one specific sub-type of cancer.

The strategy used by broad-spectrum drugs like Avastin® target all types of cancer, despite the primary location of the tumor. Avastin®'s mode of action enables it to work on all types of cancer. Because the drug is able to work on any tumor type, Avastin® targets many market segments (see Figure 15). By sequentially gaining approval for different indications, the manufacturer increased the potential market size for Avastin® to almost 1,000,000 patients. Figure 15 illustrates the breadth of Avastin®'s market, based on the number of FDA applications made for this drug. Broad-spectrum drugs, like Avastin®, may also lose market segments to narrow-spectrum drugs that are more effective.

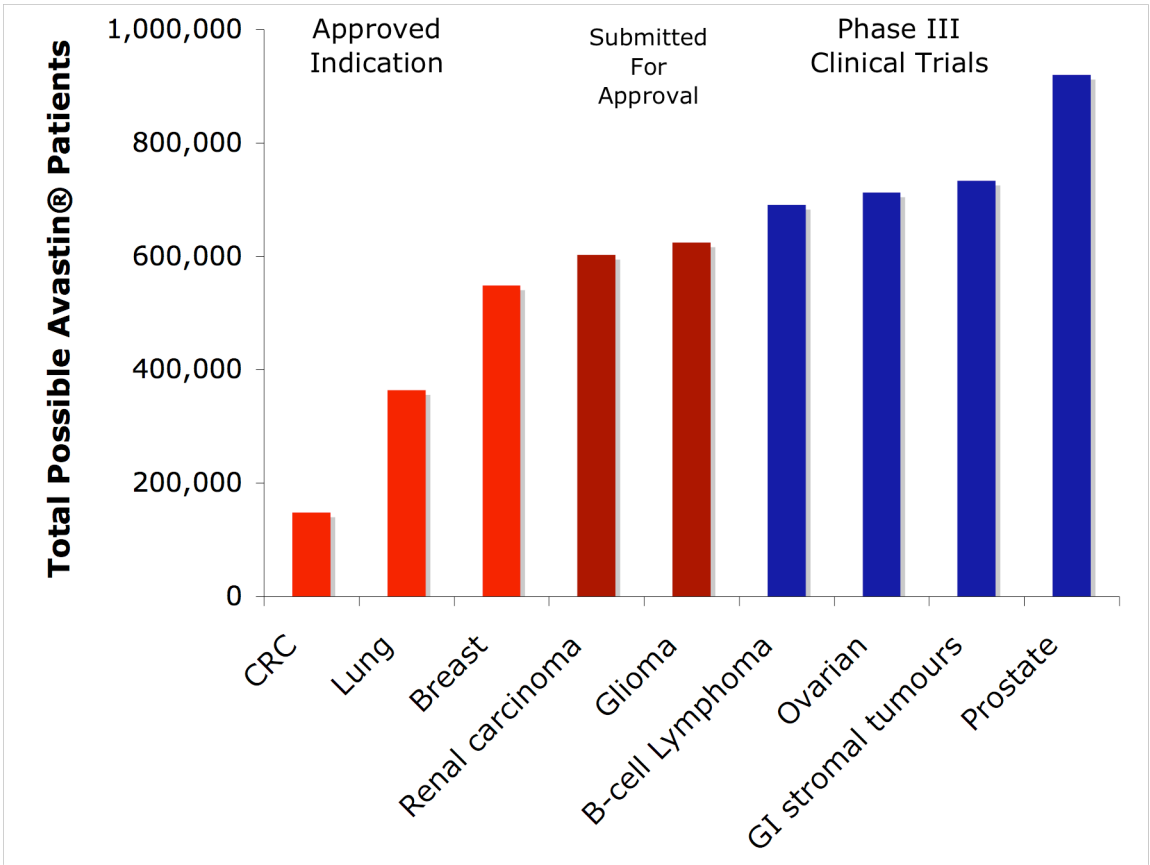


Figure 15. Avastin®'s Market Expansion
Source: Author's calculations using SEER 2008 Cancer Statistics (SEER 2008) and Genentech's development pipeline for Avastin®

6.3.2 Quality of Life-Enhancing Drugs

Another strategy used to market new anticancer drugs is to replace older, inexpensive drugs with a new, more expensive, re-formulation of the original active ingredient. These "quality of life-enhancing drugs" have contributed to the higher prices of new anticancer drugs (Schrag 2004). However, in many instances, the more expensive new drugs also offer indirect cost advantages to healthcare systems.

The replacement of 5-Flourouracil (5-FU) with a newer CRC drug, Xeloda®, is a good example. Xeloda® uses the same active ingredient to fight cancer, however, the

drug comes as a pill form. Unlike the older version, 5-FU, the pill form does not require intravenous administration in a hospital. The use of Xeloda® is, therefore, cost-effective since hospital care and administration costs are foregone (Jansman et al 2007). Although the replacement of old drugs with newer equivalents increases drug expenditures, the quality of life-enhancing drugs may also provide efficiency gains. Therefore, evaluative measures should also include non-drug costs and non-clinical benefits of new anticancer treatments.

6.4 Future Cancer Control Strategies

Current anticancer research follows recent advancements in genomic and biochemical technology. Prototypic personal genomic tests have already made their way through the approval process and into the public sector (Singer 2008). Some US breast cancer patients now have the option to pay an extra $2500 for a diagnostic test that will determine the likelihood of the disease returning after surgery (Pollack 2006). For this price, patients have a chance to avoid superfluous chemotherapy regimens. Healthcare systems may also avoid cytotoxic treatments that are more likely to cause harm to patients than to help them.

Another area of advancement is the correlation of disease progression with biomarkers. With this information, researchers may be able to tell which drug combination will be the most effective for a particular stage of disease. This information will also enable oncologists to avoid those treatments that are not likely to have any effect on the disease (Yau et al 2008).

Without doubt, the price of tomorrow's anticancer drugs will continue to rise as medical technology moves towards personalized medicines. Cost-effectiveness analysis will need to become more transparent so that decision-makers are aware of the direct and indirect benefits of new treatments. Patients can expect to receive therapies that are more clinically effective and less invasive. The integration of scientific advancements, increased social awareness and good medical care will contribute to the success of anticancer drugs in the future. Anticancer drugs will probably enter healthcare markets at higher prices. Healthcare landscapes will need to change in order to adopt anticancer drugs of the future.

6.5 The Value of Innovative Anticancer Drugs: Concluding Remarks

New anticancer drugs offer great clinical benefits to society. Patients now survive longer than they did 20 years ago because of these drugs (Chia et al 2007). These clinical benefits now come at very high prices. Healthcare systems increasingly pay more for anticancer drugs in nearly all cancer types (Warren et al 2008). The result presented within this project validates the relationship of increasingly high drug prices with gains in clinical benefits. The underlying discussions in this chapter have acknowledged that clinical benefits are only a small fraction of the social benefits offered by new drugs.

Other benefits, such as possible efficiency gains to health systems and quality of life-enhancements, contribute to the total social benefits. Despite the observed increase in health improvements, the steep rise in the price of new anticancer drugs has left critics with the concern that these expensive new drugs are not generating net social benefits.

Drug manufacturers have responded with arguments of the less tangible benefits offered by new anticancer drugs, such as the value of innovation. Indeed, there is good reason to believe that the innovation of new anticancer drugs is worth a very high price. Recently, Murphy and Topel (2006) have made a monetary estimate of how much Americans value health benefits (Murphy and Topel 2006). Their estimate used an individual's willingness to pay for drugs that would improve longevity for Americans with cardiovascular diseases and cancers. The results of Murphy and Topel's (2006) investigation are interesting. The estimated value for gains in life expectancy was about 1.2 million dollars per person. The authors further estimated that small reductions in cancer might be worth over $500 billion dollars in social value to future Americans.

This large economic value should drive the innovation of more (expensive) anticancer drugs. In fact, it will be difficult for manufacturers to keep up with the demand for new drugs against the disease. Murphy and Topel (2007) now show that drug manufacturers are not innovating fast enough to keep up with the potential social gains (Murphy and Topel 2007). The authors suggest that current pharmaceutical R&D investments are too low, and that public and private contributions should increase.

Pharmaceutical manufacturers have the main interest of generating revenue and returns to shareholders. Grabowski et al (2002) demonstrated the direct correlation of R&D investments to the number of pharmaceutical innovations that arise from these investments (Grabowski et al 2002). Lichtenberg (2001) noted that future R&D investments result from current profits on sales to healthcare markets (Lichtenberg 2001). Healthcare decision-makers have the conflicting interest of maintaining control over pharmaceutical expenditures.

Due to the conflicting interests of pharmaceutical manufacturers and healthcare systems, it is difficult to say how future drugs will diffuse into healthcare systems. In this report, we established that the trend for increased clinical benefits corresponds with increasingly high prices for anticancer drugs. We did not address the underlying issue of how healthcare systems will pay for these, increasingly expensive, drugs. The issue of high drug prices must resolve in order for society to maximize the benefits of future anticancer drugs.

Appendix I

FDA Approval History for Drugs against Breast Cancer

Drug (Trade name®, generic name)	Approval date	Line or type of therapy	Specific Indication
Nolvadex®, tamoxifen	01/31/86	Adjuvant	As a single agent to delay breast cancer recurrence following surgery
Nolvadex®, tamoxifen	03/16/89	Adjuvant	Metastatic breast cancer in premenopausal women
Nolvadex®, tamoxifen	06/21/90	Adjuvant	Axillary node negative breast cancer
Ellence®, epirubicin	09/15/99	Adjuvant	Following surgery in patients with axillary node involvement
Taxol®, paclitaxel	10/25/99	Adjuvant	Node-positive breast cancer administered after doxorubicin combination therapy
Arimidex®, anastrazole	09/05/02* 09/16/05**	Adjuvant	Hormone receptor positive postmenopausal women with early stage disease
Aromasin® exemestane	10/05/05	Adjuvant	Postmenopausal Estrogen receptor positive women with early breast cancer after two to three years of tamoxifen to complete five total years of adjuvant therapy hormonal therapy
Femara®, letrozole	10/29/04*	Adjuvant (extended)	Treatment of early breast cancer in postmenopausal women who have already received five years of adjuvant tamoxifen therapy
Taxotere®, docetaxel	08/18/04	Adjuvant	Use with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable node positive breast cancer
Adriamycin®, Doxorubicin	05/08/03	Adjuvant	Use with cyclophosphamide, in patients with axillary node involvement after resection of primary breast cancer
Herceptin®, Trastuzumab	11/16/06	Adjuvant	Early stage breast cancer after primary therapy
Epirubicin, epirubicin	09/15/06	Adjuvant,	Axillary node involvement after resection of primary breast cancer
Nolvadex®, tamoxifen	04/01/93	First	Metastatic breast cancer in men
Arimidex®, anastrazole	09/01/00	First	Postmenopausal women with Hormone receptor positive or unknown tumors and locally advanced or metastatic breast cancer
Femara®, letrozole	01/09/01 01/17/03**	First	Postmenopausal women with Hormone receptor positive or unknown tumors and locally advanced or metastatic breast cancer
Avastin®, bevacizumab	02/22/08	First	Metastatic HER2 negative breast cancer
Herceptin®, Trastuzumab	02/09/00	First	Metastatic breast cancer in combination with paclitaxel for patients with HER2 positive tumors
Teslac®, testolactone	05/27/70	n/a	breast
Thioplex®, thiotepa	12/22/94	n/a	breast
Aredia®, pamidronate	09/22/98	n/a	Osteolytic bone metastases originating from breast cancer in addition to standard forms of antineoplastic therapy
Nolvadex®, tamoxifen	12/30/77	Palliative	Breast
Zoladex Impant®, goserelin acetate	12/18/95	Palliative	Advanced breast cancer in pre- and perimenopausal women
Nolvadex®, tamoxifen	10/29/98	Risk reduction	For reducing the incidence of breast cancer in women who are at a high risk of contracting the disease

Nolvadex®, tamoxifen®, tamoxifen	06/29/00	Risk Reduction	For use in DCIS diagnosed women after surgery and radiation to reduce the risk of invasive breast cancer developing
Evista®, raloxifene hydrochloride	09/13/07	Risk reduction	Postmenopausal women with osteoporosis and reduction in risk of invasive breast cancer in postmenopausal women at high risk for invasive breast cancer
Taxol®, paclitaxol	04/13/94	Second	Treatment of breast cancer after failure of previous chemotherapy or relapse of disease before 6 months of adjuvant chemotherapy
Taxotere®, docetaxel	07/27/94* 06/22/98 **	Second	Advanced or metastatic breast cancer who have failed after or relased during of anthracycline-based therapy
Arminidex®, anastrazole	12/27/95	Second	Treatment of advanced breast cancer in postmenopausal women whose disease has progressed after tamoxifen therapy
Fareston®, toremifene	05/29/97	Second	Advanced breast cancer in postmenopausal women
Femara®, letrozole	06/25/97	Second	Advanced breast cancer in postmenopausal women
Aromasin®, exemestane	10/21/99	Second	Advanced breast cancer in post menopausal women after tamoxifen
Abraxane®, paclitaxel protein-bound particles	01/07/05	Second	Metastatic, after failure of combination therapy or relapse within 6 months of adjuvant chemotherapy
Gemzar®, gemcitabine	05/19/04	Second	Metastatic breast cancer after failure of anthracycline adjuvant chemotherapy
Tykerb®, Lapatinib, ditosylate	03/13/07	Second	Use with capectiabine for advanced or metastatic HER2+ tumors who have received prior therapy including an anthracycline, taxane and trastuzumab
Herceptin®, trastuzumab	09/25/98	Second, Third	Metastatic breast cancer when tumors express the HER2 protein and who have received one or more chemotherapy regimes, (anthracyline-based and/or paclitaxel)
Faslodex®, fulvestrant	05/25/02	Second, subsequent	Hormone receptor positive, postmenopausal women with disease progression after antiestrogen therapy
Xeloda®, capectibine	04/30/98* 09/07/01**	Second, third	Metastatic breast cancer for patients after receiving both anthracycline and paclitaxel therapy or high cumulative doses of doxorubicin.

Source: Author's representation and retrieval of data from the FDA website

http://www.accessdata.fda.gov/scripts/cder/onctools/Indicationlist.cfm?Indication=breast

*accelerated approval

**full approval

Appendix II

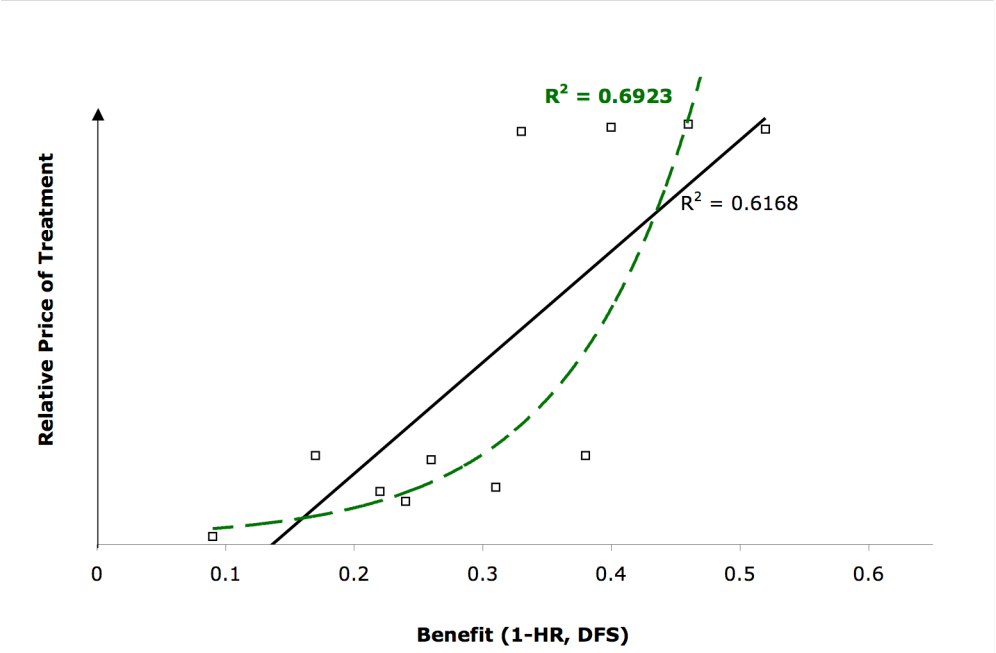
FDA Approval History for Drugs against Colorectal Cancer

Drug (Trade name®, generic name)	**Approval date**	**Line or type of therapy**	**Specific Indication**
Adrucil®, Fluorouracil,	04/25/62	n/a	Colon-rectum
Ergamisol®, levamisolee	06/18/90	adjuvant	Adjuvant treatment in combination with 5-FU after surgical resection in patients with Dukes' Stage C colon cancer
Leucovorin®, leucovorin	12/12/91	palliative	In combination with 5-FU to prolong survival in the palliative treatment of patients with advanced colorectal cancer
Camptosar®, irinotecan	06/14/96* 10/22/98**	Second	Treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU-based therapy
Camptosar®, irinotecan	04/20/00	First	Treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU-based therapy
Xeloda®, capectibine	04/30/01	First	Metastatic colorectal in combination with 5-FU
Eloxatin®, oxaliplatin	08/09/02	Second	Metastatic Recurrent, after resection, 5-FU/LV and irinotecan; In combination with 5-FU
Eloxatin®, oxaliplatin	01/09/04	First	In combination with 5-FU and Leucovorin (LV) for the treatment of patients previously untreated for advanced/metastatic colorectal cancer
Erbitux®, cetuximab	02/12/04* 10/02/07**	Second	EGFR-expressing metastatic colorectal carcinoma in combination with irinotecan for refractory patients or as a single agent in patients who are intolerant to irinotecan-based chemotherapy
Avastin®, bevacizumab	02/26/04	First	Metastatic CRC in combination with 5-FU/LV
Avastin®, bevacizumab	06/20/06	Second	Metastatic CRC in combination with FOLFOX
Erbitux®, cetuximab	02/10/07	First	Advanced CRC

Source: Author's representation and retrieval of data from the FDA website
http://www.accessdata.fda.gov/scripts/cder/onctools/Indicationlist.cfm?Indication=colon-rectum
*accelerated approval
**full approval

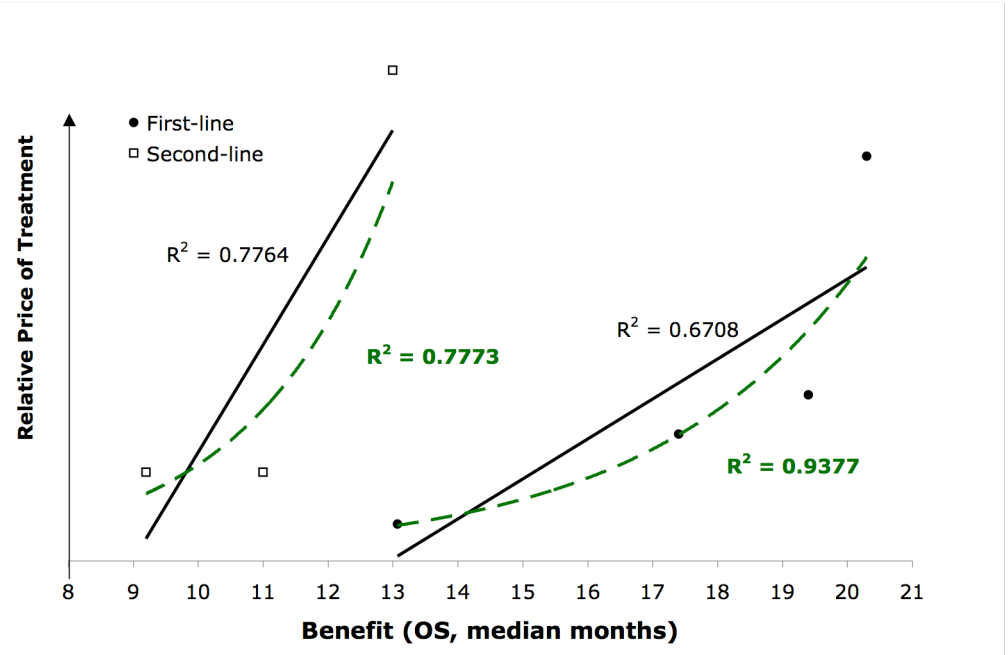
Appendix III

Regression Analysis for Figures 10 and 11



Regression Analyses of Figure 10, Price-Benefit Relationship of Adjuvant Breast Cancer Drugs

The data points for adjuvant breast treatments conforms more closely to exponential regression (green dashed) than linear (solid black). An R^2 value close to one indicates the closeness of this fit



Regression Analyses of Figure 11. Price-Benefit Relationship Drugs against Metastatic CRC

The data points for metastatic colorectal cancer treatments conform more closely to exponential regression (green dashed) than linear (solid black) in both first and second-line treatments.

References

Ackerman, F., and Heinzerling, L. (2002). "Pricing the priceless: Cost-benefit analysis of environmental protection." University of Pennsylvania Law Review **150**(5): 1553-1584.

Aspinall, M. G., Hamermesh, R. G. (2007). "Realizing the promise of personalized medicine." Harvard Business Reviews: 108-117.

Berenson, A. (2006). "A cancer drug shows promise, at a price many can't pay." The New York Times **Business**(February 15): http://www.nytimes.com/2006/02/15/business/15drug.html?pagewanted=1&_r=1.

Boadway, R., Bruce, N. (1984). "Welfare economics." Oxford **Basil Blackwell**.

Boardman, A. E., Greenberg, D. H., Vining, A. R., and Wiemer, D. L. (2006). Cost-Benefit Analysis Concepts and Practice. Upper Saddle River, New Jersey, Pearson Prentice Hall.

Boulenger, S., Nixon, J., Drummond, M., Ulmann, P., Rice, S., de Pouvourville G. (2005). "Can economic evaluations be made more transferable?" European Journal of Health Economics **6**(4).

Brodsky, L., Morrison, H., Evans, W. (2004). "Progress report on cancer control in Canada." Health Canada **Centre for Chronic Disease Prevention and Control** (Population and Public Health Branch): http://www.phac-aspc.gc.ca/publicat/prccc-relccc/chap_5_e.html.

Brouwer, W., Rutten, F., and Koopmanschap, M. (2001). Costing in Economic Evaluations, Oxford University Press: New York.

Brouwer, W., van Exel, J., Baker, R., and Donaldson, C. (2008). "The new myth: the social value of the QALY." Pharmacoeconomics **26**(1): 1-4.

Browman, G. P., Mann, B., Hagen, N., Chambers, C., Simon, A., and Sinclair, S. (2008). "6-STEPPs: A modular tool to facilitate clinician participation in fair decisions for funding new cancer drugs." Journal of Oncology Practice **4**: 2-7.

Bud, R. F. (1978). "Strategy in American cancer research after World War II: A case study." Social Studies of Science **8**: 425-459.

CBC (2007). "Petitions call for Avastin coverage." Canadian Broadcasting Corporation News **December 6**: http://www.cbc.ca/health/story/2007/12/06/avastin-petitions.html.

CBC (2008(a)). "Sask. agrees to pay for expensive cancer drug." Canadian Broadcasting Corporation News **January 39**: http://www.cbc.ca/canada/saskatchewan/story/2008/01/30/avastin-saskatchewan.html.

CBC (2008(b)). "Nova Scotia decides to fund expensive colorectal cancer drug." Canadian Broadcasting Corporation News **April 29**: http://www.cbc.ca/cp/health/080429/x042915A.html.

Chia, S. K., Speers, C. H., D'yachkova, Y., Kang, A. et al (2007). "The impact of new chemotherapeutic and hormone agents on survival in a population-based cohort of women with metastatic breast cancer." Cancer **110**(5): 973-979.

Connors, T. "Anticancer drug development: the way forward". (1996). Oncologist **1** (3):180-181

Cotterill, S. (2000). "Medical Terminology and Cancer." http://www.cancerindex.org/medterm/.

Diamandopoulus, G. T. (1996). "Cancer: An historical perspective." Anticancer Research **16**: 1595-1602.

DiMasi, J. A. (1992). "Rising research and development costs for new drugs in a cost containment environment." Pharmacoeconomics **1**(Suppl. 1): 13-20.

DiMasi, J. A., and Grabowski, H. G. (2007). "The Cost of Biopharmaceutical R&D: Is Biotech Different?" Managerial and Decision Economics **28**: 469-479.

DiMasi, J. A., Hansen, R. W., and Grabowski, H. G. (2003). "The Price of Innovation: New Estimates of Drug Costs." Journal of Health Economics **22**: 151-185.

Dinh, P., Sotirious, C., and Piccart, M (2007). "The evolution of treatment strategies: aiming at the target." Breast **2**: 10-16.

Donaldson, C., and Gerard, K. (1989). "Countering moral hazard in public and private health care systems: a review of recent evidence." Journal of Social Policy **18**(2): 235-251.

Dreyer, N. (2006). "Personalized medicine meets the real world." Pharmaceutical Executive **26**(6): 80-85.

Drummond, M. F. (2004). "Economic evaluation in health care: Is it really useful or are we just kidding ourselves?" The Australian Economic Review **37**(1): 3-11.

Drummond, M. F., O'Brein, B., Stoddart, G. L., and Torrance, G. W. (1997). "Methods for the Economic Evaluation of Health Care Programmes." Oxford Medical Publications **Oxford University Press**.

Dunham, I., et al (1999). "The DNA sequence of human chromosome 22." Nature **402**(6761): 489-495.

Ekelund, M., and Persson, B. (2003). "Pharmaceutical pricing in a regulated market." The Review of Economics and Statistics **85**(2): 298-306.

Elliot, R., and Payne, K (2005). Essentials of Economic Evaluation in Healthcare. London, The Pharmaceutical Press.

Ess, S. M., Schneewiess, S., and Szucs, T. D. (2003). "European healthcare policies for controlling drug expenditure." Pharmacoeconomics **21**(2): 89-103.

Evans, W. K., Nefsky, M., Pater, J., Browman, G., Cowan, D. H. (2002). "Cancer Care Ontario's New Drug Funding Program: controlled introduction of expensive anticancer drugs." Chronic Diseases in Canada **23**(4): 152-6.

Farkas, C., and Henske, P. (2006). "Reference pricing for drugs." Forbes **April**: http://www.forbes.com/columnists/2006/04/13/pharma-reference-pricing-cx_cf_0414pharma.html.

The following drug approval records were retrieved from the FDA's webstite: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
The final approval record number is emphasized:

FDA (1986). "FDA approved label for Nolvadex." **017970-S015**.

FDA (1989). "FDA approval label for Tamoxifen." **17970/S018**.

FDA (1990). "Supplement to FDA approval label for Tamoxifen." **01790/S020**.

FDA (1993). "FDA approval for use of Nolvadex in Male Metastatic Breast Cancer." **017970-024**.

FDA (1994). "FDA Approval for Taxol 020262/S-004." **O20262/S-004**.

FDA (1995). "FDA approval label for Arimidex." **020541/000**.

FDA (1997). "FDA Approved label for Fareston® " **0202497**

FDA (1998). "FDA Clinical Review of Herceptin®." **98-0369**.

FDA (1998b). "FDA Medical Review of Xeloda®." **02896**

FDA (1998c). "FDA approval package and label for Taxotere®." **20449/S-004**.

FDA (1999). "FDA medical review for approval of Ellence." **050778**.

FDA (1999b). "FDA approval of Taxol® for a new or modified indication." **020262/S-033**.

FDA (1999c). "FDA medical review for approval of Aromasin®." **20-753.**

FDA (1999d). "FDA approved label for Aromasin®." **20-753**.

FDA (2000). "FDA medical review for approval of Camptosar®." **20-571/S009**.

FDA (2000b). "FDA medical review for use of Arimidex®." **20-541/S-006**.

FDA (2001). "FDA medical review for approval of Xeloda®." **020896/S-009.**

FDA (2001b). "FDA medical review for Femara®." **20-726/S006**

FDA (2001c). "FDA approved label for Femara®." **20-726/S006.**

FDA (2002). "FDA medical review for approval of Eloxatin® " **21-492**.

FDA (2002b). "FDA medical review for supplementary approval of Armidex® " **20-541/S-010.**

FDA (2002c). "FDA medical review for approval of Faslodex® " **021344.**

FDA (2003). "Supplementary approval of Adriamycin® " **050629/S-014**.

FDA (2004). "FDA medical review for approval of Avastin®." **125085.**

FDA (2004b). "FDA approved label for Erbitux®." **125084/S-103**.

FDA (2004c). "FDA medical review for supplementary approval of Eloxatin®." **021492/S-002**.

FDA (2004d). "Supplementary approval of Femara®." **020726/S-011**.

FDA (2004e). "Supplementary approval of Taxotere®." **020449/S-029**.

FDA (2004f). "Medical review for supplementary approval of Gemzar®." **020509/S-029**.

FDA (2005). "Supplementary approval of Aromasin®." **020753/S-006**.

FDA (2005b). "FDA approval of Abraxane®." **021660**.

FDA (2006b). "FDA approval of Epirubicin®." **050807**.

FDA (2006c). "Supplementary approval of Herceptin®." **103792/S-5150**.

FDA (2006e). "Supplementary approval of Avastin®." **125085/S-0074**.

FDA (2007b). "Supplementary approval of Erbitux®." **125084/S103**.

FDA (2007c). "Medical review for approval of Tykerb® " **022059**.

FDA (2008). "Supplementary approval of Avastin®." **125085/S-0091**.

FDA (2008c). "Supplementary approval of Herceptin®." **103792/S-5175**.

FDA (2008d). "Searchable index for approval records of oncology drugs." http://www.accessdata.fda.gov/scripts/cder/onctools/statistics.cfm.

FHCRC (2008). "Fred Hutchinson Cancer Research Center." http://www.fhcrc.org/science/education/courses/cancer_course/clinical/treatment/curable.html.

Fleming, T. R. (2005). "Surrogate endpoints and the FDA's accelerated approval process." Health Affairs **Millwood**(24): 67-78.

Frei, E., 3rd (1985). "Curative cancer chemotherapy." Cancer Research **45**(12, part 1): 6523-37.

Garattini, S., Betele, V. (2002). "Efficacy, safety and cost of new anticancer drugs." British Medical Journal **325**: 269-271.

Genentech (2007). http://www.gene.com/gene/ir/financials/gaap/2007_q4.html.

Genentech (2008a). "Herceptin fact sheet." http://www.gene.com/gene/products/information/oncology/herceptin/factsheet.html.

Genentech (2008b). http://www.gene.com/gene/ir/financials/gaap/.

Genentech (2008c). "Herceptin® Prescribing Information." Herceptin® **Manufacturer's most updated product label**.

Goodman, L. S., Wintrobe, M. M., Dameshek, W., Goodman, M. J., Gilman, A., and Mclennan, M. T. (1946). "Nitrogen mustard therapy. Use of methyl-bi(beta-chloroethyl)amine hydrochloride and tris(beta-cholroethyl)amine hydrochloride for Hodgkin's disease, lymphosarcoma, leukemia and certain allied and miscellaneous disorders." Journal of the American Medical Association **105**: 475-476.

Grabowski, H. (2004). "Are the Economics of Pharmaceutical Research and Development Changing?" Pharmacoeconomics **22**(Suppl.): 15-24.

Grabowski, H., Kyle, M. (2007). "Generic competition and market exclusivity periods in pharmaceutical markets." Managerial and Decision Economics **28**: 491-502.

Grabowski, H., Vernon, J. (1994). "Returns to R&D on new drugs introduced in the 1980s." Journal of Health Economics **13**: 383-406.

Grabowski, H., Vernon, J., and DiMasi, J. A. (2002). "Returns on research and development for 1990s new drug introductions." Pharmacoeconomics **20**(suppl. 3): 11-29.

GTx (2008). "Prescribing information for Fareston." http://www.fareston.com/b_about/b5.html.

HC (2008). http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/phase1-decision/drug-med/index-eng.php.

Hiatt, H. H. (1975). "Protecting the medical commons: who is responsible?" New England Journal of Medicine **293**(53): 941-973.

http://www.ispor.org/PEguidelines/index.asp.

Jansman, F. G., Postma, M. J., Brouwers, R. B. J. (2007). "Cost considerations in the treatment of colorectal cancer." Pharmacoeconomics **25**(7): 537-562.

Kapiriri, L., Norheim, O. F., and Martin, D. K (2007). "Priority-setting at the micro-, meso-, and macro-level in Canada, Norway and Uganda." Health Policy **82**: 78-94.

Kardinal, C., Yarbro, J. A. (1979). "A conceptual history of cancer." Seminars in Oncology **6**: 396-408.

Laurin, A., and Soucy, J., (2000). Three decades of economic and financial change in Canada: 1969 to 1999. Government of Canada http://dsp-psd.tpsgc.gc.ca/Collection-R/LoPBdP/BP/prb015-e.htm#ECONOMIC

Lichtenberg, F. R. (2001). "Public Policy and Innovation in the U. S. Pharmaceutical Industry." Entrepreneurship and Public Policy.

Lopez-Casasnovas, G., Puig-Junoy, J. (2000). "Review of the literature on reference pricing." Health Policy **54**: 87-123.

Lu, Z. J., Comanor, W. S. (1998). "Strategic pricing of new pharmaceuticals." Review of Economics and Statistics **80**(1): 108-118.

Mason, J., Freemantle, N. (1998). "The dilemma of new drugs, are costs rising faster than effectiveness?" Pharmacoeconomics **13**(6): 653-657.

McManus, J. (2007). "Critical appraisal of Bevacizumab (Avastin) for use in metastatic colorectal cancer." NICE Critical Appraisal **Health Improvement Directorate**:

www.bdpct.nhs.uk/document_uploads/HI_Publications/Critical%20Appraisal%20of%20Bevacizumab%202007%2002.pdf.

McManus, J. (2007). "Critical appraisal of Bevacizumab (Avastin) for use in metastatic colorectal cancer." NICE Critical Appraisal **Health Improvement Directorate**: www.bdpct.nhs.uk/document_uploads/HI_Publications/Critical%20Appraisal%20of%20Bevacizumab%202007%2002.pdf.

Meyerhardt, J. A., and Mayer, R. J. (2005). "Systemic therapy for colorectal cancer." New England Journal of Medicine **352**: 476-487.

Millar, A. (2002). "Priority-setting decisions for new cancer drugs." The Lancet **359**: 1524.

Moore, S., Cobleigh, M. (2007). "Seminars in Oncology Nursing." Targeting metastatic and advanced breast cancer **23**(1): 37-45.

Murphy, K. M., and Topel, R. (2005). "The Value of Health and Longevity." NBER Working Paper No. W11405.

Murphy, K. M., and Topel, R. (2006). "The value of health and longevity." Journal of Political Economy **114**(5): 871-904.

Murphy, K. M., and Topel, R. (2007). "Social value and the speed of innovation." American Economic Review **97**(2): 433-437.

Murray, C. J. L., Evans, D. B., Acharya, A., and Baltussen, R. M. P. M (2000). "Development of WHO guidelines on generalized cost-effectiveness analysis." Health Economics **9**: 235-251.

Nagle, T. (2007). "The Price is Right?" Pharmaceutical Executive **27**(5): 40-44.

Novartis (2008). http://www.novartis.com/investors/product-sales.shtml.

O'Connell, M. J. (1989). "A phase III trial of 5-fluorouracil and leucovorin in the treatment of advanced colorectal cancer. A Mayo Clinic/North Central Cancer Treatment Group study." Cancer **63**(6 Suppl.): 1026-1030.

OECD (1994). "The reform of health care systems: a review of seventeen OECD countries." Health Policy Studies **1st ed.**(Paris: OECD).

OECD (2005). "OECD Health Data 2005: Statistics and indicators for 30 countries." Paris, Organisation for Economic Co-operation and Development.

Pazdur, R. (2008). "Endpoints for assessing drug activity in clinical trials." Oncologist **13**(Suppl 2): 19-21.

Pearce, H. L., Miller, M. A. (2005). "The evolution of cancer research and discovery at Lilly Research Laboratories." Advances in Enzyme Regulation **45**: 229-255.

Philipson, T., Berndt, E. R., Gottschalk, A. H. B., Sun, E. (2008). "Cost-benefit analysis of the FDA: The case of prescription drug user fee acts." Journal of Public Economics **92**: 1306-1325.

Pijpers, F., and Belsey, M. J. (2006). "Cancer remains the dominant disease target for biotech through to 2010." Journal of Commercial Biotechnology **12**(4): 294-298.

Pollack, A. (2006). "A crystal ball submerged in a test tube." The New York Times **April 13**.

Presswire, M. (2006). "The Current Market for Chemotherapies is estimated at US $42 Billion and is forecast to Increase Approximately 17% to US $ 49 Billion by 2012." **April 28, 2006**: http://findarticles.com/p/articles/mi_hb5243/is_200604/ai_n20137175.

Rawlins, M. (2007). "Paying for modern cancer care-a global perspective." Lancet Oncology **8**(9): 749-751.

Redaelli, A., Cranor, C. W., Okano, G. J. et al. (2003). "Screening, prevention and socioeconomic costs associated with the treatment of colorectal cancer." Pharmacoeconomics **21**: 1213-1238.

Ries, L., Melbert, D., Krapcho, M. et al. eds. (2006a). "SEER Cancer Statistics Review, 1975-2004." National Cancer Institute **Bethesda, MD**(http://seer.cancer.gov/csr/1975_2004): based on invasive colorectal cancer, age adjusted, 5-year survival rates, male and female

Ries, L., Melbert, D., Krapcho, M. et al. eds. (2006c). "SEER Cancer Statistics Review, 1975-2004." National Cancer Institute **Bethesda, MD**(http://seer.cancer.gov/csr/1975_2004): based on all invasive cancer sites, age adjusted, 5-year survival rates, male and female

Rocchi, A., Menon, D., Shailendra, V., Miller, El (2007). "The role of economic evidence in Canadian oncology reimbursement decision-making: To lambda and beyond." Value in Health.

Scherer, F. M. (2001). "The link between gross profitability and pharmaceutical R&D spending." Health Affairs **20**: 216-220.

Schrag, D. (2004). "The Price Tag on Progress-Chemotherapy for Colorectal Cancer." New England Journal of Medicine **351**(4): 317-319.

SEER (2008). "Cancer statistics." (http://seer.cancer.gov/csr/ 1975_2005/results_single/ sect_01_table.01.pdf).

Sheldon, T. (1997). "Dutch agree budget for expensive anticancer drugs." British Medical Journal **314**(7084): 848.

Singer, E. (2008). "Your Future on a Chip." Technology Review **111**(1): 24.

Spruance, S. L., Reid, J. E., Grace, M., and Samore, M. (2004). "Hazard Ratio in Clinical Trials." Antimicrobial Agents and Chemotherapy **48**(8): 2787-2792.

Strax, P. (1988). "Mass screening to reduce mortality from breast cancer." Seminars in Surgical Oncology **4**(4): 218-220.

Thomson, J., Schofield, P., Mileshkin, L., Agalianos, E., Savulescu, J., Zalcberg, J., Jefford, M. (2006). "Do oncologists discuss expensive anti-cancer drugs with their patients?" Annals of Oncology **12**: 702-708.

Triolo, V. A. (1961). "The American Association for Cancer Research 1907-1940: Historical review." Cancer Research **21**: 137-161.

Unspecified Author #1 (2006). "Colorectal cancer: bad NICE news for Avastin and Erbitux." PharmaWatch **5**(10): 10.

Unspecified Author #2 (2007). "Beyond the blockbuster." Economist **383**(8535).

Venter, J. C. (2001). "The sequence of the human genome." Science **291**(5507): 1304-51.

Vernon, J. A. (2003b). "Drug Research and Price Controls." Regulation **25**: 4.

Vining, A. R., and Wiemer, D. L. (2006). Efficiency and Cost-Benefit Analysis. Handbook of Public Policy. G. B. Peters, and Pierre, J. London, SAGE Publications Ltd.

Warren, J. L., Yabroff, R. K, Meekins, A., Topor, M., Lamont, E. B., Brown, M. L. (2008). "Evaluation of trends in the cost of initial cancer treatment." Journal of the National Cancer Institute **100**: 888-897.

Weitz, J., Koch, M., Debus, J. et al (2005). "Colorectal cancer." Lancet **365**: 153-165.

WHO (2007). http://www.who.int/global_health_histories/seminars/presentation07.pdf.

Wu, S. Y. (1980). "Measures for social rate of returns from pharmaceutical innovations." Managerial and Decision Economics **1**(4): 179-183.

Yau, T., Chan, P., Ching Chan, Y., Wong, B. C. Y., Liang, R., and Epstein, R. J. (2008). "Review article: current management of metastatic colorectal cancer-the evolving impact of targeted drug therapies." Alimentary Pharmacology & Therapeutics **27**: 997-1005.
Yin, W. "Market incentives and pharmaceutical innovation" (2008) Journal of Health Economics **27**(4): 1060-1077

Ziegelbauer, K. and Light, D. R. (2008). "Monoclonal antibody therapeutics: Leading companies to maximise sales and market share." Journal of Commercial Biotechnology **14**(1): 65-72.