DEVELOPMENT OF A VALUE BASED PRICING INDEX FOR NEW DRUGS IN METASTATIC COLORECTAL CANCER

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DEVELOPMENT OF A VALUE BASED PRICING INDEX FOR NEW DRUGS IN METASTATIC COLORECTAL CANCER

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LIST OF ABBREVIATIONS

ADRs = adverse drug reactions

BSC = best supportive care

CBA = cost benefit analysis

CEA = cost effectiveness analysis

CMA = cost minimisation analysis

CR = complete response

CUA = cost utility analysis

DALY = disability adjusted life year

FOLFOX = oxaliplatin in combination with infusional 5-fluorouracil

FOLFIRI = irinotecan in combination with infusional 5-fluorouracil

GDP = gross domestic product

KRAS = V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog

mCRC = metastatic colorectal cancer

NICE = National Institute of Clinical Excellence

PE = pharmacoeconomics

PR = partial response

PYLL = potential years of life lost

QALY = quality adjusted life year

QOL = quality of life

SD = stable disease

TTO = Time Trade-Off

U.S. = United States

VEGF = vascular endothelial growth factor

ABSTRACT

Background: Worldwide, prices for cancer drugs have been under downward pressure where several governments have mandated price cuts of branded and generic products. A better alternative to mandated price cuts would be the estimation of a launch price based on drug performance, cost effectiveness and a country's ability to pay. In this study, the development of a global pricing index for new drugs that encompasses all of these attributes in patients with metastatic colorectal cancer (mCRC) is described.

Methods: A pharmacoeconomic model was developed to simulate clinical outcomes in mCRC patients receiving chemotherapy with the addition of a "new drug" that improves survival by 1.4, 3 and 6 months. Cost and health state utility data were obtained from cancer centers and oncology nurses (total n=112) in Canada (n=24), Spain (n=24), India (n=24), South Africa (n=16) and Malaysia (n=24). A price per dose was estimated for each survival increment using a target value threshold of three times the per capita gross domestic product (GDP) for each country, as recommended by the World Health Organisation (WHO). Multivariable analysis was then used to develop the pricing index, which considers survival benefit, per capita GDP and income dispersion as measured by the Gini coefficient as predictor variables.

Results: Higher survival benefits were associated with elevated drug prices, especially in wealthier countries such as Canada and Spain. For a nation like Argentina with a per capita GDP of $15,000 and a Gini coefficient of 51, it is estimated that for a drug which provides a 4 month survival benefit in mCRC, the value based price would be $US 630 per dose. In contrast, the same drug in a wealthier country like Norway could command a price of $US 2,775 and still be considered cost effective according to the WHO criteria.

Conclusions: A global pricing index was presented that can be used to estimate a value based price in different countries for new drugs in mCRC. The application of this index to estimate a price based on cost effectiveness would be a good starting point for opening dialogue between the key stakeholders and a better alternative to governments' mandated price cuts.

Key words: Colorectal cancer, drug price, value, cost, chemotherapy

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DECLARATION

I, George Dranitsaris, hereby declare that the research on which this thesis is based on is original and that neither the entire work nor part of it has been, is being, or is to be submitted for another degree at this or any other university.

CHAPTER 1

INTRODUCTION

1.1 Introduction

Cancer has always been with human kind, with the first recorded case being discovered in Egyptian hieroglyphic tablets (Mukherjee, 2010). The underlying causes of all cancers in general are not fully known. However, one underlying theory is that cancer is a form a speciation, where cancer cells are, in a sense, a new living organism attempting to break out of the human host (Vincent, 2010). Notwithstanding the history or causes of human cancers, the majority of patients seek some form of treatment. The intent of cancer therapy is to cure the disease or to at least palliate symptoms and improve quality of life. Drugs have always been an intergral part of cancer therapy. The work presented in this thesis attempts to address a fundamental challenge faced by cancer patients around the world; timely access to effective drugs. The first chapter begins with a brief presentation of global cancer trends, highlighting that the disease remains one of the most common causes of death worldwide. It then continues with a description of pharmacotherapy in cancer care and how the high prices of new cancer drugs have limited patient access to these important agents. The impact of these high prices on health care budgets is then highlighted. The challenges that health care systems face in terms of rising drugs expenditures and how they have responded are then presented. The chapter then closes with a proposal for determining an optimal drug price based on product value. The pricing strategy proposed in this study could improve patient access by identifying a more affordable price based on the wealth of a nation.

1.2 Cancer, a global problem

The populations of many countries around the world are aging (Kinsella et al., 2005). This is of concern to health care authorities because cancer is a disease that usually occurs later in life. It has been estimated that in the United States alone, 60% of all new cancers occur in people over the age of 65 years (Surveillance Epidemiology and End Results, 2010). Since the population is aging, a sharp increase in the number of new cases can also be expected over the next 10 to 20 years. Cancer is now considered to be a chronic condition because some patients with advanced stage disease can live for five to ten years after the initial diagnosis (National Cancer Institute of Canada, 2010). From the perspective of cancer centres, these factors are causing sharp increases in the number of patients seeking treatment. As a result, health care systems around the world are being strained as they attempt to meet the needs of patients.

The primary tools used by oncologists to treat cancer consist of surgery, chemotherapy, radiation and hormonal therapy. The use of these interventions, alone or in combination, depends on the type of cancer, the extent of disease and patient factors. Surgery is usually, but not exclusively, reserved for early stage tumours where the intent is cure. Chemotherapy, radiation and hormonal therapy are used in both early stage disease and in incurable tumours that have metastasized to distant sites (Devita et al., 2001).

For many years, the backbone of cancer treatment has been the use of cytotoxic agents such as anthracylines, taxanes and platinum analogues (Table 1.1). One characteristic of traditional chemotherapy is its non-specificity to the target. As a result, side effects such as neutropenia, anemia and thrombocytopenia are common (Schiller, 2002). However over the past decade, there has been an emergence of new anticancer

drugs that are more specific to the target (Köhne et al., 2009; Mahalingam et al., 2009). These new compounds which include imatinib, bevacizumab, cetuximab and trastuzumab are collectively known as “targeted therapies” (Köhne et al., 2009; Mahalingam et al., 2009 and Motzer et al., 2007) – (see Table 1.1). Unlike traditional chemotherapy which can affect both healthy and malignant cells, targeted agents are specific to the latter. Therefore, they tend to be better tolerated than chemotherapy and the main side effects described above are less common (Köhne et al., 2009; Mahalingam et al., 2009). The use of these agents has also resulted in a prolongation of survival in some types of cancer such as breast, lung and colorectal (Van Cutsem et al., 2009; Sandler et al., 2006).

Table 1.1. Anticancer agents currently used in the treatment of solid tumour malignancies (Köhne et al., 2009; Mahalingam et al., 2009)

Anthracyclines	**Taxanes**	**non-Anthracycline**	**Targeted agents**
Doxorubicin	Paclitaxel	Capecitabine	Lapatinib
Epirubicin	Docetaxel	Vinorelbine	Trastuzumab
Liposomal doxorubicin	Abraxane	Gemcitabine	Bevacizumab
Mitoxantrone		Cisplatin	Cetuximab
Daunorubicin		Carboplatin	Panitumumab
		Oxaliplatin	Sunitinib
		Cyclophosphamide	Sorafenib
		5-fluorouracil	Pazopanib
		Methotrexate	Erlotinib
		Irinotecan	Everolimus
		Pemetrexed	Temsirolimus

1.3 Patient access to new cancer drugs

Despite the effectiveness and safety of the new targeted agents, not all cancer patients around the world have access to them. One of the single biggest barriers to drug access is price. All of these new therapies have been priced at levels that are several times higher than traditional chemotherapy (Schrag, 2004). As an illustration, sunitinib, which is an orally administered targeted agent used in advanced kidney cancer, has a cost of approximately $US 8,000 (R57,028) per month with the median duration of therapy being approximately 8 months (Motzer et al., 2007). The previous agent used in kidney cancer (interferon alfa) has a monthly cost of $US 900 (R 6,390). At the time when the pivotal study results were reported, sunitinib was associated with a statistically significant 6 month improvement in progression free survival, but the overall survival increment did not reach statistical significance (Motzer et al., 2007). Notwithstanding the decision to use sunitinib in kidney cancer, such costs are out of reach for many cancer patients even in higher income countries. For example, in the Canadian province of Ontario with a population of 12 million, approximately one-third of the population does not have private or public medical insurance (Fraser Report, 2008). As a result, about one third of such patients would have to use their own funds to pay for sunitinib. For many such patients, even in developed nations, drugs such as sunitinib are simply out of reach.

These challenges to drug access are especially relevant in developing nations. It is unclear how multinational pharmaceutical companies make the final decision on how to price a drug for a given country, but what is certain is that prices for such agents have been increasing almost exponentially, far beyond the rate of inflation (Fojo and Grandy, 2009; Hillner and Smith, 2009). Furthermore; it is not uncommon to find that prices for

specific drugs in less developed countries are comparable to the cost of the drug in the United States. For example, the annual cost of bevacizumab, a targeted agent used in colorectal cancer is $US 52,800 (R 374,880) in the United States compared to $US 45,000 (R 319,500) in South Africa. Gross Domestic Product (GDP) per capita for South Africa in 2010 was approximately $US 10,000 (R 71,000) compared to $US 47,000 (R 333,700) in the United States (World Fact Book, 2010). Hence, it is unclear why the price of a cancer drug such as bevacizumab should be comparable between two countries with such a wide variance in per capita GDP. As a result, a more transparent method needs to be developed to determine a fair price for new cancer drugs that is linked to overall clinical performance, economic efficiency and the wealth of the country.

1.4 Problem Definition

To help overcome barriers to patient access for new cancer drugs secondary to high launch prices, national governments should have the necessary tools available that would help them negotiate a more reasonable price with the manufacturer that is based on clinical performance measure by survival benefit, economic value as measured by the cost per QALY gained. Therefore, what is needed is an index for estimating a price that is based on the survival benefits that a new drug offers, an individual country's direct health care costs that could potentially be offset by a new drug (for example, hospitalisations, palliative care services) along with societal utilities for improvements in health outcomes. A range of drug prices could then be evaluated against a societal value threshold for cost effectiveness that considers the wealth of the nation (for example, less than three times the per capita GDP for a given country as recommended

by the World Health Organisation - Hillner and Smith, 2009; Murray, 2000; Sarin, 2008). Such information may then be used by national governments or formulary committees to negotiate a drug price for their patient population that is based on overall value.

In this study, the development of a value based pricing index that can be applied to new targeted therapies indicated for the treatment of metastatic colorectal cancer (mCRC) in described. Colorectal cancer was chosen because it is the second most common cause of cancer death worldwide and it is a site where several new high cost drugs have been approved for clinical use in many countries around the world (NCIC 2010; Engstrom, 2008).

1.5 Primary aim and objectives

Economic efficiency refers to the use of resources so as to maximize the production of goods and services. For pharmaceuticals, pharmacoeconomics is applied to measure the economic efficiency of two or more drugs indicated for the same medical condition (Drummond et al, 2005). Cost-effectiveness analysis (CEA) is a form of economic analysis that compares the relative costs and outcomes (effects) of two or more courses of action. A related concept is economic value. With respect to pharmaceutical, a drug is said to provide economic value if it avoids downstream direct health care costs or indirect patient related resources (Kolassa, 2009). Therefore, a drug is considered to be cost effective if it avoids down stream direct or direct health care resources.

In this study, pharmacoeconomic (PE) modeling techniques along with cost and utility data collected in Canada, Spain, South Africa, Malaysia and India were used to develop an index for determining a cost effective price for new agents in mCRC. The

index could then be used to estimate appropriate drugs prices based on societal value thresholds, the survival benefit offered by a new drug, income dispersion as measured by the Gini coefficient (De Maio, 2007) and the country specific per capita GDP.

The specific objectives of the study were to:

- Estimate societal utilities for improvements in mCRC related health outcomes in the five reference countries.
- Develop a PE model that could be used to estimate an optimal drug price for the treatment of mCRC in the five reference countries.
- From the data generated in the five reference countries, develop a pricing index for estimating an optimal drug price based on societal value thresholds, the survival benefit offered by the drug, income dispersion within a country and per capita GDP.

1.6 Overview of objectives

The first main objective of this research described in section 1.5 was addressed through the collection of cost and utility data from the five reference countries. These data were used to populate the PE model that simulated the treatment of patients with mCRC. Therefore, the second objective was met through the PE model that was made specific to each country. With the PE model, price points that were based on societal value thresholds were generated for each country. With the estimated price points, a pricing index was then developed through the application of multivariate regression analysis. To fulfill the third objective of the study, the final pricing index is able to estimate a drug price based on the survival benefit offered by the drug, income dispersion within a country and per capita GDP.

The thesis contains five articles that were recently published in peer reviewed journals. Two additional articles have been accepted for publication and are currently in press (see page 56 of the thesis). Articles two to six are the country specific publications for Canada, India, Spain, South African and Malaysia. It is within these five articles that objectives one and two have been addressed. The third and final objective has been fulfilled in the seventh publication, which describes how the global pricing index was developed and how it can be applied. There is also an editorial to the seventh publication, which describes the utility of the pricing index.

1.7 Research Hypothesis

Countries with a lower per capita GDP and lower income dispersions are likely to have a lower predicted launch price for a new drug and the estimated price would be proportional to overall survival benefit over the current standard of care.

1.8 Conclusions

What would be useful to all the key stakeholders would be the development of a drug pricing index that is linked to product performance, economic value as measured by the cost per QALY gained, a country's GDP and income dispersion within a nation. In this study, the development of such an index that can be applied to new therapies indicated for the treatment of metastatic colorectal cancer (mCRC) is described. The final index is transparent, easy to apply and uses information that is readily available to all drug formulary committees. In the next chapter, the clinical and PE literature for the key targeted agents is reviewed. This is followed by a review of the health policy issues that have been created as a result of the high cost of these agents.

CHAPTER 2

CANCER THE DISEASE

2.1 Introduction

Cancer remains a leading cause of death worldwide. As the population ages, the problem of quality patient care will become more acute. This chapter provides a descriptive overview of the many aspects of cancer. It begins with a discussion of the known causes and how patients are staged upon diagnosis. Cancer epidemiology in terms of new cases and trends in overall survival over time is then presented. The chapter continues with a discussion of the burden of illness in terms of costs to society. The chapter closes with a presentation of the current concepts of cancer care.

2.2 Disease characteristics

Cancer is a group of diseases that are characterised by uncontrolled cell growth, invasion into adjacent tissues and sometimes spread to distant parts of the body (Kinzler et al., 2002). It is these three properties of cancer cells that distinguish them from benign tumours which do not tend to spread to distant sites. All cancers contain many DNA mutations that impact cell growth and contribute to distant spread. Substances that cause DNA mutations are known as mutagens, and mutagens that cause cancer are known as carcinogens (Devita et al., 2001). There are many causes of cancer ranging from internal factors such as genetic predispositions to external factors such as tobacco, chemical agents such as asbestos, infectious pathogens and exposure to radiation (Sasco et al., 2004, Biesalski et al., 1998). As an illustration, tobacco has been implicated as the major cause of approximately 90% of human lung cancers (Cancer WHO, 2008).

The three main forms of cancer are based on the types of cells that are affected. Solid tumours, are derived from epithelial cells and represent the most common cancers such as lung, breast and colorectal (Surveillance Epidemiology and End Results, 2010). In contrast, sarcomas are malignancies derived from connective tissue while lymphomas, leukemias and myeloma originate from hematopoietic cells.

Upon diagnosis, cancer patients with solid tumours and lymphomas are staged according to the degree of tumour spread (from Stage I to IV). Descriptively, tumours are staged as follows (Devita, 2001):

- Stage I cancers are localised to one part of the body.
- Stage II cancers are locally advanced.
- Stage III cancers are also locally advanced. Whether a cancer is designated as Stage II or Stage III depends on type of cancer; for example, in lymphoma, Stage II indicates affected lymph nodes on only one side of the diaphragm, whereas Stage III indicates affected lymph nodes above and below the diaphragm. The specific criteria for Stages II and III therefore differ according to diagnosis.
- Stage IV cancers have often metastasized to other organs or throughout the body.

2.3 Cancer epidemiology

Cancer is a global issue with 7.4 million deaths per year, which is approximately 13% of all cause mortality (Cancer WHO, 2008). The incidence of cancer has also been on the rise for several reasons such as an aging population (Kinsella, 2009). It has been estimated that in the United States alone, 60% of all new cancers occur in people over the age of 65 years (Surveillance Epidemiology and End Results, 2010). Similar trends have also been identified in Europe in both men and women (Figure 2.1).

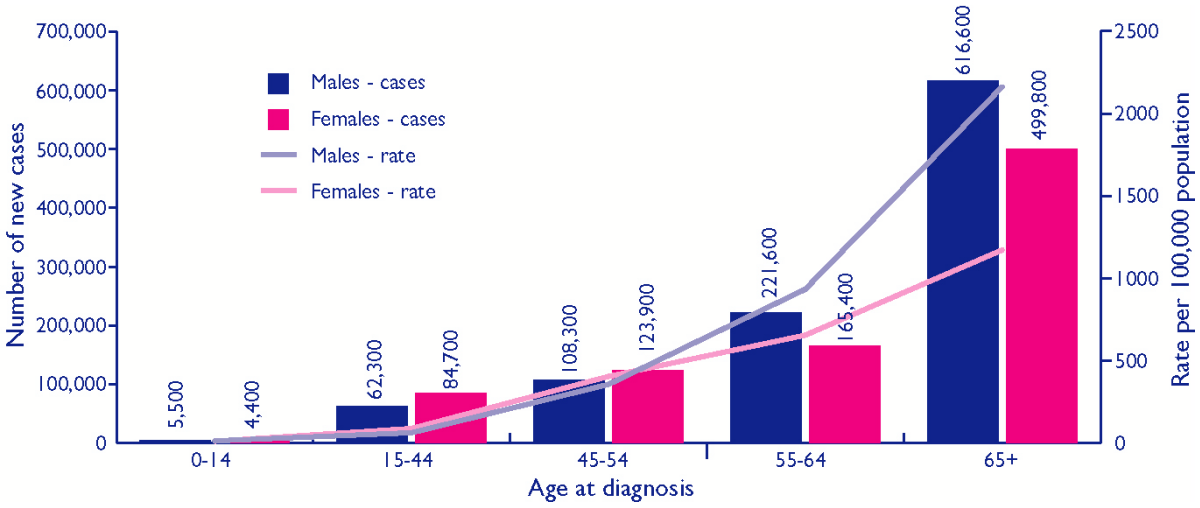

Figure 2.1 Number of new cases and age specific rates per 100,000 of the population, 2000 European estimates (source – Cancer Trends. Cancer Research UK, 1999).

The disease is now considered to be a chronic condition because some patients with advanced stage cancer receiving effective treatment can live for five to ten years after the initial diagnosis (Surveillance Epidemiology and End Results 2010, National Cancer Institute of Canada 2010). In addition, the overall rate of cancer mortality has been steadily decreasing. In one study, Wilking and Jonsson (2005) estimated the expected increases in the number of new diagnoses and cancer-related mortality in 25 European countries from 2002 to 2006 (see Table 2.1). These investigators identified a 10% increase in the number of new diagnoses over the four year period. Encouragingly, there was stability in the number of deaths over the same time period. Similar findings have also been reported by the Surveillance Epidemiology and End Results (SEER) of the United States (SEER, 2010).

Table 2.1. Number of new cancer cases and deaths: 2002 to 2006 (Stark, 2009)

EU25+CH+IS+NO[1]	Events	2002	2006	Change
All cancers except skin	No of cases	2,138,700	2,351,100	9.93%
	No of Deaths	1,188,100	1,192,500	0.37%
Breast	No of cases	277,300	328,600	18.51%
	No of Deaths	89,900	87,200	-2.97%
Colorectal	No of cases	283,600	307,000	8.27%
	No of Deaths	142,400	142,700	0.20%
Lung female	No of cases	60,500	73,500	21.46%
	No of Deaths	54,300	65,800	21.11%
Lung male	No of cases	199,900	198,100	-0.86%
	No of Deaths	182,100	175,200	-3.80%
Prostate	No of cases	201,700	311,100	54.25%
	No of Deaths	69,300	70,300	1.48%
Stomach	No of cases	92,200	81,600	-11.46%
	No of Deaths	70,200	58,400	-16.76%
Uterus	No of cases	85,900	84,900	-1.17%
	No of Deaths	26,700	24,200	-9.49%

[1]Abbreviations: EU25 = 25 European countries, CH = Switzerland, IS = Iceland, NO = Norway

2.4 The social burden of cancer

The economic burden of a disease represents all aspects in the personal cost of the illness. The cost to the patient may be financial, social, psychological or personal loss to self, family, or community. These latter costs are best reflected in lost quality of life related to the illness (Drummond et al, 2005). The societal burden may be reflected in absenteeism, productivity losses and the direct financial cost of providing services related to the delivery of health care, rather than personal impact on the individual.

The social burden of cancer consists of both direct and indirect costs of care. Direct costs are the resources used to prevent and treat the disease and can be represented by the proportion of a nation's total health care budget that is allocated for cancer. The

average for 28 European countries in 2004 was 6.4% of total health care expenditures, which ranged from 3% to 7.2% (Wilking and Jonsson, 2005; Stark, 2009). For the 19 European countries covered by Organization for European Cooperation and Development (OECD), total annual expenditures were €147 billion in 2007 or €1148 per person (Stark, 2009). Similarly in the United States, absolute cancer related expenditures rose from $1.3 billion in 1963 to $72.1 billion in 2007 (Cancer Trends, 2007).

Indirect costs represent the resources lost as a result of an illness, and primarily consist of lost productivity due to absence from work and permanent disability or death from the disease before the age of 65 years (Drummond et al., 2005, Canadian Guidelines, 2006). There are several ways that the indirect costs of cancer can be expressed. The Canadian Cancer Society reports such outcomes as the potential years of life lost (PYLL) due to cancer. For the year 2003, the Canadian Cancer Society estimated that there were approximately 1 million PYLL or one PYLL for every 33 people (NCIC, 2010). When this was compared to PYLL from all other causes of death (both disease and non-disease related), cancer deaths represented approximately 32% of the total burden of illness, even surpassing that of heart disease (National Cancer Institute of Canada, 2010).

One of the limitations of expressing indirect costs in terms of PYLL is that it does not consider disease-related morbidity. Disability adjusted life years (DALYs) is an economic measure that considers both mortality and disability associated with the condition in question (Havelaar et al., 2009). DALYs are calculated by taking the sum of life years lost due to illness and the number of years lived with disability. Using the DALY approach, cancer was responsible for 16.7% of all DALYs lost in 25 European

countries and 12.5% of all DALYs lost in United States and Canada (Wilking and Jonsson, 2005, 2007). In Europe alone, cancer at 9.8 million DALYs lost ranked third after mental illness and cardiovascular disease (Wilking and Jonsson, 2007). In summary, cancer represents a substantial burden on society, both in terms of direct and indirect costs. The burden will increase as the number of new cases increase, which is the trend seen in many countries today. However comparing total health care expenditures that are allocated to the treatment of cancer to the number of DALYs lost (that is, 6.4% versus 16.7% of all DALYs lost), cancer care would appear to be under funded.

2.5 Current concepts of care

Upon diagnosis, cancer patients with solid tumours are staged according to the degree of tumour spread (from Stage I to IV). The intent of treating patients with Stage I to III disease is clinical cure. Patients with early stage disease (typically Stage I to III) are initially treated surgically with or without radiation. This is often followed by adjuvant chemotherapy which is intended to eradicate any remaining tumour cells. Patients who are diagnosed with advanced disease (Stage IV) usually do not undergo a major surgical intervention. Instead, they would typically be offered palliative chemotherapy, radiation therapy or hormonal therapy if indicated (Devita et al., 2001). Advanced stage disease is usually terminal and the intent of treatment is to increase survival, the palliation of disease-related symptoms and improvement in patient quality of life.

The selection of treatments for advanced stage cancer is guided by patient and disease related factors (Table 2.2). Patient factors that are critical in the selection of therapy include patient age, performance status and the presence of comorbidities. Important disease related factors that guide medical decision making in the advanced

setting consist of the duration of the disease-free interval following adjuvant anticancer therapy, drugs previously used during early stage disease, response to these previous therapies, tumour burden and the presence of life threatening metastases (Cardoso et al, 2010). Once a decision for systemic therapy is made, there are several options available to the patient. These consist of chemotherapy, endocrine therapy, the newer targeted agents, radiation therapy and supportive care drugs to prevent and treat the common drug toxicities. These interventions may be used alone or in combination. The initial systemic therapy is continued until the patient experiences disease progression (Devita et al., 2001). Following an initial disease progression, it is not uncommon to offer multiple lines of therapy until the patient is no longer responding to treatment. Once all pharmacotherapeutic options are exhausted, patients are offered palliative care (Cardoso et al., 2010). Palliative care consists of radiation for bone pain, blood transfusions, analgesics for pain control, home care assistance and a possible admission into a hospice for end of life support (Zafar et al., 2010).

Table 2.2. Factors associated with treatment decisions in advanced stage cancer

Patient Factors	**Disease Factors**
Patient age and performance status	Recurrence free survival interval
Treatment objectives	Previous anticancer therapies
Existing comorbidities	Response to previous therapies
Socioeconomic factors	Number and sites of metastases
Treatment availability	Need for rapid disease control

From (Cardoso et al, 2010).

2.6 Conclusions

The past ten years has been witness to major changes in the management of cancer. In the prior decade, the approach to chemotherapy was a “one size fits all” approach where the same regimens would be offered to all patients (Mahalingam, 2009). However, an increased understanding of cancer has led to the determination that it is not homogenous, but a heterogeneous disease with responses to therapy being influenced by the presence of important prognostic factors and associated biomarkers. Coupled with advances in biotechnology, several new and important anticancer therapies have become available or are in clinical development (Alvarez et al., 2010). Therefore, this will mean that overall patient survival and quality of life should continue to increase as we enter the new decade.

CHAPTER 3

OVERVIEW OF THE CLINICAL, ECONOMIC AND HEALTH POLICY LITERATURE

3.1 Introduction

Before the development of a value based pricing model is begun, the clinical, economic and health policy literature relevant to the newer targeted anticancer drugs needs to be reviewed. This literature capture is composed of two parts. The first part of this chapter reviews the clinical and PE data associated with key targeted agents. Agent selection was based on the impact that these drugs had on the management of their selected diseases and the magnitude of the health policy issues that they raised because of their high prices. The agents selected for review consisted of rituximab, imatinib, trastuzumab, bevacizumab and cetuximab. While other commonly used targeted agents such as erlotinib, sorafenib and sunitinib are also important targeted therapies, they were not included in the literature review because the intent was to provide only a “snap shot” of selected high profile agents rather than a comprehensive review. Furthermore, bevacizumab and cetuximab are two agents that are currently used in mCRC, which is the selected disease site for developing the value based pricing index in the current study.

In the second part of the chapter, the health policy literature related to the high priced cancer drugs was reviewed. This also included an overview of how health care systems around the world have responded to the challenges created by these high prices agents. These two sections were subsequently used to prepare a review article that was recently published in *Pharmacoeconomics* (Dranitsaris et al., 2011) The article, which is presented below, will provide the core text for this chapter.

REVIEW ARTICLE

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1170-7690/10/0000-0000/$49.95/0

Advances in Cancer Therapeutics and Patient Access to New Drugs

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Contents

Abstract

Globally, there are approximately 7.4 million cancer deaths annually, approximately 13% of deaths from all causes. Cancer is a disease of older people and, as the population ages over the next 10–20 years, we can expect an increase in the cancer incidence. Encouragingly, cancer mortality has stabilized in many countries. Part of this success may be attributed to the development of new cancer agents, collectively called 'targeted therapies', that are more specific to key components of tumour growth. Worldwide, however, one of the main factors that limit patient access to these important new drugs is their cost, which is higher than traditional chemotherapy. In this review, the clinical and pharmacoeconomic data of selected targeted agents are discussed. In the second part of this article, the challenges faced by healthcare systems in making such drugs available to patients is reviewed. Current strategies used by many countries around the world to manage cancer drug budgets are presented, along with a proposed approach using pharmacoeconomic methodology that may increase patient access.

Globally, there are approximately 7.4 million cancer deaths per year, which is approximately 13% of deaths from all causes.[1] Since the population of many countries around the world is aging, it can be expected that cancer incidence will increase.[2] This is of concern to healthcare authorities because cancer is a disease that usually occurs later in life. It has been estimated that, in the US alone, 60% of all new cancers occur in people aged >65 years.[3] Cancer is now often considered to be a chronic condition because some patients with advanced stage disease can live for 5–10 years after the initial diagnosis, with effective treatment.[3,4] From the perspective of cancer care policy, these factors are causing increases in the burden of care.

Pharmacotherapy consisting of chemotherapy and hormonal agents has a central role in the management of cancer. For many years, the backbone of cancer treatment has been the use of cytotoxic agents such as anthracylines, taxanes and platinum analogues. One characteristic of traditional chemotherapy is its non-specificity to the target. As a result, adverse effects such as neutropenia, anaemia and thrombocytopenia are common.[5] However, over the past decade, there has been an emergence of new anticancer drugs that are more specific to their cancer target.[6,7] These new compounds are collectively known as 'targeted therapies'. Unlike traditional chemotherapy, which can affect both healthy and malignant cells, targeted agents are specific to the latter. Therefore, they tend to be better tolerated than chemotherapy and the adverse effects are less common.[8] One defining feature of these new targeted therapies is that their cost is higher than established chemotherapy.[9] Patient access to these new drugs has been less than optimal as healthcare systems struggle to manage their pharmacy budgets to make them available.[10] The first part of this article reviews the clinical and pharmacoeconomic data associated with key targeted agents. Agent selection was based on the impact that these drugs had on the management of their selected diseases and the magnitude of the health policy issues that they raised. In the second part of the article, the challenges faced by many countries around the world with respect to health policy and patient access to such drugs is discussed. An approach using pharmacoeconomic methodology that may increase patient access is then presented.

1. Literature Review

Two independent literature searches were conducted on PubMed, EMBASE, the Cochrane Database and Google Scholar for the years January 1995 to January 2010. The first focused on identifying the clinical and pharmacoeconomic data associated with a selection of targeted therapies currently in clinical use. The agents selected for review were rituximab, imatinib, trastuzumab, bevacizumab and cetuximab because these are high-cost targeted therapies that have faced barriers to reimbursement by government payers in many countries. While other commonly used targeted agents such as erlotinib, sorafenib and sunitinib are also important targeted therapies, they were not included in the review because our intent was to provide only a 'snap shot' of selected high-profile agents rather than a comprehensive review. For each drug, search terms consisted of 'randomized controlled trial' OR 'cost analysis' OR 'economic evaluation'. The second literature search focused on the cancer drug policy and patient access issues. Search parameters consisted of 'cancer' AND 'targeted therapies' AND 'health policy' OR 'patient access'. International media reports covering cancer drug pricing issues were also reviewed. Over 100 citations were identified and 74 papers/reports related to the selected cancer drugs or to global issues associated with drug cost and patient access.

Over the past 10 years, there have been important advances in cancer therapeutics characterized by agents that target specific components of cancer cell growth. As indicated earlier, these compounds include, but are not limited to, rituximab, imatinib, trastuzumab, bevacizumab and cetuximab and are collectively known as 'targeted therapies'. The information in sections 2–6 presents some of the important clinical and economic findings associated with these agents.

2. Rituximab

Rituximab, a monoclonal antibody, was the first targeted therapy approved in many countries

for clinical use in patients with haematological neoplasms such as lymphoma and certain types of leukaemia.[11] The target for this agent is the protein CD20, which is primarily found on the surface of B-lymphocytes associated with the above cancers.[11,12] The first major patient group that benefited from the addition of rituximab to standard chemotherapy was elderly patients with diffuse large-cell lymphoma.[12] In the pivotal study where rituximab was added to CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy (CHOP-rituximab [CHOP-R]), median overall survival was significantly improved (3.1 vs >5 years; p = 0.0073).[13,14]

Being the first targeted agent approved for clinical use, rituximab has been the subject of many pharmacoeconomic evaluations for various indications.[15-17] In one study from the French healthcare payer perspective, Best et al.[15] evaluated the cost effectiveness of CHOP-R versus CHOP alone in patients with diffuse large B-cell lymphoma. Total direct medical costs were estimated to be €13 170 higher with CHOP-R. However, when the overall survival benefit was incorporated into the analysis, the incremental cost-effectiveness ratio (ICER) was €12 259 or $US16 500 per QALY gained. The investigators concluded that the addition of rituximab was cost effective relative to other agents used in oncology.[15] Similar conclusions were also reported by other groups evaluating rituximab in some of the other approved cancer indications.[16,17]

3. Imatinib

Imatinib was the second targeted agent to be approved for clinical use worldwide. The two main disease sites for imatinib are chronic myelogenous leukaemia (CML) and gastrointestinal stromal tumours (GISTs).[18,19] The targets for imatinib are a number of tyrosine kinase enzymes, among which are ABL (the Abelson proto-oncogene), C-KIT and PDGF-R (platelet-derived growth factor receptor).[18,19] In the case of CML, imatinib works by binding to the ATP-binding site of the (BCR)-Abelson (ABL) fusion protein that results from the chromosomal abnormality known as the Philadelphia chromosome.[18] Clinical trials have demonstrated that imatinib is effective in both GIST and CML. In newly diagnosed CML patients, imatinib has demonstrated complete cytogenetic response rates of more than 80%.[18] For the treatment of advanced GIST, median overall survival was reported to be 55 months, compared with <12 months before the availability of imatinib.[19,20] Drug approval was rapidly received in the US in May of 2001 based on phase II data alone.[21] Given the impressive clinical trial results for imatinib relative to previous treatments in both disease sites, the pharmacoeconomics studies suggested that imatinib was cost effective. The costs per QALY gained were less than $US50 000 for the treatment of both CML and advanced GIST from the healthcare system perspective.[22-24]

4. Trastuzumab

Breast cancer patients with human epidermal growth factor receptor (HER)-2-positive tumours benefit from the targeted agent trastuzumab, a humanized monoclonal antibody directed against the extracellular domain of HER-2.[25] In the first randomized trial evaluating patients with metastatic breast cancer, trastuzumab combined with chemotherapy significantly prolonged both progression-free survival and overall survival when compared with chemotherapy alone.[26,27]

The evaluation of trastuzumab was then extended to patients with early-stage HER-2-positive breast cancer. Several large randomized trials have demonstrated that 1 year of trastuzumab after adjuvant chemotherapy in HER-2-positive patients was associated with a 50% relative reduction in the risk of disease recurrence.[28] After 2 years of follow-up, these findings have also translated into an incremental survival benefit of 2.7% (92.4% vs 89.7%) in favour of patients who received trastuzumab compared with those who received chemotherapy alone (hazard ratio [HR] = 0.66; p = 0.0115).[29]

The economic value of trastuzumab has been widely studied, particularly when used in the treatment of early-stage HER-2-positive breast cancer. Skedgel et al.[30] recently determined that the incremental cost per QALY gained with 1 years' treatment with trastuzumab was $Can72 292 and

$Can127 862 under a 5- and 3-year time horizon. The base-case findings were influenced by the magnitude and duration of carryover benefit associated with the drug ($Can1 = $US1 as at May 2010). In contrast, other evaluations have reported more favourable ICERs under most of the scenarios evaluated, with a range of $US5020–134 610 per QALY gained, but most were below the $US50 000 threshold.[31,32] The cause of this uncertainty could be related to the modelling assumptions used for the overall duration of benefit.

5. Bevacizumab

Blood vessels grow rapidly during tumour growth; a process known as angiogenesis. Vascular endothelial growth factor (VEGF) is a chemical signal that stimulates angiogenesis.[33] As a result, it represents a tempting target for anticancer therapy. Bevacizumab is a humanized monoclonal antibody, and the first commercially available direct angiogenesis inhibitor. It hinders tumour growth by preventing the formation of new blood vessels by targeting and inhibiting the function of VEGF.[34]

The first patient population in which bevacizumab was tested consisted of previously untreated patients with advanced-stage colorectal cancer (CRC).[35] In that first trial, 813 patients were randomized to receive chemotherapy consisting of irinotecan, bolus fluorouracil and leucovorin (IFL) with or without bevacizumab until disease progression. The median duration of survival was 20.3 months in the IFL+bevacizumab group compared with 15.6 months in the control ($HR = 0.66$; $p < 0.001$). Since the publication of the first trial, bevacizumab has shown benefit in combination with second-line chemotherapy in patients with advanced CRC.[36] The drug has also been approved by the US FDA in patients with advanced breast cancer, non-small-cell lung cancer (NSCLC), kidney cancer and glioblastoma, based on positive randomized trial results.[37-40]

The cost effectiveness of bevacizumab has been evaluated in metastatic breast cancer and CRC. Published pharmacoeconomic studies were not identified for NSCLC, kidney cancer and glioblastoma. In the case of metastatic breast cancer, a modelling study conducted in Switzerland reported that the addition of bevacizumab to weekly paclitaxel for the treatment of metastatic breast cancer resulted in an ICER of €189 427 (>$US250 000) per QALY gained versus paclitaxel alone.[41] Probabilistic sensitivity analysis demonstrated that the willingness-to-pay threshold of €60 000 was never reached. Similar conclusions were also derived when the economic value of bevacizumab was investigated for the treatment of metastatic CRC in England, Wales and Japan, with cost-effectiveness ratios ranging from $US91 000 to $US118 000 per QALY gained.[42,43]

6. Cetuximab

Cetuximab is a monoclonal antibody that binds to the extracellular ligand-binding domain and prevents epidermal growth factor receptor (EGFR) activation.[44] The drug is active in combination with chemotherapy or as a single agent in several populations, including advanced CRC, head and neck cancer, and NSCLCs.[45,46] Most recently, the drug was also found to be primarily effective in a subgroup of patients with metastatic CRC, namely those who have KRAS wild-type tumours.[47,48]

A review of the economic literature found a limited number of published pharmacoeconomic studies regarding cetuximab. The National Cancer Institute of Canada Clinical Trials Group (NCICCTG) recently reported the results of a prospective economic evaluation of cetuximab versus best supportive care in patients with chemotherapy-resistant metastatic CRC who were enrolled in a randomized trial.[49] Healthcare resources collected during the trial included all medication, physician visits, adverse effects management, the use of blood products, emergency department visits and hospitalizations. The investigators determined that the incremental cost per QALY gained with cetuximab was approximately $Can300 000. When the analysis was confined to patients with wild-type KRAS tumours, the ICER was reduced to $Can186 761 per QALY gained, suggesting improved economic value. The NCICCTG concluded that the ICER of cetuximab for this indication was high and sensitive to drug cost.[49]

Other economic evaluations have also drawn the same conclusions about cetuximab when combined with chemotherapy in metastatic CRC.[50] However, such conclusions cannot be generalized to other tumour types. A recent economic analysis[51] compared radiotherapy with or without cetuximab in locally advanced head and neck cancer. The study was conducted in Belgium, France, Italy, Switzerland and the UK using country-specific costs-of-care data. From the base-case findings, the incremental cost per QALY gained ranged from €7538 to €10 836 between the five countries.

7. Health Policy Issues in the Era of Targeted Therapies

The new targeted agents have taken patient care forward into an era of personalized medicine. However, despite their effectiveness, improved safety and cost effectiveness for some of the indications, not all cancer patients have access to them. One of the single biggest barriers to drug access is their high acquisition cost. All of these new targeted therapies have been priced at levels that are several times higher than traditional chemotherapy. In one editorial,[9] the cost of an 8-week course of chemotherapy for metastatic CRC was estimated to be less than $US300 in the mid-1990s. Ten years later, the costs for an 8-week regimen containing bevacizumab or cetuximab ranged from $US21 000 to $US31 000. These costs would be prohibitively high for most patients without good healthcare insurance. In countries with socialized healthcare systems, such drugs have either been rejected for reimbursement by national healthcare agencies, or patient access has been delayed or limited following initial regulatory approval.[10,52]

The challenge is that these incremental costs have to be considered in context with gains in overall survival and improvements in patient quality of life (QOL). In the 1990s, when fluorouracil plus leucovorin was the only active chemotherapy regimen for metastatic CRC, median overall survival did not exceed 6 months.[9] With the emergence of agents such as bevacizumab and cetuximab, overall survival in combination with first-line fluorouracil-based chemotherapy has now exceeded 20 months.[53,54] Formulary decision making can be further complicated given the design of modern randomized trials. It is often ethically mandated that patients in the control group be allowed to crossover into the experimental arm once a predefined clinical threshold in terms of progression- or disease-free survival is reached. A common impact of such crossover is contamination of the assessment of overall survival, leading to non-statistically significant differences. Therefore, the question of overall survival benefit with new agents often remains unknown, thereby complicating the associated economic analysis.

Notwithstanding this, as a society we must determine what we are willing to pay for advances in cancer care. This is one of the most difficult questions for any national cancer programme to address. There are a few countries, such as the UK, that have stated what they are willing to pay for a (quality-adjusted) life-year gained.[55] However, many nations have been reluctant to publicly state such a figure because of the ethical issue of placing a monetary value on human life.

Most developed countries spend 5–14% of their GDP on healthcare. Governments and national advisory bodies need to determine a reasonable amount that should be spent on cancer care given the burden of illness. Wilking and Jonsson[56] estimated that cancer accounts for 16.7% of all disability-adjusted life-years (DALYs) lost, with only mental health disorders and cardiovascular disease surpassing it. Considering 19 European countries, direct cancer-related expenditures were responsible for only 6.4% of total healthcare costs.[9] Cancer drugs were responsible for approximately 10% of total oncology healthcare costs. In the US, resource allocation was somewhat lower, with 4.7% of the 2004 overall healthcare budget dedicated to cancer.[57] It was also interesting to note that, in the US, absolute cancer-related expenditures rose from $US1.3 billion in 1963 to $US72.1 billion in 2004. However, the proportion dedicated to cancer remained between 4% and 6% over the 40-year period.[57] Hence, there was a large absolute increase in cancer expenditures, but relative costs remained constant. Considering the total impact of the

disease on society, there does appear to be an imbalance in overall resource allocation for cancer.

A discrepancy in cancer spending relative to the burden of disease is also suggested by the rate of patient access to new cancer drugs. In their review of drug access in Europe, Wilking and Jonsson[52,56] determined that new cancer drugs accounted for 51% of total drug sales from 1993 to 1998. However, from 1999 to 2004, new cancer drugs accounted for only 17% of total drug sales, a marked decrease from the previous 5-year period. Increasing oncology drug costs are likely a major contributor to the reduction in new drug uptake. Between 1993 and 2004, total European sales for oncology drugs increased from €840 million to €6170 million.[56] Similar trends have also been reported in the US, where cancer drug expenditures increased from $US3 billion in 1997 to $US11 billion in 2004.[57] It was also reported that over 90% of FDA new cancer drug approvals in the last 4 years have costs that exceed $US20 000 for a 12-week course of therapy.[58] Therefore, it is easy to see how the debate over investment in cancer care can shift to drug cost containment.

To address rising drug costs, countries have responded in different ways, with the intention to contain growth. The UK, Canada and Australia have used cost effectiveness through agencies such as the UK National Institute for Health and Clinical Excellence (NICE), the Pan Canadian Oncology Drug Review Program and the Australian Pharmaceutical Benefits Advisory Committee as a mechanism to limit or deny drug access.[57] Numerous other countries in Europe also consider cost-effectiveness data to some degree. In the US, where a national health technology agency to oversee new drugs does not exist, drug access is sometimes rationed by the creation of high patient co-payments in some private drug plans.[59] Both systems can act as a barrier to patient access from the time of regulatory approval. Therefore, the challenge for national governments is to determine how much of the healthcare budget to allocate for cancer, what portion, if any, should be borne by the patient and what is the minimum value that should be offered by a new cancer drug.

8. The Role of Pharmacoeconomics in Oncology

What is evident over the past 20 years is an increase in the number of cancer-related economic evaluations and health technology assessment (HTA) reports appearing in the medical literature.[56] Pharmacoeconomic evaluations are an important component of the overall process of formulary decision making.[55] However, they may have an additional and perhaps more valuable role in estimating or negotiating the cost of the drug based on societal value thresholds. Pharmacoeconomics has been used in this role for a few cancer drugs assessed by NICE for the English NHS. NICE was able to secure price reductions from manufacturers of erlotinib, lenalidomide and sunitinib based on cost effectiveness.[60] However, what has not been extensively examined is the estimation of drug price before a product receives regulatory approval.

There is one example in the cancer supportive care literature where decision analysis modelling was used to estimate drug cost before the product was launched. In that study, Dranitsaris and Leung[61] sought to estimate a unit cost of an orally administered neurokinin (NK)-1 receptor antagonist, a new class of drugs indicated for the prevention of chemotherapy-related emesis. Clinical data on emesis control were obtained from a randomized phase II trial that evaluated emesis rates following the addition of an investigational NK-1 antiemetic (by mouth twice daily) for 5 days to a control group (a single dose of granisetron and dexamethasone before cisplatin-based chemotherapy). Costs were obtained from a Canadian cancer centre, and health state utilities for the various health outcomes associated with emesis control were collected from a sample of oncology nurses. The product had not been approved for clinical use, so the investigators developed a decision analysis model to estimate a unit cost for the drug using a predefined threshold of $Can20 000 per QALY gained as the measure of 'good value for money'.[62]

The findings suggested that the product would have a cost per QALY gained at the $Can20 000 threshold if it were priced at $Can6.60 per dose,

or $Can13.20 daily (year 2003 values).[61] In hindsight, there are some important limitations to this study. The threshold for economic value at $Can20 000 per QALY gained is unrealistically low in the current oncology setting. Furthermore, it could be argued that value thresholds for supportive care agents should be lower than for drugs that improve survival because gains in life-years tend to have a larger impact on the overall cost per QALY calculation.

Nevertheless, the study did demonstrate that a systematic process could be used to estimate a reasonable range of prices before a product becomes commercially available. The advantages of this technique are that it is relatively straightforward to perform, is transparent and the decision model can be easily applied to other jurisdictions such as lower income countries using local cost data and thresholds for economic value. Such information can be of value to both drug manufacturers and formulary committees because it would facilitate negotiations for identifying an optimal price for a given jurisdiction.

8.1 Defining Value

Value represents a composite measure of drug utility consisting of clinical, economic and QOL-related attributes. Although it is an imperfect measure, the QALY as part of the ICER analysis attempts to incorporate all three of these product attributes into a single outcome. One of the major challenges against the use of pharmacoeconomic modelling for estimating a drug cost before product launch is in establishing the threshold for value within a given country. As an illustration, the UK NICE has established a threshold for drug coverage at £30 000 per QALY gained.[55] In the Netherlands, the unofficial threshold is €18 000 per QALY.[56] In many other jurisdictions a $US50 000 cost per QALY threshold has been used,[62] which was based on a 1982 valuation and is now equivalent to approximately $US197 000 per QALY in year 2007 values (after a 5.5% annual adjustment in healthcare inflation).[63] However, the $US50 000 threshold continues to be used and quoted in the pharmacoeconomic literature. One approach to address this dilemma would be for formulary committees to establish their own local thresholds for accepting new drugs through a review of their national human life valuation literature or through the use of focus groups involving the key stakeholders.

Notwithstanding this, a key problem in using such thresholds is that the wealth of an individual country is not taken into consideration. To address this, the WHO has proposed to use multiples of a country's per capita GDP to establish thresholds for economic value.[63-65] Products less than or equal to the per capita GDP would be considered very cost effective, one to three times would be cost effective and more than three times would be cost ineffective.[63] Using South Africa as an illustration (i.e. per capita GDP = $US10 000), the three-time threshold for cost effectiveness of new anticancer drugs would be approximately $US30 000 per QALY gained.[66] For a lower income country such as India (per capital GDP = $US3000),[66] the cost per QALY gained threshold would be $US9000. In contrast, the threshold for economic value for a high-income country such as Norway would be $US150 000 per QALY gained.[66] Therefore, the cost for the same drug would be proportionally less in India, higher in Norway and intermediate in South Africa.

The use of thresholds based on per capita GDP in combination with pharmacoeconomic modelling to establish a value-based price for a new drug is an intriguing approach and could set the foundation for improving global patient access because wealthier nations would be expected to pay more for drugs and would subsequently subsidize the developing world. However, this approach would only be applicable in countries that have socialized healthcare systems and would also depend on the manufacturer's willingness to launch their product in less developed countries.

9. Improving Patient Access to New Cancer Drugs: Current and Future Strategies

Over the last decade, the number of new cancer patients has continued to rise.[3,4] But more encouragingly, the number of cancer-related deaths

Table I. Number of new cases and deaths in selected cancers 2002–6 (adapted from Stark,[67] with permission)

EU25 + CH + IS + NO and events	2002 (n)	2006 (n)	Change (%)
All cancers except skin			
Cases	2 138 700	2 351 100	9.93
Deaths	1 188 100	1 192 500	0.37
Breast			
Cases	277 300	328 600	18.51
Deaths	89 900	87 200	–2.97
Colorectal			
Cases	283 600	307 000	8.27
Deaths	142 400	142 700	0.20
Lung female			
Cases	60 500	73 500	21.46
Deaths	54 300	65 800	21.11
Lung male			
Cases	199 900	198 100	–0.86
Deaths	182 100	175 200	–3.80
Prostate			
Cases	201 700	311 100	54.25
Deaths	69 300	70 300	1.48
Stomach			
Cases	92 200	81 600	–11.46
Deaths	70 200	58 400	–16.76
Uterus			
Cases	85 900	84 900	–1.17
Deaths	26 700	24 200	–9.49

CH = Switzerland; **EU25** = 25 European countries; **IS** = Iceland; **NO** = Norway.

has stabilized over the same time period (table I). At least part of this reduction in cancer-related mortality has been attributed to new cancer drugs such as the ones described in this review.[14,20,28] The initial success of these targeted therapies will ensure the continued development and approval of more such agents. Therefore, the combination of more patients alive with cancer and more new cancer drug approvals will continue to elevate total drug expenditures.

Rising drug costs should also be of concern to the pharmaceutical industry and other key stakeholders because they are easily identifiable by government agencies with a mandate to reduce costs. Governments may mandate price controls on the pharmaceutical industry in order to contain drug expenditures. This has recently been the case in Europe. At the time of writing of this article, Greece and Spain have mandated price cuts of up to 23% for branded products.[68,69] The German Government has followed a similar example, where healthcare plans will now be allowed to negotiate a discounted price for the product after the first year.[70] As part of the new law, discounts of up to 16% will take effect, as will a ban on price increases for branded products. The final negotiated discounted price will be based on the benefits offered by the product. Therefore, the intent is to make economic evaluations an integral part of price negotiations with manufacturers.[70]

These developments were foreseen by Dr Steve Harr, a Morgan Stanley research analyst who warned the pharmaceutical industry in 2005 that excessive drug costs could be bad for business because they could trigger government controls, hurting the industry in the long term.[71] Dr Harr stated that "soaring cancer-drug prices, generating fat profit margins, aren't sustainable."[71] Some large pharmaceutical companies did heed Dr Harr's advice and have implemented price caps and patient assistance programmes for some products in order to avoid price controls. As a recent example, AstraZeneca fixed the UK price of gefitinib at £12 200, irrespective of the duration of treatment, and there will be no charge for patients who are treated for less than 3 months.[72]

In addition to price cap programmes that limit drug expenditures and improve access, risk-sharing partnerships between the pharmaceutical industry and national healthcare systems may also improve patient access to innovative new treatments.[73] However, such agreements need careful planning before implementation. In a recent article by Towse and Garrison,[74] key factors associated with the success of risk-sharing agreements were discussed. For risk-sharing agreements to become more prevalent with high-cost pharmaceuticals, a workable process for collecting post-launch effectiveness data must be developed and adequately funded, and a binding contract between the payer and the pharmaceutical company must be created to address issues such as drug price adjustments and rebates following the availability of new post-launch evidence. Towse and Garrison[74] indicated that risk-sharing

partnerships are, in principle, attractive options that may increase patient access to new drugs and help contain costs. However, until more evidence is collected from the current programmes, it will be difficult to determine if they will represent a real solution to challenges in drug access.

A final approach that may help contain costs, enhance outcomes and facilitate the appropriate access of cancer drugs is better patient selection. For example, the therapeutic benefit of cetuximab appears to be limited to CRC patients with KRAS wild-type tumours, which make up approximately 60% of the CRC population.[47,48] Limiting cetuximab to KRAS wild-type tumours will help contain costs and ensure that the drug is being used in those patient subgroups where the economic value is optimized.

Notwithstanding this, improved drug access should not be limited to patients in wealthy nations but rather a goal that is extended to all societies globally. There is an obvious concern that new targeted therapies are beyond the financial means of patients in the developing world. One approach that could address this need would be to use the pharmacoeconomic modelling techniques described earlier along with the value thresholds proposed by the WHO (i.e. less than three times the per capita GDP) to estimate a value-based drug price for lower income countries prior to its introduction. The pharmaceutical manufacturer would then launch at the lower price on the strict and enforceable condition that the drug will not be exported to a wealthier nation (i.e. the phenomenon know as parallel trade) by an intermediary for the intention of profit making. For instance, parallel trade could be addressed through a centralized single-source drug distribution process, along with a preauthorized list of prescribers.

Reducing drug prices to lower levels would improve patient access in less developed countries. However, central to the pricing debate and the issue of increased access is the matter of commercial viability based on the manufacturer's cost of goods and operational overhead expense. It is unclear whether manufacturers would realize greater short-term benefit from a scenario in which the drug is sold at a high price to a few people, versus one where the drug is sold at a lower cost but to a much larger group of people. However, in the long term, it seems likely that pharmaceutical manufacturers will have to adapt their business models to better address the unmet needs of developing countries where high-volume, low-price therapies will predominate.

10. Conclusions

The new targeted therapies have contributed to an important advance in cancer care. However, the high costs of these drugs are limiting patient access in many parts of the world. Therefore, a new paradigm needs to be developed in collaboration with all of the key stakeholders. The new system must reward drug innovation, enhance global patient access and, above all, be sustainable. The application of pharmacoeconomic modelling techniques in combination with value thresholds based on the wealth of a nation is one approach that may contribute to enhanced patient access.

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3.2 International drug pricing issues

NICE of the UK has taken a leading role in indirect price negotiations with drug manufacturers. NICE has been very active in the development of patient access schemes that have effectively resulted in price reductions, while leaving the list price untouched. As an illustration, AstraZeneca fixed the price of gefitinib at 12,200 GBP, irrespective of the duration of treatment, and there will be no charge for patients who are treated for less than three months (NICE, 2010). From the manufacturer's point of view, retaining the list price of a drug has important implications across Europe.

In the pharmaceutical industry, parallel trade occurs when drug prices are highly variable between countries because of price regulation. In these situations, a wholesaler in a lower price country would be able to achieve a better price by selling the product "in a high-price country" rather than on the domestic market of the original country. As an illustration, prices of branded drugs in Greece tend to be the lowest in the European Union. Therefore, a wholesaler in Greece would be able to buy a drug at a lower price and then sell it at a substantial profit in Germany, where drug prices tend to be the higher (Arfwedson, 2004). Parallel trade is of concern to the pharmaceutical industry because it can have a major effect on profits. But more importantly, parallel trade also undermines intellectual property and can act as a disincentive for investment in research and development. The consequences of parallel trade could hurt patients in the long term because it curtails innovation. Therefore, the pharmaceutical industry strives to maintain comparable drug prices across Europe. As a result, the patient access schemes negotiated by NICE on behalf of the National Health Services do not affect the list price of the drug.

The third factor that could have an impact on global drug prices is the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS). This is an international agreement that establishes minimum standards for all forms of intellectual property, including pharmaceuticals. TRIPS requires member states to provide strong protection for intellectual property rights (WHO, 2000). However, disagreements can develop. The most prominent conflict in the case of pharmaceuticals has been with the selling of AIDS drugs in Africa at prices comparable to Western countries. African governments would not afford to pay higher prices and this led to an international outcry by patient advocacy groups. Eventually, there was a loosening of the agreement which allowed countries to export life-saving drugs to developing countries at a lower cost in times of a national health care crisis. Alternatively, TRIPS allows the government of the country in need to issue a compulsory license, which would enable local production of the patented drug (Shashikant, 2005). This has already occurred with some AIDS drugs and may be extended to cancer products is the launch prices are deemed excessive by a national government. Therefore, the pharmaceutical industry needs to exercise care in establishing the launch price in a less developed country. Early dialogue under the framework of a “fair” and “affordable” price is encouraged to avoid local manufacturing of a new and clinically important cancer drug.

3.3 Conclusions

The literature review provided evidence to support the clinical use of selected targeted therapies. However, clinical efficacy does not necessarily translate into cost effectiveness. As highlighted in the review article, several of the drugs, particularly bevacizumab and cetuximab which are both approved for use in mCRC, have been shown through PE studies to be cost ineffective (Tappenden et al., 2007; Mittmann

et al., 2009). The primary driver behind such conclusions has been the high price of these agents, which is several times higher than traditional chemotherapy (Schrag et al., 2004). The impact of these high prices has been to deny or limit patient access to these important agents because national health care systems around the world are refusing to reimburse (NICE, 2010). This is unacceptable for patients, but the challenge is to determine a final drug price that offers value and is affordable to a national health care system. Therefore, a new paradigm needs to be developed that is transparent and potentially acceptable to all of the key stakeholders. The new system must reward drug innovation, enhance global patient access and above all be sustainable. The application of PE modeling techniques in combination with value thresholds based on the wealth of a nation is one approach that may contribute to enhanced and sustainable patient access.

CHAPTER 4

FORMULARY DECISION MAKING IN THE ERA OF TARGETED THERAPIES

4.1 Introduction

Drug formulary committees worldwide face tremendous challenges associated with the high cost of the new targeted anticancer agents. They must identify strategies that will make these drugs available to patients within the confines of a limited drug budget. The chapter begins with a presentation of trends in global health care expenditures with a focus on the rising cost of pharmaceuticals. The impacts of these trends are illustrated followed by a discussion on how governments around the world have responded. The chapter also describes the role of health technology assessment in deciding on which cancer drugs to add to a national drug formulary. The concept of pharmacoeconomics and how it is applied to the field of oncology in then presented. A definition of the concept of "value", as how it relates to reimbursement decisions for oncology drugs is then provided.

4.2 The rising cost of pharmaceuticals

Total spending on pharmaceuticals has been increasing rapidly, well beyond the rate of inflation (Orszag and Ellis, 2007; Jackevicius et al., 2009). In many countries, drug expenditures in general have also outpaced total health care spending and higher drug prices have been a contributing factor (Figure 4.1) – (Organization for Economic Co-operation and Development, 2005). Contributing causes include an ageing population, a more aggressive treatment culture, availability of more effective and higher priced drugs that have replaced medical procedures previously requiring hospitalization and increased use of preventive medicines (Hoffman et al., 2009; Guo et al., 2008). Rising drug costs have now become a global concern as

institutionalized health care systems struggle to offer modern treatments within limited budgets. Some view this as threatening the health care systems that are integral to the modern social contract (Prescribing Caution, 2005).

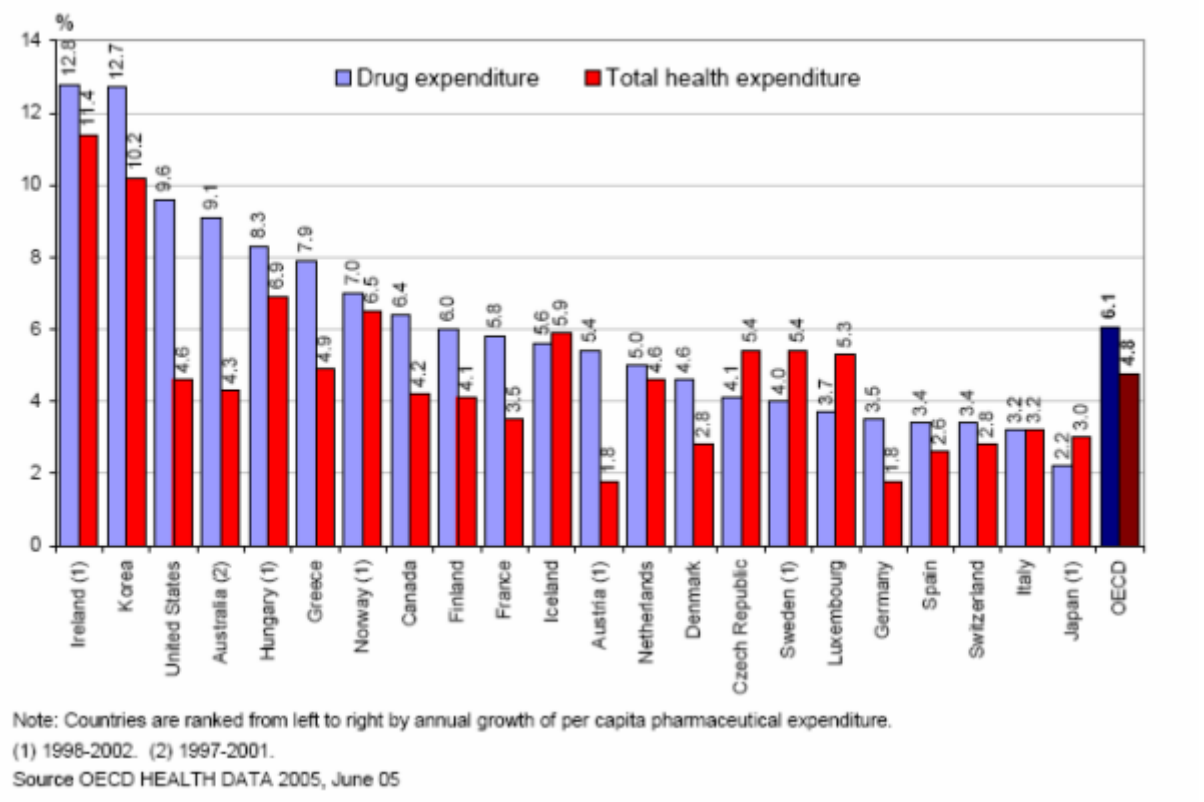

Figure 4.1. Annual growth in drug and total health care expenditures: 1998 to 2003

The main components of health care costs consist of expenditures for hospitals, physician fees and pharmaceuticals. Of these, curtailing spending on drugs is the easiest and perhaps most politically acceptable target for cost containment initiatives. Many reasons are offered for the mounting political and fiscal pressure being brought to bear: high prices, opaque processes for the evaluation of pharmaceutical efficacy, shoddy or biased research, a culture that emphasizes marketing over efficacy and safety, and too close relations between regulators

representing the public interest and the corporations that they regulate. At root, the key unknown is the overall value that a new drug offers society.

To address rising drug costs, nationalized health care systems have responded in different ways. The United Kingdom (UK), Canada and Australia have used cost effectiveness ratios developed by agencies such as the National Institute of Clinical Excellence (NICE), the Pan Canadian Oncology Drug Review Program and the Australian Pharmaceutical Benefits Advisory Committee as a basis to limit or deny access to underperforming drugs (Wilking and Jonsson, 2005). Several other European countries also consider cost effectiveness data to some degree. In contrast, the United States the Agency for Healthcare Research and Quality does not possess direct influence on formulary listing decisions. However, drug access is sometimes managed by the creation of payment tiers shifting more of the cost of expensive drugs to the patient in commercial and government drug plans (Faden, 2009).

Risk sharing programs where national health care systems only reimburse drug costs for patients responding to treatment are also being created (de Pouvourville, 2006). As a recent example, AstraZeneca recently fixed the price of the anticancer agent gefitinib at 12,200 GBP, irrespective of the duration of treatment, and there will be no charge for patients who are treated for less than three months (Church, 2010). Other examples of cost containment strategies include price cap schemes that limit annual expenditures for certain high cost drugs and, in a more positive light, the use of validated predictive markers (such as the human epidermal growth factor receptor-2 for trastuzumab) where the drug is reimbursed in specific patient subgroups who are most likely to derive optimal benefit (Piccart-Gebhart et al., 2005). Such initiatives have helped to reduce drug expenditures, but demographics

have caused absolute drug expenditures to continue to rise (Dranitsaris et al., 2011).

As an immediate response, several countries in Europe have now mandated price controls. In Spain and Greece, the respective governments recently announced price cuts of up to 30% of branded products (Spain announces big price cuts, 2010; Greece price cuts, 2010). Annual drug expenditures in Spain were approximately 12.5 billion euros in 2009, a 4.4% increase from the previous year. Therefore, it was projected that these price cuts would save the national health care system 1.3 billion euros. France has also announced drug funding restrictions for both brand and generic products (FiercePharma, 2010).

Government mandated cuts of branded drugs do not serve patients in the long term because such actions will only serve as a disincentive for pharmaceutical companies to invest in new drug discovery. Furthermore, companies may withdraw their products and choose to not launch new drugs in the future. All of these factors will further limit patient access to new agents. A better alternative to such actions would be to set product price based on several factors such as performance under a controlled clinical trial setting, a nation's ability to pay a price premium for exceptional products, how uniformly income is distributed within a given country, and the overall cost effectiveness of the product measured against some reasonable societal value threshold. A review of the oncology literature has revealed that such alternatives encompassing all of these factors have not been explored.

4.3 Formulary approval of new drugs to treat cancer

Once a cancer drug receives regulatory approval, a process of formulary decision making is initiated in most developed countries. For a product to receive reimbursement, it must be seek approval for formulary entry at a national or regional

level. This process involves a review of the safety and efficacy data and an assessment of the product's budget impact. In some jurisdictions such as the United Kingdom, Canada, Australia and several countries in Europe, a health technology assessment (HTA) with an associated pharmacoeconomic (PE) evaluation is required (Figure 4.2) - (National Centre for Pharmacoeconomics, 2011). For products to achieve formulary access, the HTA process must confirm/verify safety and efficacy against the current standard of care and the PE evaluation must verify the products cost effectiveness (Drummond et al., 2007; Wilking and Jonsson, 2007). Products deemed by the HTA authority to be cost ineffective usually receive a negative recommendation for formulary listing (Drummond et al., 2007; Wilking and Jonsson, 2005).

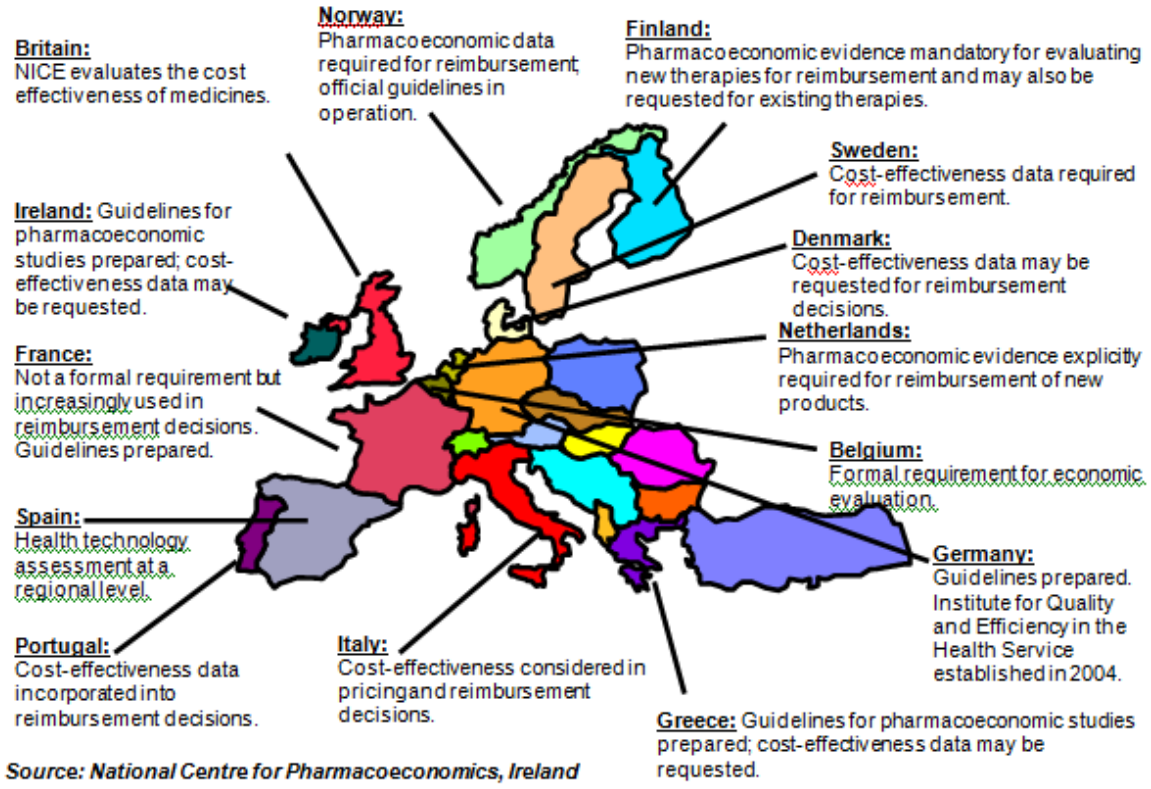

Figure 4.2. The role of pharmacoeconomic evaluations in Europe on 2011, Source: National Centre for Pharmacoeconomics, Ireland, 2011.

There are several agencies around the world that are actively involved in performing PE evaluations as part of a formal HTA process in order to provide advice on new oncology products. An HTA database maintained by the Swedish Council of Health Technology Assessment was reviewed to determine changes in the number of annual HTA reports related to cancer (Wilking and Jonsson, 2007). What has been evident over the past 20 years was the sharp increase in the number of cancer related economic evaluations appearing in the medical literature. In 1991, there were no cancer related PE publications contained within the HTA database. However by 2005, there were no cancer related HTA reports added to the database (Figure 4.3).

It is also interesting to note that a majority of the publications were from the United Kingdom, Canada, the Netherlands, Sweden, and Australia; countries where a full economic analysis is required before a reimbursement decision for a new drug is made (Wilking and Jonsson, 2007; Ganfi et al., 2003; Glennie et al., 1999). Since the targeted therapies are available at costs substantially higher that traditional chemotherapy, HTAs and associated PE evaluations are now routinely undertaken (Dranitsaris et al., 2011).

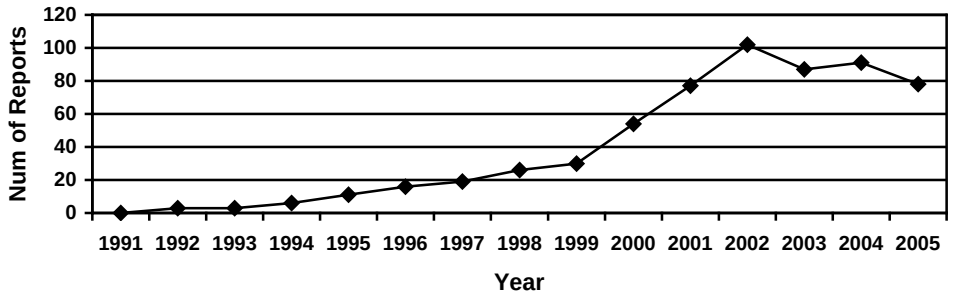

Figure 4.3. Number of cancer health technology assessment reports from 1991 to 2005 (Wilking and Jonsson, 2005)

4.4 The role of pharmacoeconomics in oncology

During the formulary decision making process, drug cost is an important factor. Cost, however, is a crude measure of the value of a new anticancer drug. A comprehensive PE study is warranted before a new agent becomes available for clinical use. The basic premise of PE evaluations is to compare the costs and consequences of alternative pharmaceutical interventions, and to determine which treatment offers the best value for limited resources. There are four mains types of PE evaluations: (1) cost-benefit analysis (CBA) expresses years of life gained in monetary terms; (2) cost-minimisation analysis (CMA) compares costs of competing strategies which yield the same clinical outcomes; (3) cost-effective analysis (CEA) determines a ratio of cost to effectiveness (measured on some natural unit such as life years gained), and is expressed as dollars per outcome gained; (4) cost-utility analysis (CUA) compares quality-adjusted life-years (QALYs) gained with incremental costs of two competing interventions (Drummond et al., 2005).

With respect to oncology drugs, CUA can be complex but is the most common method used because it considers cost, overall survival and quality of life differences between two competing therapies (Goodwin et al., 1998, Canadian 2006). Once the analysis is completed, the outcome of a CUA is an incremental cost per QALY gained when one treatment is used in place of another. At this point, a formulary committee needs to make a value decision on the final incremental cost per QALY ratio. If the reported incremental cost per QALY ratio is acceptable relative to a pre-established benchmark for economic value, then the product can be added to the drug formulary (Hillner and Smith, 2009).

4.5 Estimating drug price with pharmacoeconomic modeling

PE evaluations provide an important component to the overall process of formulary decision making. However, they may have an additional and perhaps more valuable role in estimating or negotiating a drug price with manufacturers based on societal value thresholds. PE has been used in this role for a few cancer drugs assessed by NICE of the United Kingdom. NICE was able to secure price reductions from manufacturers for the cancer drugs erlotinib, lenalidomide and sunitinib based on cost effectiveness thresholds and PE modeling (Church, 2009). However, what has not been extensively examined is the estimation of drug price before the product receives regulatory approval.

There is a single example in the cancer care literature where PE modeling was used to estimate drug price before a product was approved by regulatory authorities. In that study, Dranitsaris and Leung sought to estimate a unit price of an orally administered neurokinin-1 (NK-1) receptor antagonist, a new class of drugs indicated for the prevention of emesis from chemotherapy (Dranitsaris and Leung, 2004). Clinical data on emesis control were obtained from a randomized phase II trial which evaluated emesis rates following the addition of an investigational NK1 antiemetic (by mouth twice daily) for 5 days to a control group consisting of a single dose of granisetron and dexamethasone before cisplatin-based chemotherapy. Cost was obtained from a Canadian cancer centre, and health state utilities for the various health outcomes associated with emesis control were collected from a sample of oncology nurses. The product had not been approved for clinical use, so the investigators developed a decision analysis model to estimate a unit price for the drug using a predefined threshold of $Can 20,000 per QALY gained as the measure of "*good value for money"* (Dranitsaris and Leung, 2004).

The findings suggested that the product would have a cost per QALY gained at the $Can 20,000 threshold if it were priced at $Can 6.60 per dose, or $Can 13.20 daily (2003 Canadian dollars). In the sensitivity analysis, the unit price of the new antiemetic could increase to $Can 20.32 per dose if the granisetron and dexamethasone prophylaxis were extended to three days post chemotherapy (that is, the standard of care). In hindsight, there are some important limitations to this study. The threshold for economic value at $Can 20,000 per QALY gained is unrealistic in today's oncology setting, and the phase II randomized trial did add the investigational NK-1 antagonist to an appropriate duration of granisetron and dexamethasone treatment. Nevertheless, the study did demonstrate that a systematic process could be used to estimate a reasonable range of prices before a product becomes commercially available. The advantages of this technique are that it is relatively straightforward to perform, transparent and the decision model can be easily applied to other jurisdictions using local cost data and thresholds for economic value. Such information could be used by drug manufacturers and formulary committees to facilitate negotiations for optimal pricing in a given jurisdiction.

4.6 Defining value

One of the major challenges against the use of PE modeling for estimating drug price is in establishing the threshold for value within a given country. As an illustration, NICE of the United Kingdom has established the threshold for drug coverage at £30,000 per quality adjusted life year (QALY) gained (Drummond et al., 2007). In the Netherlands, the unofficial threshold is € 18,000 per QALY (Wilking and Jonsson, 2005). In many other jurisdictions, a $ 50,000 cost per QALY threshold has been used (Laupacis, 1992), based on a 1982 valuation for renal dialysis, which is now equivalent to approximately $ 197,000 per QALY in 2007 U.S. dollars (after a

5.5% adjustment in health care inflation) – (Hillner and Smith, 2009). One approach to address this dilemma would be for formulary committees to establish their own local thresholds for accepting new drugs through a review of their national human life valuation literature.

Notwithstanding, a key problem in using any such thresholds is that the wealth of an individual country is not taken into consideration. To address this, the World Health Organization (WHO) has proposed to use multiples of a country's per capita gross domestic product (GDP) to establish thresholds for economic value (Hillner and Smith, 2009; Murray et al., 2000; Sarin, 2008). Products less than or equal to the per capita GDP would be considered very cost effective, one to three times would be cost effective and more than three times would be cost ineffective (Hillner and Smith, 2009). Using South Africa as an illustration (that is, per capita GDP = $US 10,000 or R 71,000), the three time threshold for cost effectiveness of new anticancer drugs would be approximately $US 30,000 per QALY gained (World Fact Book, 2010). For a lower income country such as India (per capital GDP = $US 3,100), the cost per QALY gained threshold would be $US 9,300. In contrast, the threshold for economic value for a high income country such as Norway would be $US 150,000 per QALY gained. The use of thresholds based on per capita GDP with PE modeling to establish a value-based price for a cancer drug is novel because it incorporates product attributes such as disease response, survival, quality of life improvements and of equal importance, a country's ability to pay.

4.7 Current models for drug pricing

Before applying PE modeling for estimating a cost effective drug price, it is important to understand the techniques that pharmaceutical companies use determine a final drug price. This is a difficult undertaking because drugs are not like

consumer goods. Patients often receive their medication through a hospital or in a retail setting, and the prescriber is usually not involved in the financial transaction. Hence, the prescriber often does not know the acquisition cost of the drug. Pharmaceuticals are also considered to be “negative goods” because in many cases, the patient would rather not take the drug and the rationale or necessity for the prescription administration is often unknown (Kolassa et al., 2009). In addition, the patient may not recognize or gain satisfaction from health status improvement when a drug’s effectiveness pertains to ‘silent killers’ such as hypertension or hyperlipidemia. These and other factors supposedly lead to pricing “models” for pharmaceuticals that are very different than those used for other consumer goods such as cars and television sets.

The process of drug pricing is complex and involves multiple steps such as identification of the product’s value proposition, creation of financial models outlining the burden of disease, assessment of the reimbursement environment, willingness-to-pay thresholds with payers and prescribers in the market place and the development of an overall pricing strategy for the life cycle of the product (Nagle et al., 2011; Kolassa et al., 2009). This approach is sound in principle, yet may lead to a price that is not acceptable to payers because it may be considerably higher relative to the current standard of care, without clear evidence of substantial clinical benefit.

To apply current pricing models, data about perceived value are collected through willingness to pay surveys or conjoint analyses involving patients, payers or physicians (Kolassa et al., 2009). However, willingness to pay surveys determine price points and measure intention but do not necessarily reflect the actions patients or payers will take when ultimately faced with the decision. Respondents in such surveys often involve physicians, who are often far removed from the decision to add

the drug to the formulary or to purchase it. Patients and payers may also consider different product value attributes to those of physicians. As an illustration, patients may place higher value on an oral agent versus an intravenously administered drug because the former avoids a visit to the physician's office. In contrast, physicians practicing in the United States may place a higher value on the intravenous product if it translates into rapid symptom control coupled with increased revenue for which they can bill.

Pharmaceutical companies also develop return on investment (ROI) models to determine a final launch price of a product (Nagle et al., 2011; Kolassa et al., 2009). Time-to-market greatly affects ROI models because they are based on the long and expensive pre-market investment period, followed by a relatively short period of revenue generation, which has been estimated to be 12 to 13 years (Scherer, 2004). Patent life is typically 20 years from the time of filing a submission, which is usually done before clinical testing on humans begins. All of these factors tend to drive the launch price of a product upwards as the industry attempts to maximize revenue within a shortened commercialization period. This is often done without extensive consideration of the value that a new drugs offers in terms of improved efficacy, overall survival and reduction of downstream health care costs (Schrag, 2004; Fojo and Grandy, 2009). Furthermore, the current pricing models do not routinely consider the wealth of a nation, or the extent of income dispersion among the population. The net impact of these factors has been to increase in the price of drugs, particularly for diseases such as cancer (Schrag, 2004). Therefore, new approache that a linked to product performance, economic efficiency and a country's ability to pay premium prices are needed for estimating the launch price of new drugs.

4.8 Conclusions

The new targeted therapies have contributed to an important advance in cancer care. However, their high costs are limiting patient access as health care systems around the world attempt to contain rising health care expenditures by limiting or rejecting the use of new agents. Therefore, a new paradigm for determine a fair value based drug price is needed, which can then be the starting point for initiating dialogue between the key stakeholders. The new system must reward drug innovation, enhance global patient access to important agents and above all be sustainable. The application of PE modeling techniques in combination with value thresholds based on the wealth of a nation is one approach that can be used to estimate a final drug price. In this study, PE modeling techniques were used to create a value based pricing index for new drugs in mCRC. It was created from data collected in Canada, Spain, South Africa, Malaysia and India. The final index could then be used to estimate appropriate drugs prices based on societal value thresholds, the survival benefit offered by a new drug, per capita GDP and income dispersion for a given country.

CHAPTER 5

RESEARCH METHODS

5.1 Introduction

This chapter presents the methodology used to undertake the study and meet the overall objectives. This includes a description of the reference countries, the development of the PE model that was used to undertake the analysis, the source of the clinical, utility and economic data that was used to populate the model in each country and the value thresholds that were used to estimate a value based price for each of the reference countries. The final part of the methods section describes the statistical techniques that were used to develop the value based pricing index for new drugs in mCRC.

5.2 Reference countries

Data were collected from the following five countries: Canada, Spain, South Africa, Malaysia and India with the per capita GDPs ranging from $US 39,000 to $US 3,100 (R 286,000 to R 22,000) respectively (see Table 5.1). Country selection was based on both cultural factors such as religion/beliefs about health, economic considerations (that is, the GDP per capita) and the type of health care system employed (only public versus a mix of public and private). With the range of per capita GDPs being from $US 3,100 to $US 39,000, approximately 140 countries worldwide would be encompassed thereby expanding the potential application of the pricing index (World Fact Book, 2010).

Table 5.1. Description of reference countries

Country	Population	GDP per Capita[1,2,4] ($US)	Gini Coefficient[2]	Health Care System
Canada	33 million	$ 39,000 (R 286,000)	32.6	Public only
Spain	45 million	$ 35,000 (R 257,000)	34.7	Public-private mix
Malaysia	28 million	$ 14,800 (R 105,080)	49.2	Public-private mix
South Africa	49 million	$ 10,000 (R 70,600)	57.8	Public-private mix
India	1.1 billion	$ 3,100 (R 22,000)	36.8	Public-private mix

[1]The World Fact Book, 2010. [2]The cost per QALY value threshold for estimating a value based price for that country was three times the per capita GDP for that country.
[3]The Gini coefficient is a measure of income dispersion. A value of 0 represents absolute equality, and a value of 100 is absolute inequality (De Maio et al., 2007). [4]$1U.S. = R7.10, as of December, 2010.

5.3 Cost utility analysis

There are multiple PE methodologies such as cost minimization, cost benefit and cost effectiveness analysis available and some are more appropriate than others for a given drug. With respect to oncology products, cost utility analysis (CUA) can be complex but is the most common method used because it considers cost, overall survival and quality of life differences between two competing therapies (Goodwin, 1998). In contrast, cost minimization analysis (CMA) is a simpler approach for measuring the economic value of alternative cancer therapies. The primary requirement for a CMA is that all clinical outcomes such as overall survival, drug toxicity and quality of life (measured as health state utilities) be equivalent (Drummond et al., 1995). However, such occurrences are uncommon in oncology. Two drugs, even with equivalent survival often have differences in safety and methods of administration, the most inconvenient of which affects patient preferences and utilities.

Therefore, the clinical, economic and respondent utility data collected in each country were combined for a CUA comparing the cost effectiveness of a hypothetical "new drug" when added to the standard chemotherapy for mCRC to chemotherapy alone over a range of gains in overall survival relative to a series of drug prices. This approach is sound and has been successfully used by the candidate in the estimation of optimal drug price before the launch of a product that is now comerically available (Dranitsaris and Leung, 2004). Therefore, the analysis allowed the estimation of a unit price for a targeted cost per QALY gain.

5.4 Pharmacoeconomic model development

mCRC was chosen because several new anticancer agents have been approved in this disease site but their high cost has led to their outright refusal for reimbursement by some government payers (Mittmann et al., 2009; NICE, 2010). The clinical and economic outcomes for mCRC were modelled using the principles of decision analysis. The current standard of care for the first line treatment of mCRC is oxaliplatin in combination with infusional 5-fluorouracil (FOLFOX). In patients who have disease progression or intolerable toxicity, second line irinotecan in combination with infusional 5-fluorouracil (FOLFIRI) is a recommended treatment (Price et al., 2010; Barugel et al., 2009). Data from a large randomised trial also verified that sequential schedules of FOLFOX and FOLFIRI (or the reverse order) are equally effective and have thus emerged as the first and second line standard of care for patients with mCRC (Tournigand et al., 2004). The addition of an anti-vascular endothelial growth factor (VEGF) such as bevacizumab during chemotherapy for mCRC has also been recommended by clinical guidelines (Engstrom et al., 2008).

A decision model for the sequential treatment of mCRC with FOLFOX (± an anti-VEGF agent – the "new drug" in this study) and then followed by FOLFIRI upon disease progression was created with the DATA model building program, developed by Treeage Software Inc. (Figure 5.1). The analytic timeframe was from the first cycle of FOLFOX chemotherapy until death. The primary outcome for measuring successful initial therapy was clinical benefit, defined as complete tumour response (CR), partial response (PR) or stable disease (SD) based on the Response Evaluation Criteria in Solid Tumors [Therasse et al., 2000]). Three clinical oncologists (one from Canada, the United Kingdom and South Africa) who had experience in colorectal cancer evaluated the face and content validity of the model.

The model began at the decision node (square) where the first line treatment choice would be either FOLFOX + "the new drug (bevacizumab)" or FOLFOX alone (Figure 5.1 and 5.2). During the first two cycles of chemotherapy, patients would be assessed for intolerable toxicity. For those patients with severe toxicity, first line therapy would be discontinued in its entirety and second line FOLFIRI would be offered until disease progression. Upon progression, all patients would receive best supportive care until death. In contrast, patients who do not experience severe toxicity from first line FOLFOX (± "the new drug") would also receive treatment until disease progression. They would then be offered second line FOLFIRI alone and the new drug would be discontinued. Upon progression, all patients would receive best supportive care until death (Table 5.2). To simplify the modeling, epidermal growth factor receptor (EGFR) inhibitors such as cetuximab in mCRC patients with KRAS ild type tumours were not considered. Furthermore, such agents would be available to both treatments options in the model, so their inclusion would not impact the final results.

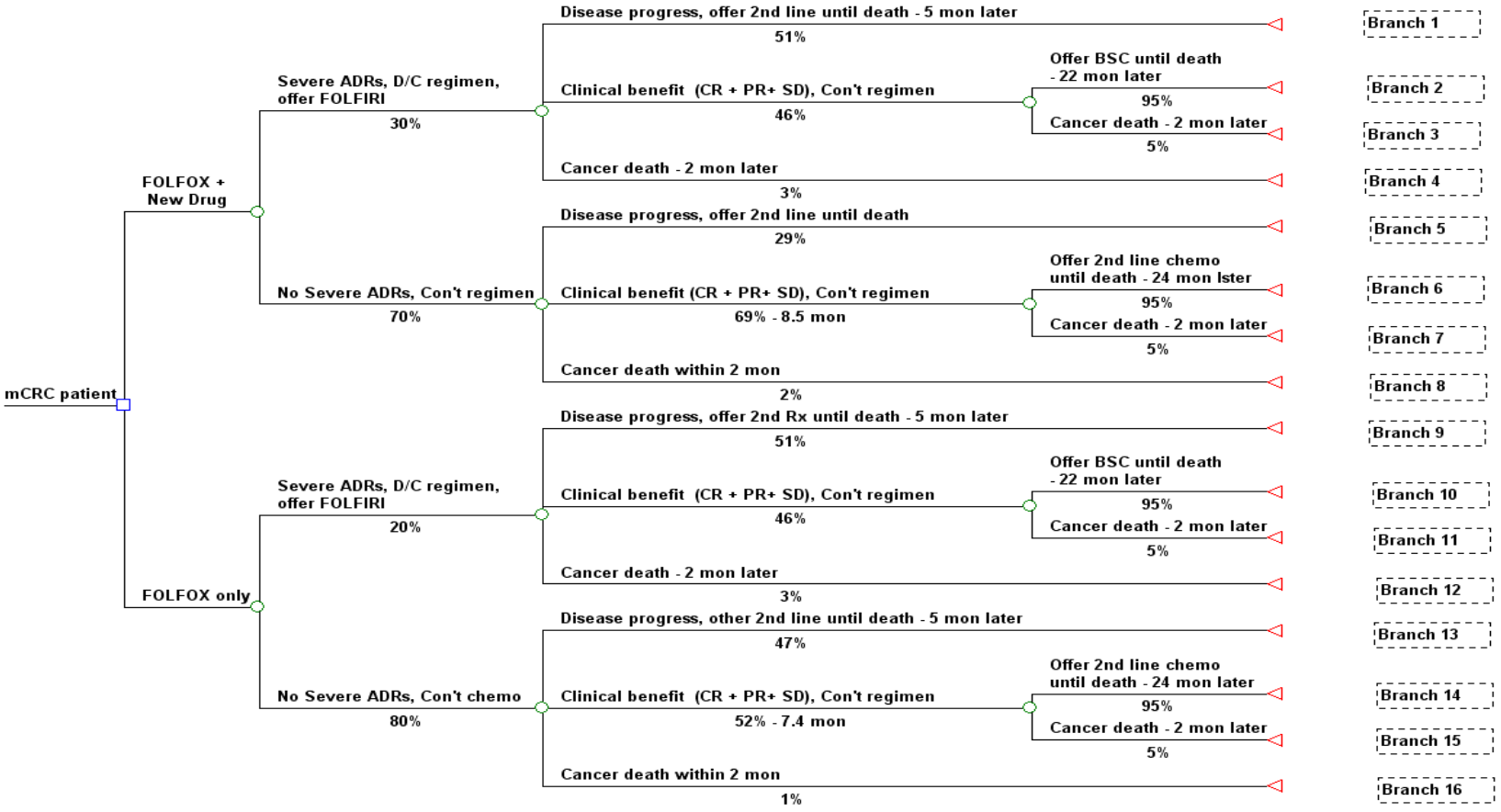

Figure 5.1. Decision analysis model for the treatment of metastatic colorectal cancer.

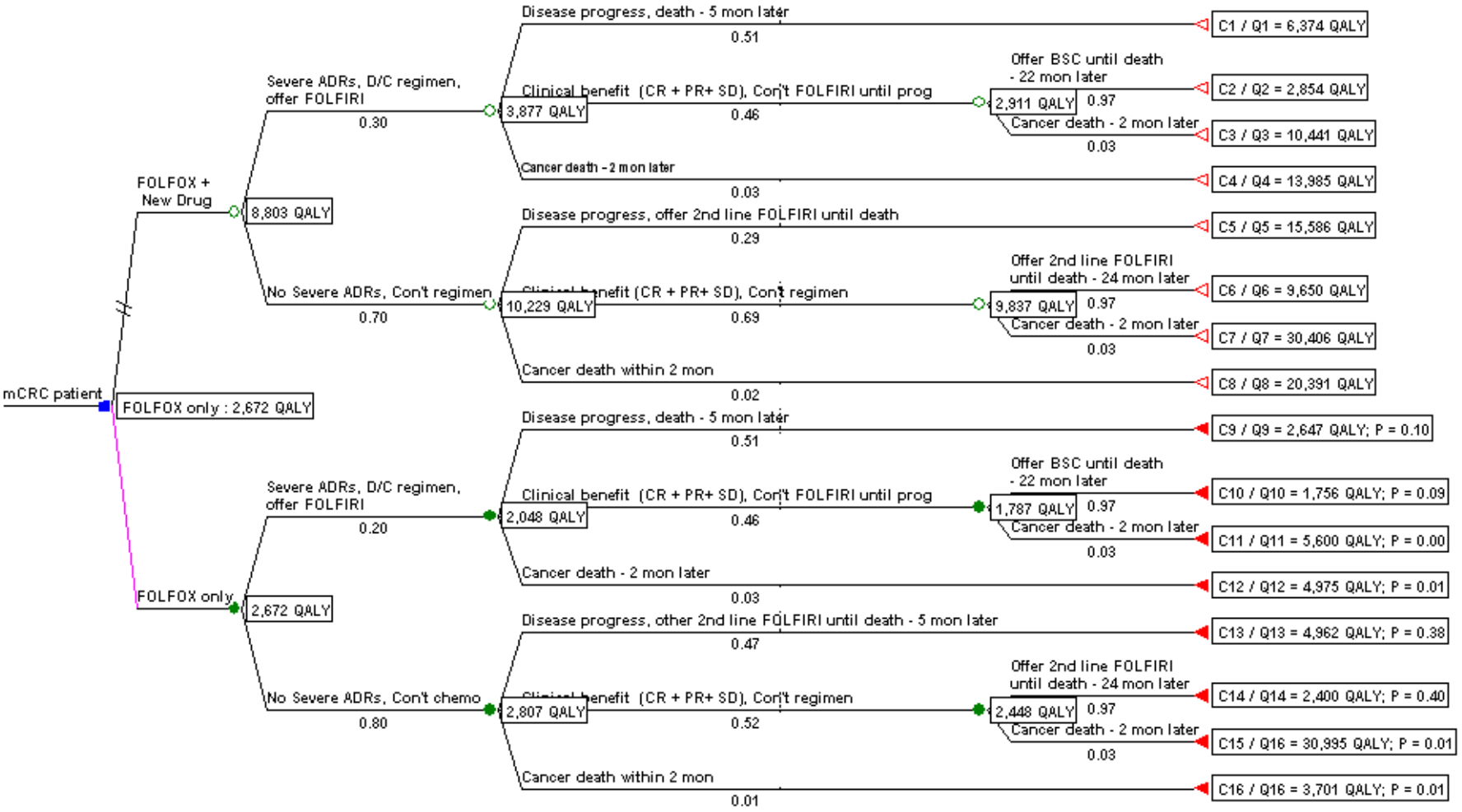

Figure 5.2. Fully rolled back decision analysis model with individual payoffs.

Table 5.2. Health state utilities derived using the Time Trade-Off technique.

Sixteen Health Outcomes Evaluated in the Decision Model	Time in Health State[a]	Utility Estimate[b] [mean (95%CI)]
FOLFOX + "new drug" → Folfiri → BSC until death		
Branch #1: Stopped FOLFOX + the "new drug" after 2 cycles due to side effects and was then treated with FOLFIRI for 4 cycles. There was disease progression. The patient received BSC and died 6 months later.	10 months	0.61 (0.54 - 0.68)
Branch #2: Stopped FOLFOX + the "new drug" after 2 cycles due to side effects and was then treated with FOLFIRI. There was a response to FOLFIRI and the patient went on to receive 8 cycles. Upon progression, the patient received BSC and died 22 months later.	28 months	0.63 (0.55 - 0.72)
Branch #3: Stopped FOLFOX + the "new drug" after 2 cycles due to side effects and was then treated with FOLFIRI. There was a response to FOLFIRI and the patient went on to receive 8 cycles. Upon progression, the patient received BSC and died 2 months later.	8 months	0.65 (0.57 - 0.73)
Branch #4: Stopped FOLFOX + the "new drug" after 2 cycles due to side effects and was then treated with FOLFIRI for 2 cycles. However, the patient died due to cancer progression within the first 2 months.	4 months	0.47 (0.37 - 0.88)
Branch #5: Tolerated side effects but had disease progression after 4 cycles of FOLFOX + the "new drug". The patient was then treated with FOLFIRI for 4 cycles but the disease did not respond. The patient received BSC and died 2 months later.	6 months	0.61 (0.51 - 0.72)
Branch #6: Tolerated side effects and responded FOLFOX + the "new drug". The patient went on to receive a total of 17 cycles of first line therapy. Upon progression, the patient went on to receive 6 cycles of FOLFIRI. Upon progression, the patient received BSC and died 21 months later.	33 months	0.72 (0.63 - 0.81)
Branch #7: Tolerated side effects and responded FOLFOX + the "new drug". The patient went on to receive a total of 17 cycles of first line therapy. Upon progression, the patient went on to receive 2 cycles of FOLFIRI but died 2 months later.	11 months	0.69 (0.62 - 0.76)
Branch #8: Tolerated side effects and but had disease progression after 2 cycles of FOLFOX + the "new drug". The patient died due to the cancer one month later.	2 months	0.44 (0.32 - 0.56)

Table 5.2. Continued…

FOLFOX → FOLFIRI → BSC until death		
Branch #9: Stopped FOLFOX after 2 cycles due to side effects and was then treated with FOLFIRI for 4 cycles. There was disease progression. The patient received BSC and died 6 months later.	10 months	0.64 (0..57 - 0.70)
Branch #10: Stopped FOLFOX after 2 cycles due to side effects and was then treated with FOLFIRI. There was a response to FOLFIRI and the patient went on to receive 8 cycles. Upon progression, the patient received BSC and died 22 months later.	28 months	0.63 (0.55 - 0.72)
Branch #11: Stopped FOLFOX after 2 cycles due to side effects and was then treated with FOLFIRI. There was a response to FOLFIRI and the patient went on to receive 8 cycles. Upon progression, the patient received BSC and died 2 months later.	8 months	0.69 (0.62 - 0.76)
Branch #12: Stopped FOLFOX after 2 cycles due to side effects and was then treated with FOLFIRI for 2 cycles. However, the patient died due to cancer progression within the first 2 months.	4 months	0.49 (0.38 - 0.60)
Branch #13: Tolerated side effects but had disease progression after 4 cycles of FOLFOX. The patient was then treated with FOLFIRI for 4 cycles but the disease did not respond. The patient received BSC and died 2 months later.	6 months	0.62 (0.51 - 0.72)
Branch #14: Tolerated side effects and responded FOLFOX. The patient went on to receive a total of 15 cycles of first line therapy. Upon progression, the patient went on to receive 6 cycles of FOLFIRI. Upon progression, the patient was offered BSC and died 21 months later.	32 months	0.68 (0.56 - 0.80)
Branch #15: Tolerated side effects and responded FOLFOX. The patient went on to receive a total of 15 cycles of first line therapy. Upon progression, the patient went on to receive 2 cycles of FOLFIRI but died 2 months later.	11 months	0.71 (0.64 - 0.78)
Branch #16: Tolerated side effects and but had disease progression after 2 cycles of FOLFOX. The patient died due to cancer progression one month later.	2 months	0.44 (0.32 - 0.56)

[a]As presented in each branch of the decision analysis model. [b]A quality of life score for a health state between 0 and 1, with 0 = death and 1 = optimal health. Abbreviations: FOLFOX = oxaliplatin+ infusional 5-FU. FOLFIRI = irinotecan + infusional 5-FU, BSC = best supportive care

5.5 Clinical data

The clinical data required to populate the model consisted of early treatment discontinuations because of toxicity, achievement of clinical benefit (that is, non progressive disease), duration of clinical benefit, risk of cancer related death during active treatment and number of chemotherapy cycles administered. These data were obtained through a literature search of randomized trials evaluating FOLFOX (± bevacizumab) in the first line setting and second line FOLFIRI in the treatment of mCRC. A literature search of Medline, Embase and the Cochrane databases was performed from 2000 through 2010 for human clinical studies involving FOLFOX, FOLFIRI and bevacizumab as first and second line therapy in mCRC. The primary objective of the review was to identify the most up-to-date clinical data for populating the model. Care was taken to avoid inclusion of duplicate publications.

5.6 Collection of cost and utility data to populate the model for each country

Direct medical cost data to populate the model were collected from large cancer centers in each of the reference countries. Public payer costs were used for those countries where public health care was available. Health care resource use included costs for drug acquisition, preparation and administration, patient monitoring, side effects management and all related physician fees. Palliative care costs for terminally ill cancer patients were obtained from the palliative care literature in the respective

countries (Batiste-Gomez et al 2006; Uys et al, 2002). The health-related utility estimates were individual preferences for the alternative health outcomes as described in the model (Figure 5.1). In the current study, quality adjusted life years (QALYs) were measured as "healthy month equivalence" using the Time Trade-Off (TTO) technique (Torrance, 1987; Gafni, 1997).

The TTO is a preference based approach designed to measure a respondent's preferences and quality of life (QOL) for alternative health states. After background information is presented on a particular health state (e.g. a cancer that is not responding to treatment) and the time period within that state, respondents are asked to trade length of life in the poorer health state for a lesser period of time in a state of optimal health and quality of life (Torrance, 1987; Gafni, 1997). As an illustration, a respondent may prefer to live 6 months of optimal health rather than the 12 months with a progressive non-responding cancer. Under this scenario, the utility associated with having a non-responding cancer for 12 months would be 0.5 (that is, 6 / 12) on a scale between 0 and 1, where 0 represents death and 1 is a state of optimal quality of life. In the economic model, all of the possible outcomes (i.e. health states) were valued this way and then used to weight the time spent in each health state in terms of QOL.

Intuitively, the ideal population for measuring health states utilities and treatment preferences should be cancer patients with the disease in question who are in a position to receive the new treatment. However, it has been recommended in the Canadian Guidelines for Economic Evaluations and by the Panel on Cost-Effectiveness in Health and Medicine of the United States that treatment preferences be measured from members of the general public who are potential candidates of the new medical intervention (Canadian Agency for Drugs and Technology in Health, 2006; Russell et al,

1996). However based on our experience, members of the general public have difficulty in understanding cancer related understanding utility questionnaires. As a compromise, a patient surrogate group consisting on oncology nurses and pharmacists was used to provide insight from both the perspective of the patient and members of the general public. There is also evidence in the oncology literature to suggest that nurses are suitable patient surrogates for objective outcomes, and that utility estimates derived from such a sample do not substantially alter the findings of cost utility studies (Ortega et al., 1996; Leung et al., 1999). Therefore, a patient surrogate sample consisting of 24 oncology nurses and pharmacists from each of the five countries provided utility values for the model. With a sample of 24 respondents for each country, healthy month equivalence was measured with a precision of ± 1.0 month, with a 95% probability.

Potential respondents were approached and were asked to participate in the study. If they were interested, respondents were presented information on the background, aims and objective to the study. They were also assured that complete confidentiality would be maintained and their names would not appear in any report or publication arising from this research. After informed consent was obtained, each participant was interviewed for 30 to 45 minutes by trained local field investigators. Respondents were presented with information on FOLFOX, bevacizumab and FOLFIRI consisting of the methods of administration, efficacy and the side effects reported in the literature (Appendix 1 and 2). The interview was then continued with a description of the 16 health states and the length of time a patient would live in each health state (Figure 5.1). The respondents were then asked how many months of "optimal health" they considered being equivalent to the time spent in each of the less than optimal health states described in the model. These measures were then used to weigh each branch

of the model by the quality of life experienced by a patient living through that time period. An identical process was used for each of the 16 outcomes (Figure 5.1).

A standardised questionnaire supported by printed interview tools with graphical displays was used to facilitate the participant's understanding of the Time Trade-off technique (Appendix 1 and 2). To minimize the framing effect, all pathways were presented in a consistent manner pictorially. Demographic data were also collected from each participant, and consisted of years of oncology and colorectal cancer experience, involvement in the development of systemic treatment guidelines for colorectal cancer, familiarity with the cost of anticancer drugs and family history of colorectal cancer.

5.7 Estimating a value based drug price for each country

The clinical, economic and respondent utility data from each country were then combined into a cost-utility analysis to estimate a price per dose for the "new drug" in the first line treatment of mCRC. The base case analysis assumed that the addition of the new drug to standard chemotherapy would provide a survival benefit of 1.4 months as reported for bevacizumab (Saltz et al., 2008). The primary objective of the analysis was to estimate a price for the "new drug" using a targeted incremental cost of three times the per capita GDP for each of the five countries (see Table 5.1). Indirect costs were not included because there was no data available on the association between bevacizumab usage and indirect cost avoidance. Future costs and benefits were not discounted because of the short time periods involved. However, the stability of the baseline results for each country was evaluated by a one-way sensitivity analysis. This consisted of substituting the 95% confidence intervals (CI) for the health-state utilities as

well as variations in the overall survival benefit and costs of care. The overall survival benefit from the "new drug" was also increased by approximately two and four times (that is, to 3 and 6 months) to account for gains that are considered clinically relevant for new drugs in mCRC. Costs of care were also varied by ± 15% to capture any potential differences across the reference country.

5.8 Development of an index for estimating drug price

After application of the PE model for a cost utility analysis, the evaluation in each country provided three price points for the "new drug" that were linked to the associated gains in survival (that is, 1.4, 3 and 6 months). A multivariable regression analysis, which was adjusted for clustering on the variable "country", was then conducted with "drug price" as the dependent variable and survival gain, per capita GDP and the Gini coefficient, which is a measure of income dispersion (a value of 0 represents absolute equality, and 100 is absolute inequality) as independent variables. Given the small sample size consisting of only 15 price points in total from the five countries, nonparametric bootstrapping was applied. Resampled data (1000 iterations) were used to generate bootstrap estimates of the regression coefficients of the multivariable model. All of the statistical analyses were performed using Stata, release 11.0 (Stata Corp., College Station, Texas, USA).

5.9 Ethical considerations

The study protocol and all associated questionnaires were reviewed and approved by the Research Ethics Committee (Human) (REC-H) of the Nelson Mandela Metropolitan University. Respondents (that is, nurses and pharmacists) were not

interviewed until informed consent was received. Respondents were also assured that complete confidentiality would be maintained and their names would not appear in any publication arising from this research. The study followed the principles of the Helsinki Declaration (World Medical Association, 2002).

5.10 Study limitations

The clinical outcomes for the "hypothetical new drug" were estimated based on the clinical data from bevacizumab, targeted therapy that is currently approved for use in mCRC. However, it is uncertain how generalizable the data for this agent will be for drugs currently in clinical development. These limitations were evaluated in the sensitivity analysis. Oncology nurses and pharmacists were used as patient surrogates in the utility assessments. Even though all respondents had oncology experience, they may not fully understand the impact that new therapies will have on a patient's quality of life. Another limitation is related to the economic parameters that were considered. Only direct health care and drug-related expenditures were included and indirect costs (e.g. patient travel to the clinic, lost productivity) secondary to drug toxicity or disease progression were not considered in the analysis. This may decrease the final estimated price for the drug. A major advantage of the final pricing index is the ability to apply it to approximately 140 countries whose per capita GDP falls within the range evaluated in this study. However, external validation in other countries outside of our GDP range is warranted.

5.11 Conclusions

This chapter presented the methodology used to collect the data, build the PE model and then generate the point estimates from each of the five countries that were needed to develop the final pricing index. The method for estimating the price points was a standard cost utility approach, but it was unique because the outcome was a final price for a predetermined value threshold as oppose to a cost per QALY gained. With the price points from each country, multivariate analysis was then used to develop the final index that can be used to estimate a final price using three key independent variables; survival gain, per capita GDP and income dispersion. In chapter six, the results of the pricing analysis from the five countries are presented followed by the final value based pricing index.

CHAPTER 6

RESULTS

6.1 Introduction

This chapter presents the seven scientific papers that were generated from this research. At the writing of the thesis, seven of seven papers have been accepted for publication in peer reviewed journals. The first paper was a review of the literature, which was presented in chapter two of this thesis. The second, third, fourth, fifth and sixth papers describe the PE modeling results for Canada, India, Spain, Malaysia and South Africa. The seventh paper, which presents the final value based pricing index for new drugs in mCRC, was accepted for publication in the European Journal of Cancer (Impact factor 4.4). This paper received fast track publication (submitted February 21, 2011 and accepted without revision on March 14, 2011). There was also an accompanying editorial to the paper, which has been included below. In addition to the publications, a total of six abstracts from this research were accepted for presentation at professional meetings. This consisted of one oral presentation 13th annual meeting of the International Society of Pharmacoeconomics and Outcomes Research (Prague, 2010) and five poster presentations. One of the posters was presented at the annual meeting of the American Society of Clinical Oncology (Chicago, 2011).

6.2 Published Articles

1. Dranitsaris G, Truter I, Lubbe MS, Amir E, Evans W. Advances in cancer therapeutics and patient access to new drugs. *Pharmacoeconomics* 2011;29:213-24.
2. Dranitsaris G, Truter I, Lubbe MS, Cottrell W, Spirovski B, Edwards J. The application of pharmacoeconomic modeling to estimate a value based price for new cancer drugs. *Journal of Evaluation in Clinical Practice* 2010; November 18.
3. Dranitsaris G, Truter I, Lubbe MS, Sriramanakoppa N, Mendonca V, Mahagaonkar S. Improving patient access to cancer drugs in India: Using economic modeling to estimate a more affordable drug cost based on measures of societal value. *International Journal of Technology Assessment in Health Care* 2011;27:23-30.
4. Dranitsaris G, Ortega A, Lubbe MS, Truter I. A pharmacoeconomic modeling approach to estimate a value based price for new oncology drugs in Europe. *Journal of Oncology Pharmacy Practice* 2011;March 7.
5. Dranitsaris G, Truter I, Lubbe MS, Sriramanakoppa N, Mendonca V, Mahagaonkar S. Using pharmacoeconomic modeling to determine a value-based price of new pharmaceuticals in Malaysia. *Malaysian Journal of Medical Sciences* 2011; (in press).
6. Dranitsaris G, Truter I, Lubbe MS, Fourie S. Using measures of societal value and economic modeling to estimate prices for cancer drugs in South Africa. *European Journal of Hospital Pharmacy Science* 2011; (in press).
7. Dranitsaris G, Truter I, Lubbe M. The development of a value based pricing index for new drugs in metastatic colorectal cancer. *European Journal of Cancer* 2011;47:1299-304.

6.3 Abstracts Presented at Professional Meetings

1. Dranitsaris G, Truter I, Lubbe MS, Cottrell W, Spirovski B, Edwards J. The application of pharmacoeconomic modeling approach to estimate a value based price for new cancer drugs in a publicly funded health care system. Oral presentation at the 13th annual meeting of the International Society of Pharmacoeconomics and Outcomes Research, November 6 to 9, 2010. Prague, Czech Republic.
2. Dranitsaris G, Truter I, Lubbe MS, Sriramanakoppa N, Mendonca V, Mahagaonkar S. Improving patient access to drugs in India: Using economic model to estimate a drug cost based on measures of societal value. Poster presentation at the 13th annual meeting of the International Society of Pharmacoeconomics and Outcomes Research, November 6 to 9, 2010. Prague, Czech Republic.
3. Dranitsaris G, Truter I, Lubbe MS, Sriramanakoppa N, Mendonca V, Mahagaonkar S. Using pharmacoeconomic modeling to determine a value based price for new pharmaceuticals in Malaysia. Presented at the 16th annual meeting of the International Society of Pharmacoeconomics and Outcomes Research, May 21 to 25, 2011. Baltimore, United States.
4. Dranitsaris G, Truter I, Lubbe MS, Fourie S. Using measures of societal value and economic modeling to estimate prices for cancer drugs in South Africa. Presented at the 16th annual meeting of the International Society of Pharmacoeconomics and Outcomes Research, May 21 to 25, 2011. Baltimore, United States.

5. Dranitsaris G, Truter I, Lubbe M. The development of a value based pricing index for new drugs in metastatic colorectal cancer. Presented at the 16th annual meeting of the International Society of Pharmacoeconomics and Outcomes Research, May 21 to 25, 2011. Baltimore, United States.
6. Dranitsaris G, Truter I, Lubbe M. The development of a value based pricing index for new drugs in metastatic colorectal cancer. Presented at the annual meeting of the American Society of Clinical , June 3 to 7, 2011. Chicago, United States.

6.4 Dranitsaris G, Truter I, Lubbe M, Sriramanakoppa N, Mendonca VM, and Mahagaonkar SB. Improving patient access to cancer drugs in India: Using economic modeling to estimate a more affordable drug cost based on measures of societal value. ***International Journal of Technology Assessment in Health Care*** **2011; 27:23-30.**

International Journal of Technology Assessment in Health Care, **27:1** (2011), 23–30.

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Improving patient access to cancer drugs in India: Using economic modeling to estimate a more affordable drug cost based on measures of societal value

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Background: Using multiples of India's per capita gross domestic product (GDP) as the threshold for economic value as suggested by the World Health Organization (WHO), decision analysis modeling was used to estimate a more affordable monthly cost in India for a hypothetical new cancer drug that provides a 3-month survival benefit to Indian patients with metastatic colorectal cancer (mCRC).
Methods: A decision model was developed to simulate progression-free and overall survival in mCRC patients receiving chemotherapy with and without the new drug. Costs for chemotherapy and side-effects management were obtained from both public and private hospitals in India. Utility estimates measured as quality-adjusted life-years (QALY) were determined by interviewing twenty-four oncology nurses using the Time Trade-Off technique. The monthly cost of the new drug was then estimated using a target threshold of US$9,300 per QALY gained, which is three times the Indian per capita GDP.
Results: The base-case analysis suggested that a price of US$98.00 per dose would be considered cost-effective from the Indian public healthcare perspective. If the drug were able to improve patient quality of life above the standard of care or survival from 3 to 6 months, the price per dose could increase to US$170 and US$253 and offer the same value.
Conclusions: The use of the WHO criteria for estimating the cost of a new drug based on economic value for a developing country like India is feasible and can be used to estimate a more affordable cost based on societal value thresholds.

Keywords: Drug pricing, Cost analysis, Chemotherapy, Value

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India is a culturally diverse country occupying approximately 2.4 percent of the world's land area, but supporting 17.5 percent of the global population (13). With a population of 1.17 billion people, it is the world's second most populous country after China (20). The majority of the people live in small villages where agriculture and associated activities predominate. Based on a 2001 census, approximately 72 percent of the population lives in 638,000 villages across the country (20).

The healthcare system in India consists of both government-financed public hospitals and private institutions. In 2002, there were 15,393 hospitals in India with approximately two-thirds being public (23). However, because of chronic under-funding, most public healthcare facilities are only able to offer basic care. Therefore, the better funded private sector provides approximately 60 percent of all comprehensive outpatient care in India and up to 40 percent of all inpatient care (22;23). To gain access to private hospitals, patients must have health insurance or they must pay out of pocket. Unfortunately, only approximately 11 percent of the population has any form of health insurance, and this is often inadequate (23). Patients with sufficient private insurance have better access to modern health care, but only 1 percent of the Indian population fall into this category. Since so few patients have adequate health insurance, personal funds have to be used to obtain treatment. In one report, it was estimated that out of pocket payments for medical care accounted for 98.4 percent of total healthcare expenditures (23).

Given the lack of adequate health insurance, only approximately 50 million Indians (i.e., 4.2 percent of the population) are able to afford modern medicines, which are available at comparable costs to the United States and Europe (22;23). To increase patient access to new and vital drugs, the Indian government has created an essential drugs list. When drugs are added to this list, the government imposes price controls to ensure that these vital agents become affordable to the population. Under a new policy originally proposed in 2006, the government revealed its intention to increase the number of essential drugs for price control from 79 to 354, which would bring almost a third of the pharmaceutical industry under such control (22;23). Given their high cost, cancer drugs are likely to be affected by this policy (11). This would no doubt create tension between foreign drug firms who want to sell their products at an adequate margin to ensure a profit and the government's desire to increase patient access to new agents. To address this impasse, new drug pricing strategies need to be found that will ensure the commercial viability of innovative therapies while making such agents affordable to the extended Indian population.

One approach that may facilitate the identification of an optimal list price would be through the application of pharmacoeconomic (PE) modeling techniques. The basic premise of PE evaluations is to compare the costs and consequences of a new drug to determine if it offers the best value for money relative to the standard of care (1;11). Such analyses are usually undertaken after the unit cost of the drug has been set following regulatory approval. However, PE may have an additional and perhaps more valuable role in estimating or negotiating the price of the drug based on societal value thresholds. PE has been used in this capacity for the evaluation of numerous biologics, including novel oncologic agents assessed by Institute of Clinical Excellence (NICE) for the United Kingdom (UK) (4). This approach can also be used to estimate a more affordable price of a drug for the Indian healthcare setting.

Quality-adjusted life-years, or QALYs, are a way of measuring the impact of disease. They include both the quality and the quantity of life lived and are used to quantify the relative benefit of two competing medical interventions. One of the major challenges against the use of PE modeling for estimating drug cost is in setting the value threshold for a given country. As an illustration, NICE of the UK has established a threshold for drug coverage at £30,000 per QALY gained (8). In many other jurisdictions, a US$50,000 cost per QALY threshold has been used (17); which was based on a 1982 valuation (15). A problem in using such thresholds is that the wealth of the individual country is not taken into consideration. To address this, the World Health Organization (WHO) has proposed to use multiples of a country's per capita gross domestic product (GDP) to establish thresholds for economic value (15;19;26). Products less than or equal to the per capita GDP would be considered very cost-effective, one to three times would be cost-effective and more than three times would be cost-ineffective (15). For a country like India (i.e., per capita GDP = $US3,100) (2), the three times threshold for cost-effectiveness of new anticancer therapies would be approximately US$9,300 per QALY gained. In contrast, the threshold for economic value for a higher income country such as Norway would be US$150,000 per QALY gained. Therefore, the list price for a drug sold in India would be substantially less than the list price in Norway, and these price figures would be proportional to their respective national per-capita GDP.

The use of thresholds based on per capita GDP in combination with PE modeling to establish a value-based price for a drug is an interesting approach, because it could set the foundation for improving global patient access. Wealthier nations would then be expected to pay more for drugs and these higher revenues would subsequently subsidize access for the developing world. To illustrate the application of this drug pricing strategy, decision analyses modeling was used in the current study to estimate the price per dose of a hypothetical new cancer drug that would provide an overall survival benefit of 3 months over the standard of care. Clinical data for the case study are based on a combination of bevacizumab plus chemotherapy in a first-line treatment setting of metastatic colorectal cancer (mCRC) (3). Bevacizumab was chosen because it has a high acquisition cost and its economic value has been questioned in recent PE studies (28;29).

METHODS

Economic Model

mCRC was chosen for this analysis because the sequential use of specific chemotherapy regimens is well established. In patients with mCRC, randomized trials have demonstrated that irinotecan (FOLFIRI) or oxaliplatin (FOLFOX) in combination with infusional 5-fluorouracul (5-FU) and leucovorin are highly active and superior to the previous standard of 5-FU/leucovorin alone (5;14). Data from a large randomized trial also verified that sequential schedules of FOLFOX and FOLFIRI (or the reverse order) are equally effective and have thus emerged as the first- and second-line standard of care for patients with mCRC (32). Clinical practice guidelines also recommend the addition of an anti-vascular endothelial growth factor (VEGF) such as bevacizumab at some point during chemotherapy for mCRC (9). FOLFOX, FOLFIRI, and bevacizumab are all available in India, but access is limited by a patient's ability to pay.

A decision model for the sequential treatment of mCRC with FOLFOX (± an anti-VEGF) followed by FOLFIRI upon disease progression was developed with the DATA software (Treeage Software Inc.) (Supplementary Figure 1, which can be viewed online at www.journals.cambridge.org/thc2011003). The analytic timeframe was from the first cycle of FOLFOX chemotherapy until death, and an Indian healthcare system perspective (both public and private) was taken. The primary outcome for measuring successful initial therapy was clinical benefit, defined as either complete tumor response (CR), partial response (PR), or stable disease (SD) based on the Response Evaluation Criteria in Solid Tumors [*RECIST*]) (30). Three clinical oncologists, each with experience in treating colorectal cancer, evaluated the face and content validity of the model.

The model began at the decision node (square) where the first-line treatment choice would be either FOLFOX + "the new drug" or FOLFOX alone (Supplementary Figure 1). During the first two cycles of chemotherapy, patients would be assessed for intolerable toxicity. For those patients with severe toxicity, first-line therapy would be discontinued in its entirety and second-line FOLFIRI would be offered until disease progression. Upon progression, all patients would receive best supportive care until death. In contrast, patients who did not experience severe toxicity from first-line FOLFOX (± "the new drug") would continue receiving treatment until disease progression. They would then be offered second-line FOLFIRI alone and the new drug would be discontinued. Upon progression, all patients would receive best supportive care until death (Supplementary Figure 1).

Clinical Data

The clinical data required to populate the model consisted of early treatment discontinuations because of toxicity, achievement of clinical benefit, duration of clinical benefit, risk of cancer-related death during active treatment, and number of chemotherapy cycles administered. These data were obtained through a literature search of randomized trials evaluating FOLFOX (± bevacizumab) in the first-line setting and second-line FOLFIRI in the treatment of mCRC. Two randomized trials were identified that provided the required data for the decision model (Table 1) (25;32).

Estimation of Treatment Costs

The duration of investigation ran from the start of first and second-line sequential chemotherapy therapy until death. Costs for anticancer drugs, materials, patient monitoring and other related hospital resources (e.g., laboratory and diagnostic tests) were obtained from two private and two public institutions. The costs collected in the study were in Indian Rupees and then converted to US$ per the currency conversion prevailing in 2010 (conversion factor 1 US$ = 45 Indian Rupees).

Patient Preferences for Alternative Health States

The health-related quality of life values measured in the analysis were patient preferences for alternative health outcomes, as depicted in the decision analysis model. In the current study, quality-adjusted progression-free periods were measured as "healthy months equivalent" for the time spent in each outcome of the decision model using the Time Trade-Off (TTO) technique (12;31). The scores in months were then converted to utility measures between 0 and 1, where 0 represented death and 1 was a state of perfect health or optimal quality of life.

Intuitively, the ideal population for measuring health state utilities and treatment preferences should be cancer patients with the disease in question who are in a position to receive the new treatment. However, it has been recommended in the Canadian Guidelines for Economic Evaluations and by the Panel on Cost-Effectiveness in Health and Medicine of the United States that treatment preferences be measured from members of the general public who are potential candidates of the new medical intervention (1;24). As a compromise in this study, a patient surrogate group was used that would provide insight from both the perspective of the patient and members of the general public because the latter sample often has difficulty in understanding utility questionnaires. Therefore, a patient surrogate sample consisting of twenty-four oncology nurses provided utility values for the model. With a sample of twenty-four respondents, healthy month equivalence was measured with a precision of ± 1.0 month, with a 95 percent probability. Such a sample has been successfully used by our group in several economic evaluations of cancer drugs (6;7;18). There is also evidence in the oncology literature suggesting that nurses are suitable patient surrogates for objective outcomes and that utility estimates derived from such a sample do not substantially alter the findings of cost-utility studies (18;21).

Table 1. Published Randomized Trials Providing Clinical Data to Populate the Economic Model

Reference	Treatment arms	Clinical outcomes
Saltz et al. (2008)	FOLFOX/XELOX + bevacizumab	Disease progression = 29% Median PFS = 9.4 months Median duration of response = 8.45 months Treatment discontinuations = 30% Death during treatment = 2% Serious side effects (grade III/IV) = 16% Specific grade III/IV side effects Deep vein thrombosis = 8% Diarrhea = 18% Bleeding = 2% Neutropenia = 50%
	FOLFOX/XELOX + placebo	Disease progression = 47% Median PFS = 8.0 months Median duration of response = 7.4 months Treatment discontinuations = 20% Death during treatment = 1% Serious side effects (grade III/IV) = 8% Specific grade III/IV side effects Deep vein thrombosis = 5% Diarrhea = 11% Bleeding = 1% Neutropenia = 44%
Tournigand et al. (2004)	Second Line FOLFIRI	Disease progression = 51% Death during treatment = 3% Median PFS = 10.9 months Median number of cycles = 6

Note. PFS, progression-free survival; OS, overall survival; FOLFOX, oxaliplatin in combination with infusional 5-fluorouracul; FOLFIRI, irinotecan in combination with infusional 5-fluorouracul.

After informed consent was obtained, each participant was interviewed for 30 to 45 minutes by trained local field investigators. Respondents were presented with information on FOLFOX, bevacizumab, and FOLFIRI consisting of the methods of administration, efficacy, and the side effects reported in the literature (25;32). Bevacizumab was not identified by name but simply referred to as the "new drug." The interview was then continued with a description of the sixteen health states, and the length of time a patient would live in each health state (Supplementary Figure 1). The respondents were then asked how many months of "optimal health" they considered being equivalent to the time spent in each of the less than optimal health states described in the model. These measures were then used to weigh each branch of the model by the quality of life experienced by a patient living through that time period.

Cost-Utility Analysis

The clinical, economic, and respondent preference data were then combined into a cost-utility analysis of the "new drug" for the first-line treatment of mCRC. The base-case analysis assumed that the addition of the "new drug" to standard chemotherapy would provide a survival benefit of 3 months. The primary objective of the analysis was to estimate an appropriate price per dose for the "new drug" by using the target benchmark cost of US$9,300 per QALY gained, which is three times the Indian per capita GDP. Indirect costs were not included because there were no data available on the association between bevacizumab usage and indirect cost avoidance. Future costs and benefits were not discounted because of the short time periods involved. However, the stability of the baseline results was evaluated by a comprehensive sensitivity analysis. This consisted of substituting the 95 percent confidence intervals (CI) for the health-state utilities as well as variations in the overall survival benefit, costs of care, and the target threshold for economic value in India. Individual analyses were conducted from both the public and private healthcare perspective.

RESULTS

Clinical outcomes data and costs used to populate the model are presented in Tables 1 and 2. The economic data revealed that expenses for chemotherapy, side-effect management, and best supportive care are considerably lower in the public than the private system in India. This may be a reflection of the modest level of care offered to patients in public hospitals and of the ability of the private sector to mark up the cost of goods and health services.

Table 2. Hospital Costs for the Treatment of Metastatic Colorectal Cancer in India

Recourse item	Public hospitals	Private hospitals
FOLFOX chemotherapy[a]	US$238 / cycle	US$664 / cycle
FOLFIRI chemotherapy[b]	US$301 / cycle	US$691 / cycle
Cost for a permanent chemotherapy discontinuation because of toxicity[c]	US$23.73	US$556
Cost to administer the "new drug" after FOLFOX chemotherapy	US$4.60	US$11.50
Cost of best supportive care[d]	US$29.98/month	US$162/month

Note. FOLFOX, oxaliplatin in combination with infusional 5-fluorouracul; FOLFIRI, irinotecan in combination with infusional 5-fluorouracul.
[a]Oxaliplatin in combination with infusional 5-fluorouracul. Cost per cycle includes resources for drug administration and routine patient monitoring. In the hospitals that provided data for this study, patients are admitted for two days to receive the chemotherapy.
[b]Irinotecan in combination with infusional 5-fluorouracul.
[c]Patients would be admitted for 3 days for the management of side effects and for reassessment.
[d]After failing two lines of chemotherapy, patients would receive best supportive care on an outpatient basis until death.

The second component required for the cost-utility analysis was health state utilities for the time period spent in each of the 16 health states (Supplementary Figure 1). Utilities for each outcome were estimated from a sample of twenty-four oncology nurses. There were thirteen respondents from private hospitals and the remainder were from public institutions. The sample had an average of 5.4 years of direct oncology experience (range, 3–15 years) and all had experience in the treatment of colorectal cancer patients. In addition, 22 of 24 (91.7 percent) respondents had direct clinical experience in the administration and follow-up care associated with FOLFOX (mean years = 4.8) and FOLFIRI (mean years = 3.2) chemotherapy. However, only 9 of 24 (37.5 percent) had experience with the newer targeted therapies such as bevacizumab and cetuximab.

The health state utilities from the oncology nurses are presented in Supplementary Table 1, which can be viewed online at www.journals.cambridge.org/thc2011003. The results suggested that patient utilities were influenced by the severity of drug toxicity, the likelihood of achieving a response to chemotherapy and the risk of rapid cancer death. The health states with the lowest utilities (i.e., branches 4 and 12 of the model, Supplementary Figure 1) were those where first-line therapy had to be stopped because of severe toxicity, the patient then had an early progression during second-line treatment followed by a rapid cancer death. It was also interesting to note that, in all of the related scenarios, comparative branches that included treatment with the "new drug" tended to have lower health state utilities (Supplementary Table 1). This is likely related to the additional side effects that would occur with the addition of an anti-VEGF agent like bevacizumab to chemotherapy (Table 1).

Cost Utility Analysis for the Public and Private Healthcare Systems

The outcomes data from the clinical trial, the estimated costs associated with each treatment and the health state utility estimates were combined into the cost-utility analysis. The price per dose of the "new drug" was then varied until the incremental cost-effectiveness ratio reached a threshold of US$9,300 per QALY gained. Using this approach from the public healthcare system perspective, the base-case analysis suggested that a price of US$98.00 would be considered cost-effective for India according to the WHO criteria (15;19;26).

A series of one-way sensitivity analyses were then conducted using the upper 95 percent CI for the health state utilities, variations in treatment costs, overall survival benefit, and the targeted cost per QALY threshold. When the costs of therapy were varied by ± 15 percent, the results were relatively stable (Table 3). The two biggest factors to impact the base-case findings were the health state utilities associated with the new drug and the overall survival gain. The monthly drug price rose to US$170 when the upper 95 percent CI of the health state utilities for the new drug were applied to the model. Similarly, increasing the overall survival benefit from 3 to 6 months allowed the monthly drug price to increase to $U.S.253 while retaining the same value. These findings indicate that the two most important factors driving the cost-effectiveness of any new cancer drug is its ability to significantly improve quality and quantity of life.

While bevacizumab is available in India, its purchase price is approximately US$2184 per dose for an average mCRC patient, which is similar to the price charged in the United States and Europe. As a result, only patients with adequate insurance and or sufficient personal resources would have access to this drug. A sensitivity analysis was conducted where the current price of bevacizumab was applied to the model. The results revealed that the incremental cost per QALY gained would be greater than US$200,000. When a US$50,000 cost per QALY threshold was used instead of the WHO criteria, the price per dose of the new drug rose to US$770.00. In summary, the sensitivity analyses suggested that a price of approximately US$98.00 for a new drug that would prolong patient survival by 3 months would be considered cost-effective in India.

A similar series of analysis was conducted with cost data collected from private hospitals. Unlike the results from the public system, we were unable to find a price per dose for the new drug that would result in a US$9,300 cost per

Table 3. Sensitivity Analysis on the Unit Price per Dose for the "New Drug"

Sensitivity maneuvre	Public hospitals	Private hospitals
Base-case[a]	US$98.00	Not reached
Upper 95% CI of health state utilities for chemotherapy + the "new drug"	US$170	US$48.00
Changing cost of FOLFOX chemotherapy by ±15%	US$93 to US$107	Not reached
Changing cost of FOLFIRI chemotherapy by ±15%	US$99 to US$103	Not reached
Changing cost of BSC cost by ±15%	US$97 to US$99	Not reached
Changing cost of ADR cost by ±15%	US$97 to US$99	Not reached
Changing survival benefit of the "new drug" from 3 to 6 months	US$253	US$130
Changing survival benefit of the "new drug" from 3 to 1 month	Not reached	Not reached
Using the current cost of bevacizumab (US$2184 per dose) in India	Not reached	Not reached
Setting the threshold for cost-effectiveness at US$50,000 per QALY gained	US$770	US$650

Note. CI, confidence interval; FOLFOX, oxaliplatin in combination with infusional 5-fluorouracul; FOLFIRI, irinotecan in combination with infusional 5-fluorouracul; BSC, best supportive care; ADR, adverse drug reaction costs; QALY, quality-adjusted life-year.
[a]For a target threshold of US$9,300 per QALY when the new drug is added to FOLFOX chemotherapy.

QALY gained (Table 3). Under most of the sensitivity scenarios evaluated, a price for the "new drug" could also not be found (Table 3). The only exception was when the upper 95 percent CI of health state utilities for chemotherapy + the "new drug" were used. This allowed the price of the drug to be US$48.00. The main reason behind these results was the fact that the addition of an effective new drug would increase the total number of chemotherapy cycles administered. This would drive up the costs and overcome any incremental benefit in quality of life and overall survival. However, the intent of the WHO criteria for cost-effectiveness is its application towards publicly funded healthcare systems. The criteria seem to provide a reasonable threshold for estimating the cost-effectiveness of a new drug in a developing country like India.

DISCUSSION

In this study, decision analysis was used to estimate the price of a hypothetical new drug that provides a 3-month survival benefit when added to chemotherapy in the first-line treatment of mCRC. The primary analysis was conducted from the Indian public healthcare system perspective using the WHO criteria for cost-effectiveness. In the base-case analysis and in most of the scenarios evaluated, a price per dose of approximately US$98.00 was suggested by the data as being cost-effective. The price of the drug could increase to US$253 per month if the survival benefit were to approach 6 months. However, in the treatment of solid tumor patients with metastatic disease, a 6-month survival gain is rarely achieved. Most new cancer drugs approved for use over the past 3 years have not been able to improve survival beyond 3 months (10;16;25;33).

The findings of this study suggest that the WHO criteria for cost-effectiveness can be applied to a developing country like India for estimating an appropriate price which may be more affordable to the public healthcare system. Reducing drug acquisition prices to these levels would improve patient access. However, central to the pricing debate is the matter of commercial viability based on the manufacturer's cost of goods and operational overhead expense. It is unclear whether manufacturers would realize greater short-term benefit from a scenario where the drug is sold at a high price to a few people (as with bevacizumab in India), versus a case where the drug is sold at a lower cost but to a much larger group of people. In India, only 50 million people of a population of 1.17 billion are able to afford modern medicines (22;23). Could a reasonable level of profit be achieved if a drug were to become more affordable to the remaining 1.165 billion?

An exercise to identify a price point where revenue between the two scenarios reaches equivalence is a worthy analysis to undertake. However, if the status quo is maintained, then one of two possible outcomes may materialize. The Indian government may issue a compulsory license, which would enable local production of the patented drug. This is possible under the Trade Related Intellectual Property Rights agreement of the World Trade Organization and has already occurred with some HIV drugs (27). Alternatively, the government may mandate price controls by adding a new cancer agent to the Essential Drugs List (22;23). Either way, total revenues for the product would be compromised.

One of the challenges faced by the pharmaceutical industry in making a drug available at a lower price in less-developed countries is the phenomenon known as parallel trade. In this situation, the drug is imported to a wealthier nation by an intermediary for the intention of profit making. Cooperation between the global pharmaceutical industry and the government of the developing nation will be needed to make a lower price policy viable. A strict and enforceable system would have to be developed that would reduce the likelihood of parallel trade. One approach could be through a centralized single source drug distribution process along with a preauthorized list of prescribers. Notwithstanding, the PE modeling approach presented in this paper along with the WHO criteria for cost-effectiveness can be a useful tool in identifying an optimal drug price for all of the key stakeholders. The proposed methodology will also focus negotiations

on cost-effectiveness and value based pricing as opposed to intellectual property litigation and mandated price controls.

There are several limitations in the application of this technique. Our modeling exercise was theoretical. For the proposed methodology to be viable, complete data from randomized trials on a drug by drug basis is required. One of the limitations of using the per capita GDP for value based pricing is that it represents a national average and does not consider income dispersion. For our modeling strategy to be applied, a new drug must demonstrate either an improvement in QOL over the standard of care or a survival of sufficient magnitude to identify a final price point for cost-effectiveness. However, many of the newer oncology drugs have not been able to demonstrate such benefits (10;16;25;33). Lastly, indirect costs such as time off work secondary may be relevant in this setting, but were not considered in this analysis.

CONCLUSIONS

Modern cancer medicines are often out of reach for many patients in developing countries. To help improve patient access, a process to estimate an optimal drug price based on predetermined thresholds of societal value is presented. The advantages of this technique are that it is relatively straightforward to perform, transparent, and the modeling can be easily applied to any jurisdiction using local cost data. Such information can be of value to both drug manufacturers and governments because it would facilitate value based drug price negotiations. However, the challenge would be to identify an ideal list price that would strike a balance between that which patients/governments can afford to pay and the commercial viability of the product.

SUPPLEMENTARY MATERIAL

Supplementary Table 1
Supplementary Figure 1
www.journals.cambridge.org/thc2011003

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CONFLICT OF INTEREST

All authors report having no potential conflicts of interest.

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A pharmacoeconomic modeling approach to estimate a value-based price for new oncology drugs in Europe

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Abstract

Background. Several European governments have recently mandated price cuts in drugs to reduce health care spending. However, such measures without supportive evidence may compromise patient care because manufacturers may withdraw current products or not launch new agents. A value-based pricing scheme may be a better approach for determining a fair drug price and may be a medium for negotiations between the key stakeholders. To demonstrate this approach, pharmacoeconomic (PE) modeling was used from the Spanish health care system perspective to estimate a value-based price for bevacizumab, a drug that provides a 1.4-month survival benefit to patients with metastatic colorectal cancer (mCRC). The threshold used for economic value was three times the Spanish *per capita* GDP, as recommended by the World Health Organization (WHO).

Methods. A PE model was developed to simulate outcomes in mCRC patients receiving chemotherapy ± bevacizumab. Clinical data were obtained from randomized trials and costs from a Spanish hospital. Utility estimates were determined by interviewing 24 Spanish oncology nurses and pharmacists. A price per dose of bevacizumab was then estimated using a target threshold of €78,300 per quality-adjusted life year gained, which is three times the Spanish *per capita* GDP.

Results. For a 1.4-month survival benefit, a price of €342 per dose would be considered cost effective from the Spanish public health care perspective. The price may be increased to €733 or €843 per dose if the drug were able to improve patient quality of life or enhance survival from 1.4 to 3 months.

Conclusions. This study demonstrated that a value-based pricing approach using PE modeling and the WHO criteria for economic value is feasible and perhaps a better alternative to government mandated price cuts. The former approach would be a good starting point for opening dialog between European government payers and the pharmaceutical industry.

Keywords
Drug pricing, Europe, cost analysis, chemotherapy, value

Introduction

Cancer remains a global issue due to its effect on human quantity and quality of life. It was reported that in 2008, there were approximately 7.4 million

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cancer deaths from the disease, which was approximately 13% of all cause mortality.[1] In 25 European countries, cancer was responsible for 16.7% of all disability adjusted life years lost, which ranked third after mental illness and cardiovascular disease.[2] However, one of the positive developments in cancer management over the past decade is that overall patient mortality is no longer increasing but has stabilized and has even decreased in some tumor sites.[3–5]

A contributing factor has been the introduction of new oncology products.[4,5] These agents, which include trastuzumab, rituximab, imatinib, and bevacizumab target specific components of the cancer cell and are usually better tolerated than conventional chemotherapy.[6,7] However, an important attribute of these new agents is their price is substantially higher than older anticancer drugs. In a recent editorial, the annual price for a full course of therapy for the targeted agents erlotinib, sorafenib, bevacizumab, and cetuximab was estimated to be $U.S.15,752, $U.S.34,373, $U.S.80,352, and $U.S.90,816, respectively.[8] This can compromise patient access to new drugs in both private and publicly funded health care systems.[9] It was also reported that over 90% of new FDA cancer drug approvals in the last 4 years had prices that exceed $20,000 for a 12-week course of therapy.[10] The impact of these rising drug prices has been to strain cancer care budgets. From 1993 to 2004, total European expenditures for oncology drugs increased seven times from €840 million to €6170 million.[5] Similar trends have also been reported in the US where cancer drug expenditures increased from $3 billion in 1997 to $11 billion in 2004.[10] In many countries, drug expenditures in general have also outpaced total health care spending and higher drug prices have been a contributing factor (Figure 1).

Countries, particularly in Europe have responded in different ways to address rising drug expenditures. Greece, France, and Spain have mandated government price controls of up to 23% for branded products.[11–13] The Italian Medicines Agency also announced possible cuts of up to 40% for selected cancer drugs that failed to meet expectations under a 'pay for performance' program.[14] The United Kingdom (UK) and Germany have taken a step further and are planning to introduce a value-based pricing scheme for new products. In Germany, the new law that should take effect in 2011 will allow the national health plans to negotiate a discounted price for the product after the first year following product launch.[15] As part of the new law, brand name pharmaceutical companies will be allowed to

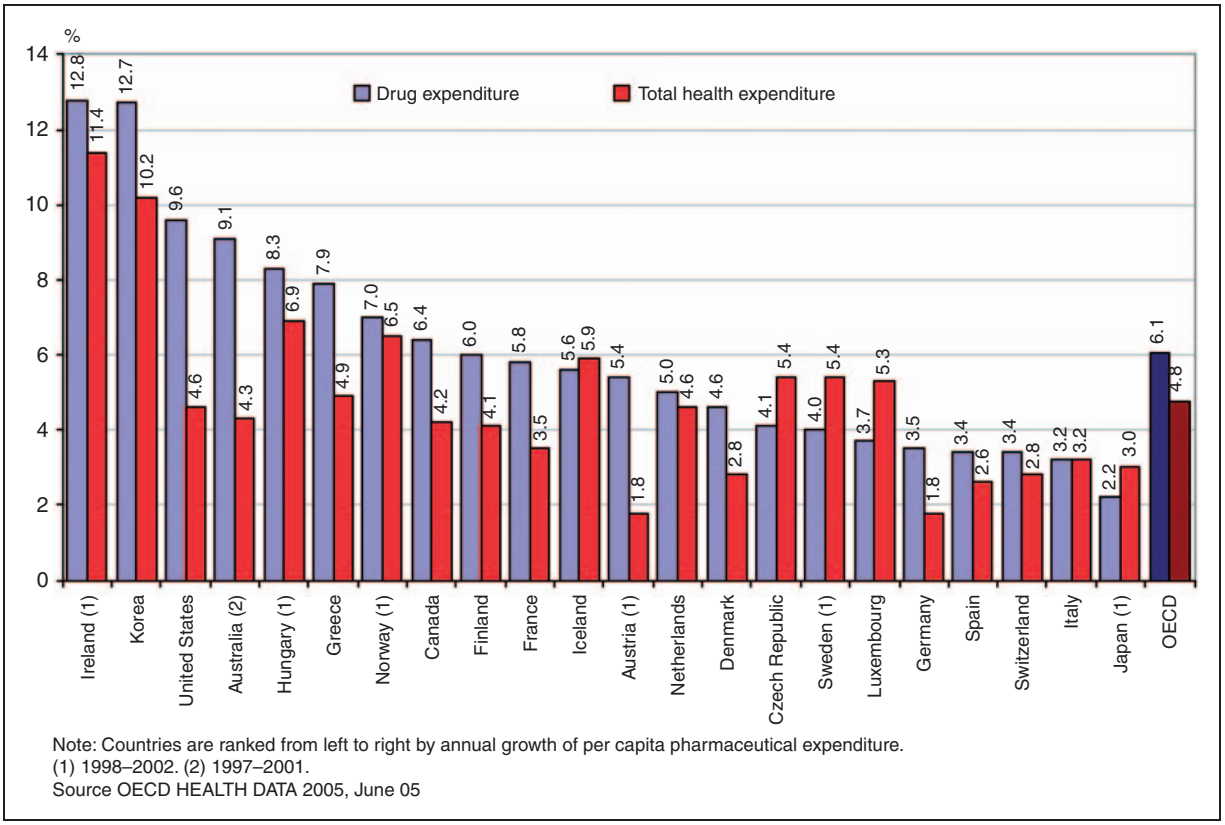

Figure 1. Annual growth in drugs expenditures and in total health care expenditures: 1998 to 2003.

set the price in the first year. After that time, the company will need to demonstrate the drug's benefits in order to maintain that price. If this has been not achieved, insurance companies will be permitted to negotiate a price reduction. The final price will be based on the magnitude of benefit offered by the product both within a clinical trial and following approval. Therefore, the objective is to make cost benefit analyses part of price negotiations.

Following the German example, the government of the UK has also proposed a new value-based pricing scheme for drugs.[16] In the UK, there is legislation that regulates profit but not price. It is not clear what the new scheme will look like, but new product pricing will likely be based on the incremental cost per quality-adjusted life year (QALY) gained threshold, which is £30,000 in the UK.[17] This threshold, which is equivalent to approximately $U.S.50,000 was based on a 1982 valuation for kidney transplantation.[18,19] Several countries in Europe use comparable thresholds for drug formulary decision making. However, a problem in using such thresholds is that the wealth of an individual country is not taken into consideration. To overcome this drawback, the World Health Organization (WHO) has recommended to use multiples of a country's *per capita* gross domestic product (GDP) to establish value thresholds for drug cost effectiveness.[19–21] Based on the WHO criteria, products more than three times the *per capita* GDP would be cost ineffective.[19] Using Spain as an illustration (i.e., *per capita* GDP = $U.S.33,700), the threshold for cost effectiveness of new cancer drugs would be $U.S.101,100 or €78,300 per QALY.[22] This is a higher one but perhaps more appropriate threshold for assessing the economic value of modern cancer drugs.

The use of thresholds based on *per capita* GDP in combination with pharmacoeconomic (PE) modeling to establish a value-based price for a cancer drug is novel because it incorporates product attributes such as disease response, survival, and quality of life improvements. To demonstrate its application, PE modeling was used to estimate the price of bevacizumab, a drug that provides a survival benefit to patients with metastatic colorectal cancer (mCRC) when added to first line chemotherapy.[23] Bevacizumab was chosen because its economic value has been questioned in recent PE studies making it a candidate for government mandated price cuts.[24,25] The analysis was conducted from the Spanish health care perspective because this is one of the countries where government mandated price controls are currently being imposed. Therefore, we seek to demonstrate that a value-based approach to estimate a drug price using *per capita* GDP thresholds is feasible and a better alternative to government imposed price controls.

Methods

Development of PE model

A decision model for the treatment of mCRC was developed with DATA software (Treeage Software Inc., Williamstown, MA, USA). The analytic timeframe was from cycle one of first line chemotherapy until death and a Spanish health care system perspective was taken. Oxaliplatin in combination with infusional 5-fluorouracil (FOLFOX) is a recommended standard of care for the first line treatment of mCRC.[26] If treatment related toxicity or disease progression develops, then irinotecan in combination with infusional 5-fluorouracil (FOLFIRI) is a recommended second line treatment.[27,28] It has also been demonstrated from a large randomized trial that sequential schedules of FOLFOX and FOLFIRI (or the reverse order) are equally effective and are now the first and second line standards of care for patients with mCRC.[28] Clinical practice guidelines also recommend the addition of an anti-vascular endothelial growth factor such as bevacizumab with either first or second line chemotherapy for mCRC.[29]

Using these treatment algorithms, a PE model was developed for the sequential treatment of mCRC with FOLFOX (±bevacizumab) followed by FOLFIRI upon disease progression (Figure 2). The primary outcome of the model was the achievement of successful therapy defined as complete tumor response (CR), partial response (PR), or stable disease during and following active therapy. However, all outcomes of the PE model resulted in eventual death, which is the ultimate consequence in this patient population. The face and content validity of the model was evaluated by three clinical oncologists who had experience in CRC.

The model began at the decision node where a selection for first line therapy would have to be made between FOLFOX + 'the new drug (bevacizumab)' or FOLFOX alone (Figure 2). During the first two cycles of chemotherapy, patients would be assessed for intolerable toxicity. In cases of severe toxicity, first line therapy would be permanently discontinued and second line FOLFIRI would be offered until disease progression or treatment-related death. When disease progression occurs, best supportive care would be offered until death. Treatment would be continued until disease progression in patients who tolerate first line FOLFOX (±'the new drug'). This would then be followed by second line FOLFIRI but the new drug would be discontinued. Upon progression following second line FOLFIRI, all patients would receive best supportive care until death (Figure 2). Epidermal growth factor receptor inhibitors such as cetuximab in mCRC patients with KRAS wild-type tumors were not

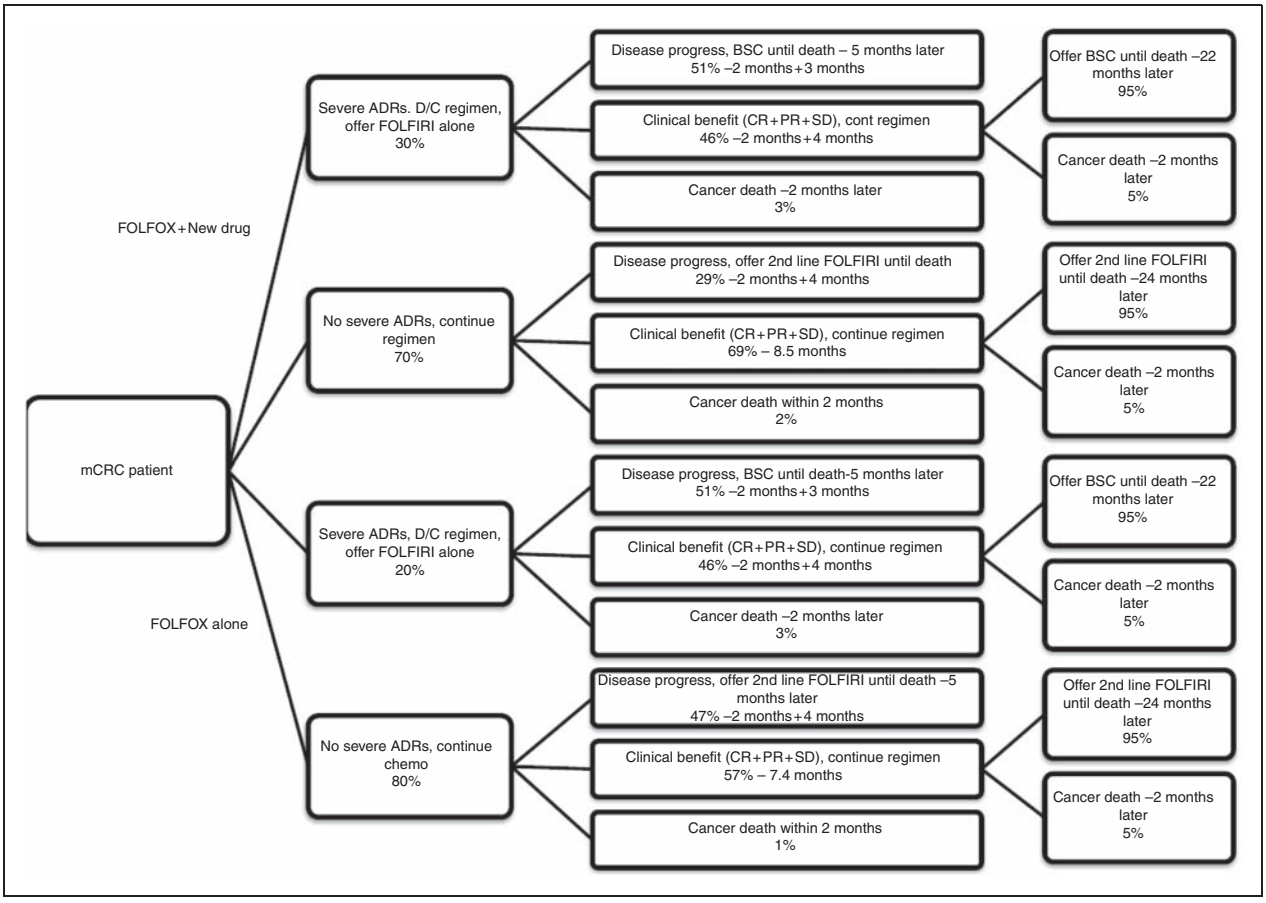

Figure 2. Decision analysis model for the treatment of metastatic CRC.

considered because we did not want to over complicate the modeling. Furthermore, such agents would be available to both treatments options in the model, so their inclusion would not impact the final results.

Clinical data

The relevant clinical data to populate the model consisted of early treatment discontinuations due to toxicity, the achievement of clinical benefit (CR, PR, or disease stabilization), duration of clinical benefit, risk of cancer-related death during active treatment and the number of chemotherapy cycles administered. To obtain these data, a literature search of Medline, Embase, and the Cochrane databases was performed from 2000 through 2010 for human clinical studies involving FOLFOX, FOLFIRI, and bevacizumab as first and second line therapies in mCRC. The main objective of the review was to identify the most up-to-date clinical data for populating the model. Care was taken to avoid inclusion of duplicate publications.

Estimation of treatment costs

The analytic time period for this investigation was from the start of first and then second line sequential chemotherapy until disease progression and eventual death. Costs for anticancer drugs, materials for drug delivery, patient monitoring, and other related hospital resources (e.g., laboratory and diagnostic tests) were obtained from a Spanish hospital. Palliative care costs for terminally ill cancer patients were obtained from the Spanish palliative care literature.[30] All costs in the current study were reported in 2010 Euros. Costs from previous years were converted into 2010 estimates using the Spanish consumer price index for health care.

Treatment preferences and health state utilities

Using the Time Trade-off technique, quality-adjusted life periods were measured as 'healthy months equivalent' for the time spent in each outcome of the decision model (Figure 2).[31,32] Healthy month equivalence scores measure patient utilities for a given health state. A lower healthy month equivalence for the total

time spent in a given health state suggests poorer quality of life during that time period (e.g., a time period where a cancer progression occurs). The scores in months were then converted to utility measures between 0 and 1, where 0 represented death and 1 was a state of perfect health or optimal quality of life. The healthy month equivalence was also converted into QALYs by dividing by 12 months and then entered into the associated branches of the decision analysis model.

Intuitively, the ideal population for measuring health states utilities and treatment preferences should be cancer patients with the disease in question who are in a position to receive the new treatment. However, in this study, oncology nurses and pharmacists were used as a patient surrogate sample because it was felt that terminally ill mCRC patients would have difficulty in understanding the Time Trade-off technique. There is also some evidence in the oncology literature to suggest that nurses and pharmacists can be suitable patient surrogates for objective outcomes, and that utility estimates derived from such a sample do not substantially alter the findings of cost utility studies.[33] With a sample of 24 respondents, healthy month equivalence was measured with a precision of ±1.0 month, with a 95% probability.

After informed consent was obtained, each participant was interviewed for 15–30 min by trained local investigator. Respondents were presented with information on FOLFOX, bevacizumab, and FOLFIRI consisting of the methods of administration, efficacy, and the side effects reported in the literature. The interview was then continued with a description of the 16 health states and the length of time a patient would live in each health state (Figure 2). The respondents were then asked how many months of 'optimal health' they considered being equivalent to the time spent in each of the less than optimal health states described in the model. These measures were then used to weigh each branch of the model by the quality of life experienced by a patient living through that time period. An identical process was used for each of the 16 outcomes (Figure 2). A standardized questionnaire supported by printed interview tools with graphical displays was used to facilitate the participant's understanding of the Time Trade-off technique. To minimize the framing effect, all pathways were presented in a consistent manner pictorially.

Value-based pricing analysis for the Spanish health care system

A cost utility analysis was undertaken to estimate a value-based price for the 'new drug' in the first line treatment of mCRC. The initial analysis assumed that the addition of the 'new drug (bevacizumab)' to first line oxaliplatin-based chemotherapy would provide a survival benefit of 1.4 month as reported in the literature.[34] The primary outcome of interest was to estimate a price per dose for the 'new drug' using a targeted incremental cost of €78,300 per QALY gained, which is three times the Spanish *per capita* GDP.[22] The evaluation did not include indirect costs because such data were not available for bevacizumab. In addition, future costs and benefits were not discounted because of the short-time periods involved. However, the stability of the baseline results was evaluated by a one-way sensitivity analysis. This consisted of substituting the 95% confidence intervals (CI) for the health state utilities as well as variations in the overall survival benefit and costs of care. Specifically, the survival gain was varied to 3 and 6 months from the baseline of 1.4 month. Costs were changed by ±15% to account for variations in costs across Spain.

Results

The literature search identified the relevant randomized trials to populate the PE model (Table 1). The first trial evaluated FOLFOX or a clinically similar regimen XELOX (capecitabine plus oxaliplatin) ± bevacizumab in the first line treatment of mCRC.[34] A total of 1401 patients were randomized to receive FOLFOX/XELOX + bevacizumab ($n = 699$) or FOLFOX/XELOX + placebo ($n = 701$). Median progression free survival was 9.4 months in the bevacizumab group compared to 8.0 months with placebo (HR = 0.83; $p = 0.023$). This resulted in a 1.4-month survival gain in favor of bevacizumab. Overall, 30% of patients in the bevacizumab group required a permanent treatment discontinuation because of adverse events compared to 20% in the control (Table 1).

Data on the safety and efficacy of second line FOLFIRI following first line FOLFOX were obtained from a randomized sequential trial reported by Tournigand et al.[28] Patients were randomized to receive sequential FOLFOX followed by FOLFIRI upon progression or the reverse sequence (Table 1). There was no significant difference in progression free and overall survival (FOLFOX − FOLFIRI = 21.5 *vs.* FOLFIRI − FOLFOX = 20.6 months; $p = 0.99$) between the two sequences.[28] With second line FOLFIRI, 51% of patients experienced disease progression for an overall progression free survival of 2.5 months, respectively.[28] Approximately, 3% of patients died within the first 60 days of second line FOLFIRI (Table 1).

Table 1. Published randomized trials providing clinical data to populate the economic model

Reference	Treatment arms	Clinical outcomes
Saltz et al.[34]	FOLFOX/XELOX + placebo	Disease progression = 47% Median PFS = 8.0 months Median duration of response = 7.4 months Overall survival = 21.3 months Treatment discontinuations = 20% Death during treatment = 1% Serious side effects (grade III/IV) = 8% *Specific grade III/IV side effects* Deep vein thrombosis = 5% Diarrhea = 11% Bleeding = 1% Neutropenia = 44%
	FOLFOX/XELOX + bevacizumab	Disease progression = 29% Median PFS = 9.4 months Median duration of response = 8.45 months Overall survival = 19.9 months Treatment discontinuations = 30% Death during treatment = 2% Serious side effects (grade III/IV) = 16% *Specific grade III/IV side effects* Deep vein thrombosis = 8% Diarrhea = 18% Bleeding = 2% Neutropenia = 50%
Tournigand et al.[28]	Second Line FOLFIRI	Disease progression = 51% Death during treatment = 3% Median PFS = 10.9 months Median number of cycles = 6

Abbreviations: PFS = progression-free survival, OS = overall survival, FOLFOX = oxaliplatin in combination with infusional 5-fluorouracil, and FOLFIRI = irinotecan in combination with infusional 5-fluorouracil.

Table 2. Mean cost per cycle of FOLFOX and FOLFIRI

Resource Item[a]	FOLFOX	FOLFIRI
Drug acquisition[a]	€521	€421
Ancillary drugs[b]	€129.73	€59.84
Preparation and administration[c]	€85.75	€57.66
Patient monitoring[d]	€88.69	€126.32
Protocol start-up costs[e]	€221.16	€239.09
Total cost per cycle	€825	€665

[a]Assuming a 60-kg patient with a body surface area of 1.6 m^2.
[b]Includes standard premedication and antiemetics.
[c]Includes materials, supplies, personnel, chemotherapy unit stays, and physician visits.
[d]Standard laboratory and diagnostic tests.
[e]These costs are a one-time cost in order to prepare the patient for the associated chemotherapy protocol. In the case of FOLFOX and FOLFIRI, preparations and materials for infusional 5-fluorouracil made up the bulk of the costs. For the economic analysis, the start-up costs were only applied once over the estimated median number of cycles delivered, thus avoiding double counting.

Table 3. Hospital costs for the treatment of metastatic CRC in Spain

Recourse item	Hospital cost
FOLFOX chemotherapy[a]	€825/cycle
FOLFIRI chemotherapy[b]	€665/cycle
Cost for a permanent chemotherapy discontinuation because of toxicity[c]	€1778
Cost to administer the 'new drug' after FOLFOX chemotherapy	€62.76
Cost of best supportive care[d]	€1654/month

[a]Oxaliplatin in combination with infusional 5-fluorouracil. Cost per cycle includes resources for drug administration and routine patient monitoring.
[b]Irinotecan in combination with infusional 5-fluorouracil.
[c]Patients would be admitted for 3 days for the management of side effects and for reassessment. The principle side effects that would lead to the discontinuation of therapy would be febrile neutropenia and grade III/IV diarrhea.
[d]From Gomex-Batiste.[30]

Estimation of treatment costs

From the unit cost estimates in Spain, the cost per cycle of FOLFOX was estimated to be €825. However, before the first cycle of FOLFOX, the protocol start-up costs were estimated to be approximately €221 (Table 2). The costs per cycle for FOLFIRI were slightly less at €665 with the associated start-up costs being €239. Additional costs required to populate the model which included costs for the management of severe toxicity, administration of the 'new drug,' and best supportive care are presented in Table 3. These estimates were then incorporated into the PE model for the subsequent pricing analysis.

Health state utility assessments

Health state utilities for the time period spent in each of the 16 health outcomes were the second component required for the analysis (Figure 2). Utilities for

each outcome were estimated from a sample of 24 respondents, consisting of oncology nurses ($n = 7$) and pharmacists ($n = 17$). The sample had a mean age of 38.2 years, an average of 10.9 years of direct oncology experience (range 0.1–40 years) and all but two had experience in the treatment of CRC patients. In addition, 22 of 24 (91.2%) respondents had direct clinical experience in the preparation/administration and follow-up care associated with FOLFOX (mean years = 6.1) and FOLFIRI (mean years = 5.4) chemotherapy. Furthermore, 100% and 95.8% had experience with the newer targeted therapies bevacizumab and cetuximab. Lack of drug cost knowledge could affect treatment preferences. Respondents were asked to state their knowledge of costs for modern oncology drugs. The findings revealed that 91.7% were 'very familiar' or 'somewhat familiar' with the cost of drugs used to treat cancer. The final series of demographic questions focused on respondent's family history of CRC. Eleven of 24 (45.8%) subjects had a positive family history for CRC.

The health state utilities from the respondents are presented in Table 4. The results suggested that patient utilities were most influenced by the severity of side effects and the speed of disease progression. The health states with the lowest utilities (i.e., branches 1, 4, 9, and 12 of the model – Figure 2) were those where first line therapy had to be stopped because of severe toxicity, the patient then had an early progression during second line treatment followed by cancer death a few months later. The branches with among the highest utilities (i.e., branches 7 and 15) were those where the patient tolerated the treatment, responded to first line therapy and then went on to receive maximum cycles. However, an unexpected finding was that the two scenarios of rapid cancer death within 2 months of starting chemotherapy (i.e., branches 8 and 16) were associated with high health state utilities (Table 4). The interpretation of this latter finding is that in cases of terminal disease, respondents may not be averse to a rapid death that would avoid prolonged pain and suffering. Alternatively, some respondents with only a short time to live may not be willing to trade length of life because they would want some time to settle their affairs and say good bye to loved ones.

Another observation was that branches which included treatment with the 'new drug' had comparable health state utilities to those where chemotherapy alone was given (Table 4). The hypothesis is that respondents were more concerned with achieving a disease response than the inconvenience and added risk of toxicity with the 'new drug.' Therefore, they were willing to endure toxicity from the addition of the new drug if it were to prolong life.

Value-based pricing analysis

Using the cost and utility data collected from the Spanish respondents along with a value threshold of €78,300 per QALY gained, the PE model was used to estimate a price for bevacizumab that would be considered cost effective. Assuming that bevacizumab would provide a 1.4-month survival benefit when added to FOLFOX chemotherapy, it could be priced at €342 per dose and be considered cost effective from the Spanish health care system perspective according to the WHO criteria.[19–21] This is substantially lower than the current price of bevacizumab which is greater than €900 per dose for a 60-kg patient.

The stability of the base case price point was tested with a series of one-way sensitivity analyses. These consisted of using the lower and upper 95%CI of the health state utilities, variations (±15%) in the cost of chemotherapy, best supportive care, and the management of side effects from anticancer therapy. In addition, the overall survival benefit of adding the new drug to FOLFOX chemotherapy was changed to 3 and 6 months, respectively. The results indicated that variations in the above costs had only minor effects on the overall price point for the new drug (Table 5). However, variations in the utilities and in the survival benefit did have a substantial effect on the price point.

The drug price rose to €733 when the upper 95%CI of the health state utilities for the new drug were applied to the model. In contrast, the price point for cost effectiveness was reduced to €318 when the lower 95%CI was used (Table 5). Similarly, increasing the overall survival benefit to 3 and 6 months allowed the drug price to increase to €843 and €2138 while retaining the same level of cost effectiveness. When the survival benefit was reduced to only 1 month, the price of the 'new drug' would have to be $342 per dose in order to achieve a cost per QALY of €78,300. To summarize, the major factors that would affect the economic value of a new drug for mCRC would be its ability to improve patient quality of life and overall survival by at least 3 months.

Discussion

The price of pharmaceuticals, particularly anticancer agents have been increasing more rapidly than any other component of health care.[35,36] Rising drug costs have now become a global concern as public systems struggle to offer modern treatments within a limited health care budget. Some view this as threatening the health care systems that are integral to the modern social contract itself.[8,37] Therefore, a new process for estimating drug price based on reasonable thresholds for economic value is required. Such thresholds should

Table 4. Health state utilities derived using the Time Trade-off technique

Sixteen health outcomes evaluated in the decision model	Time in health state[a]	Utility estimate[b] [mean (95%CI)]
FOLFOX + 'new drug' → FOLFIRI → BSC until death		
Branch #1: Stopped FOLFOX + the 'new drug' after two cycles due to side effects and was then treated with FOLFIRI for four cycles. There was disease progression. The patient received BSC and died 6 months later.	10 months	0.53 (0.46–0.60)
Branch #2: Stopped FOLFOX + the 'new drug' after two cycles due to side effects and was then treated with FOLFIRI. There was a response to FOLFIRI and the patient went on to receive eight cycles. Upon progression, the patient received BSC and died 22 months later.	28 months	0.65 (0.57–0.87)
Branch #3: Stopped FOLFOX + the 'new drug' after two cycles due to side effects and was then treated with FOLFIRI. There was a response to FOLFIRI and the patient went on to receive eight cycles. Upon progression, the patient received BSC and died 2 months later.	8 months	0.67 (0.58–0.76)
Branch #4: Stopped FOLFOX + the 'new drug' after two cycles due to side effects and was then treated with FOLFIRI for two cycles. However, the patient died due to cancer progression within the first 2 months.	4 months	0.52 (0.42–0.62)
Branch #5: Tolerated side effects but had disease progression after four cycles of FOLFOX + the 'new drug.' The patient was then treated with FOLFIRI for four cycles but the disease did not respond. The patient received BSC and died 2 months later.	6 months	0.61 (0.55–0.68)
Branch #6: Tolerated side effects and responded FOLFOX + the 'new drug.' The patient went on to receive a total of 17 cycles of first line therapy. Upon progression, the patient went on to receive six cycles of FOLFIRI. Upon progression, the patient received BSC and died 21 months later.	29 months	0.69 (0.61–0.76)
Branch #7: Tolerated side effects and responded FOLFOX + the 'new drug.' The patient went on to receive a total of 17 cycles of first line therapy. Upon progression, the patient went on to receive two cycles of FOLFIRI but died 2 months later.	11 months	0.81 (0.74–0.89)
Branch #8: Tolerated side effects and but had disease progression after two cycles of FOLFOX + the 'new drug.' The patient died due to the cancer 1 month later.	2 months	0.84 (0.75–0.94)
FOLFOX → FOLFIRI → BSC until death		
Branch #9: Stopped FOLFOX after two cycles due to side effects and was then treated with FOLFIRI for four cycles. There was disease progression. The patient received BSC and died 6 months later.	10 months	0.54 (0.47–0.62)
Branch #10: Stopped FOLFOX after two cycles due to side effects and was then treated with FOLFIRI. There was a response to FOLFIRI and the patient went on to receive eight cycles. Upon progression, the patient received BSC and died 22 months later.	28 months	0.66 (0.59–0.74)
Branch #11: Stopped FOLFOX after two cycles due to side effects and was then treated with FOLFIRI. There was a response to FOLFIRI and the patient went on to receive eight cycles. Upon progression, the patient received BSC and died 2 months later.	8 months	0.68 (0.59–0.77)
Branch #12: Stopped FOLFOX after two cycles due to side effects and was then treated with FOLFIRI for two cycles. However, the patient died due to cancer progression within the first 2 months.	4 months	0.53 (0.43–0.63)
Branch #13: Tolerated side effects but had disease progression after four cycles of FOLFOX. The patient was then treated with FOLFIRI for four cycles but the disease did not respond. The patient received BSC and died 2 months later.	6 months	0.61 (0.55–0.68)
Branch #14: Tolerated side effects and responded FOLFOX. The patient went on to receive a total of 15 cycles of first line therapy. Upon progression, the patient went on to receive six cycles of FOLFIRI. Upon progression, the patient was offered BSC and died 21 months later.	32 months	0.65 (0.57–0.73)
Branch #15: Tolerated side effects and responded FOLFOX. The patient went on to receive a total of 15 cycles of first line therapy. Upon progression, the patient went on to receive two cycles of FOLFIRI but died 2 months later.	11 months	0.80 (0.72–0.87)
Branch #16: Tolerated side effects and but had disease progression after two cycles of FOLFOX. The patient died due to cancer progression 1 month later.	2 months	0.84 (0.75–0.94)

Abbreviations: FOLFOX = oxaliplatin + infusional 5-FU. FOLFIRI = irinotecan + infusional 5-FU, BSC = best supportive care.
[a]As presented in each branch of the decision analysis model.
[b]A quality of life score for a health state between 0 and 1, with 0 = death and 1 = optimal health.

Table 5. Sensitivity analysis on the unit price for the 'new drug.'

Sensitivity manoeuvre[a]	Price per dose
Base case	€342
Lower and upper 95%CI of health state utilities for chemotherapy + the 'new drug'	€318 to €733
Changing cost of FOLFOX chemotherapy by ±15%	€323 to €361
Changing cost of FOLFIRI chemotherapy by ±15%	€340 to €344
Changing cost of BSC cost by ±15%	€282 to €402
Changing cost of ADR cost by ±15%	€339 to €345
Changing survival benefit of the 'new drug' from 1.4 to 3 months	€843
Changing survival benefit of the 'new drug' from 1.4 to 6 months	€2138

Abbreviations: FOLFOX = Oxaliplatin in combination with infusional 5-fluorouracil, FOLFIRI = Irinotecan in combination with infusional 5-fluorouracil, BSC = best supportive care, and ADR = adverse drug reaction costs.
[a]For a target threshold of €78,300 per QALY when the new drug is added to FOLFOX chemotherapy.

consider the wealth of a nation but at the same time provide price points for new agents that would provide a return of investment to the innovating company.

In this study, we present a process that uses PE modeling along with the WHO criteria for economic value to determine price points for new cancer drugs. Using mCRC patients from Spain as our case study, we demonstrated that prices ranging from €843 to €2138 would be considered cost effective for a new drug that is able to improve survival by 3–6 months, respectively. Considering a drug like bevacizumab which provided the clinical data for the case study, the price estimates generated suggest that it has priced excessively, given the modest 1.4-month survival gain and the lack of quality of life data in mCRC patients.

Our proposed approach to drug pricing has several advantages such as improved transparency to many stakeholders and also the ability to link product performance to price. We would also argue that it is preferable to current draconian measures such as mandated government price controls which may compromise patent care and threaten innovation.[11–13] In the very least, our proposed value-based pricing approach provides the starting point for committed negotiations between payers and the pharmaceutical industry.

There are a number of limitations in the application of this technique that have to be discussed. For our modeling strategy to be applied, a new drug must demonstrate either an improvement in quality of life over the standard of care or a survival of sufficient magnitude to identify a final price point that would be commercially viable for the manufacturer. Our modeling exercise was theoretical using simple decision analysis. For the proposed methodology to be viable, complete data from randomized trials on a drug by drug basis are required to conduct more robust economic modeling such as Markov processes. We used oncology nurses and pharmacists to provide the utility data. Even though there are data suggesting that such a sample provides acceptable data for cost utility studies,[33] mCRC patients would have been preferable. The objective of our analysis was to provide a systematic process that would make important drugs available to patients at a price that is considered to be cost effective. This does not necessarily mean that annual drug expenditures will be contained. True therapeutic innovation requires an investment by society. Therefore, increased spending for innovative drugs should be expected and planned for by formulary committees. The budgetary planning process is also complicated and many other factors such as price cuts from the manufacturer during a drugs life cycle and the existence of lower priced alternatives need to be considered. At the time of the publication, price cuts of up to 30% for oxaliplatin and irinotecan were implemented in Spain. However in our sensitivity analysis, the lowest range in the cost of these drugs that we considered was 15%. Nevertheless, reductions of oxaliplatin and irinotecan costs of up to 30% would have only had a minimal impact on our base case results because such costs were not major drivers in estimating the final price points for cost effectiveness.

Conclusions

A value-based pricing approach using PE modeling and the WHO criteria for economic value is feasible and a better alternative to government mandated price cuts. The former approach would also be a good starting point for opening dialogue between government payers and the pharmaceutical industry because it would link drug price to overall product performance.

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The application of pharmacoeconomic modelling to estimate a value-based price for new cancer drugs

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Abstract

Rationale, aims and objectives Value-based pricing has recently been discussed by international bodies as a means to estimate a drug price that is linked to the benefits it offers patients and society. The World Health Organization (WHO) has recommended using three times a country's per capita gross domestic product (GDP) as the threshold for economic value. Using the WHO criteria, pharmacoeconomic modelling was used to illustrate the application of value-based price towards bevacizumab, a relatively new drug that provides a 1.4-month survival benefit to patients with metastatic colorectal cancer (mCRC).

Methods A decision model was developed to simulate outcomes in mCRC patients receiving chemotherapy ± bevacizumab. Clinical data were obtained from randomized trials and costs from Canadian cancer centres. Utility estimates were determined by interviewing 24 oncology nurses and pharmacists. A price per dose of bevacizumab was then estimated using a target threshold of $CAD117 000 per quality adjusted life year gained, which is three times the Canadian per capita GDP.

Results For a 1.4-month survival benefit, a price of $CAD830 per dose would be considered cost-effective from the Canadian public health care perspective. If the drug were able to improve patient quality of life or survival from 1.4 to 3 months, the drug price could increase to $CAD1560 and $CAD2180 and still be considered cost-effective.

Discussion The use of the WHO criteria for estimating a value-based price is feasible, but a balance between what patients/governments can afford to pay and the commercial viability of the product in the reference country would be required.

Introduction

Cancer remains a global health problem. In 2008, there were approximately 7.4 million cancer deaths from the disease, which was approximately 13% of deaths from all causes [1]. Given our ageing population, the number of new cancer diagnoses are also expected to increase over the next 20 years [2]. But encouragingly, the number of cancer deaths has stabilized over the past 5 years [2–4]. Part of this stabilization in overall mortality has been attributed to the clinical approval and availability of new cancer drugs [4,5].

One defining feature of the newer oncology products is that they are available at a substantially higher cost than traditional chemotherapy [6]. In one editorial, the cost of an 8-week course of chemotherapy for metastatic colorectal cancer (mCRC) in the mid-1990s was estimated to be less than $US300 [7]. Ten years later, the costs for an 8-week regimen containing the monoclonal antibodies bevacizumab or cetuximab ranged from $US21 000 to $US31 000. These costs would be prohibitively high for most patients in the USA without good health care insurance. In countries with socialized health care systems, either such drugs have been rejected for reimbursement by national health care agencies or patient access has been delayed or limited following initial regulatory approval [5,8].

The challenge is that these incremental costs have to be taken into context with gains in overall survival and improvements in patient quality of life. In the 1990s when fluorouracil plus leucovorin was the only active chemotherapy regimen for mCRC, median

overall survival did not exceed 6 months [7]. With the emergence of agents like bevacizumab and cetuximab, overall survival in combination with first line fluorouracil-based chemotherapy has now exceeded 20 months [9,10]. Therefore as a society, we must determine what we are willing to pay for a life year gained [6].

Quality adjusted life years (QALYs) are a way of measuring the total impact of a disease such as cancer. They include both quality and the quantity of life and are used to quantify the relative benefit of two competing medical interventions. Through the application of pharmacoeconomic (PE) analysis, the incremental cost per QALY gained between a new treatment and the standard of care is then determined, which is then followed by a funding decision [11]. Such evaluations are typically conducted once a new product is approved for clinical use and the price per dose has been set. However, PE may have an additional and perhaps more valuable role in estimating or negotiating the price of the drug based on societal value thresholds and before it becomes commercially available. PE has been used for negotiating a final price for a few cancer drugs assessed by the National Institute of Clinical Excellence (NICE) of the United Kingdom (UK) [12]. Hence, this approach can also be used to estimate a value-based price for the drug prior to regulatory approval.

One of the major challenges against the use of PE analysis for estimating a value-based drug price is in establishing the threshold for value within a given country. Many nations have been reluctant to publicly state such a figure because of the ethical issue of placing a monetary value on human life. To address this, the World Health Organization (WHO) has proposed to use multiples of a country's per capita gross domestic product (GDP) to establish thresholds for economic value [13–15]. Products less than or equal to the per capita GDP would be considered very cost-effective, one to three times would be cost-effective and more than three times would be cost-ineffective [13]. Using Canada as an illustration (i.e. per capita GDP = $US39 000), the three-time threshold for cost-effectiveness of new anticancer drugs would be approximately $US117 000 per QALY gained [16]. For a lower income country such as India (per capital GDP = $US3100), the cost per QALY gained threshold would be $US9300.

The use of thresholds based on per capita GDP in combination with PE modelling to establish a value-based price for a drug is an interesting approach because it would determine a final price based on the attributes of the product in terms of disease response, survival and quality of life benefits. To illustrate the application of this drug pricing strategy, PE modelling was used in the current study to estimate the price of bevacizumab, a cancer drug that is commercially available. However in this analysis, bevacizumab was defined as the 'new drug'. The clinical scenario for the case study was bevacizumab in combination with the first line chemotherapy for treatment of mCRC [17]. This agent was chosen because it has a high acquisition price and its economic value has been questioned in recent PE studies [18,19].

Methods

Economic model

The clinical and economic outcomes for mCRC were modelled using the principles of decision analysis. mCRC was chosen because the sequential use of specific chemotherapy regimens is well established. The current standard of care for the first line treatment of mCRC is oxaliplatin in combination with infusional 5-fluorouracil (FOLFOX). In patients who have disease progression or intolerable toxicity, second line irinotecan in combination with infusional 5-fluorouracil (FOLFIRI) is a recommended treatment [20,21]. Data from a large randomized trial also verified that sequential schedules of FOLFOX and FOLFIRI (or the reverse order) are equally effective and have thus emerged as the first and second line standard of care for patients with mCRC [22]. The addition of an anti-vascular endothelial growth factor (VEGF) such as bevacizumab at some point during chemotherapy for mCRC has also been recommended by clinical practice guidelines [23].

A decision model for the sequential treatment of mCRC with FOLFOX (±an anti-VEGF agent) and then followed by FOLFIRI upon disease progression was developed with the DATA software (Treeage Software Inc., Williamstown, MA, USA) (Fig. 1). The analytic timeframe was from the first cycle of FOLFOX chemotherapy until death and a Canadian health care system perspective was taken. The primary outcome for measuring successful initial therapy was clinical benefit, defined as complete tumour response (CR), partial response (PR) or stable disease (SD) based on the Response Evaluation Criteria in Solid Tumors. Three clinical oncologists who had experience in colorectal cancer evaluated the face and content validity of the model.

The model began at the decision node (square) where the first line treatment choice would be either FOLFOX + 'the new drug (bevacizumab)' or FOLFOX alone (Fig. 1). During the first two cycles of chemotherapy, patients would be assessed for intolerable toxicity. For those patients with severe toxicity, first line therapy would be discontinued in its entirety and second line FOLFIRI would be offered until disease progression. Upon progression, all patients would receive best supportive care until death. In contrast, patients who do not experience severe toxicity from first line FOLFOX (±'the new drug') would also receive treatment until disease progression. They would then be offered second line FOLFIRI alone and the 'new drug' would be discontinued. Upon progression, all patients would receive best supportive care until death (Fig. 1). To simplify the modelling, epidermal growth factor receptor (EGFR) inhibitors such as cetuximab in mCRC patients with KRAS wild-type tumours were not considered. Furthermore, such agents would be available to both treatments options in the model, so their inclusion would not impact the final results.

Clinical data

The clinical data required to populate the model consisted of early treatment discontinuations because of toxicity, achievement of clinical benefit (CR + PR + SD), duration of clinical benefit, risk of cancer-related death during active treatment and number of chemotherapy cycles administered. These data were obtained through a literature search of randomized trials evaluating FOLFOX (±bevacizumab) in the first line setting and second line FOLFIRI in the treatment of mCRC. A literature search of Medline, Embase and the Cochrane databases was performed from 2000 to 2010 for human clinical studies involving FOLFOX, FOLFIRI and bevacizumab as first and second line therapy in

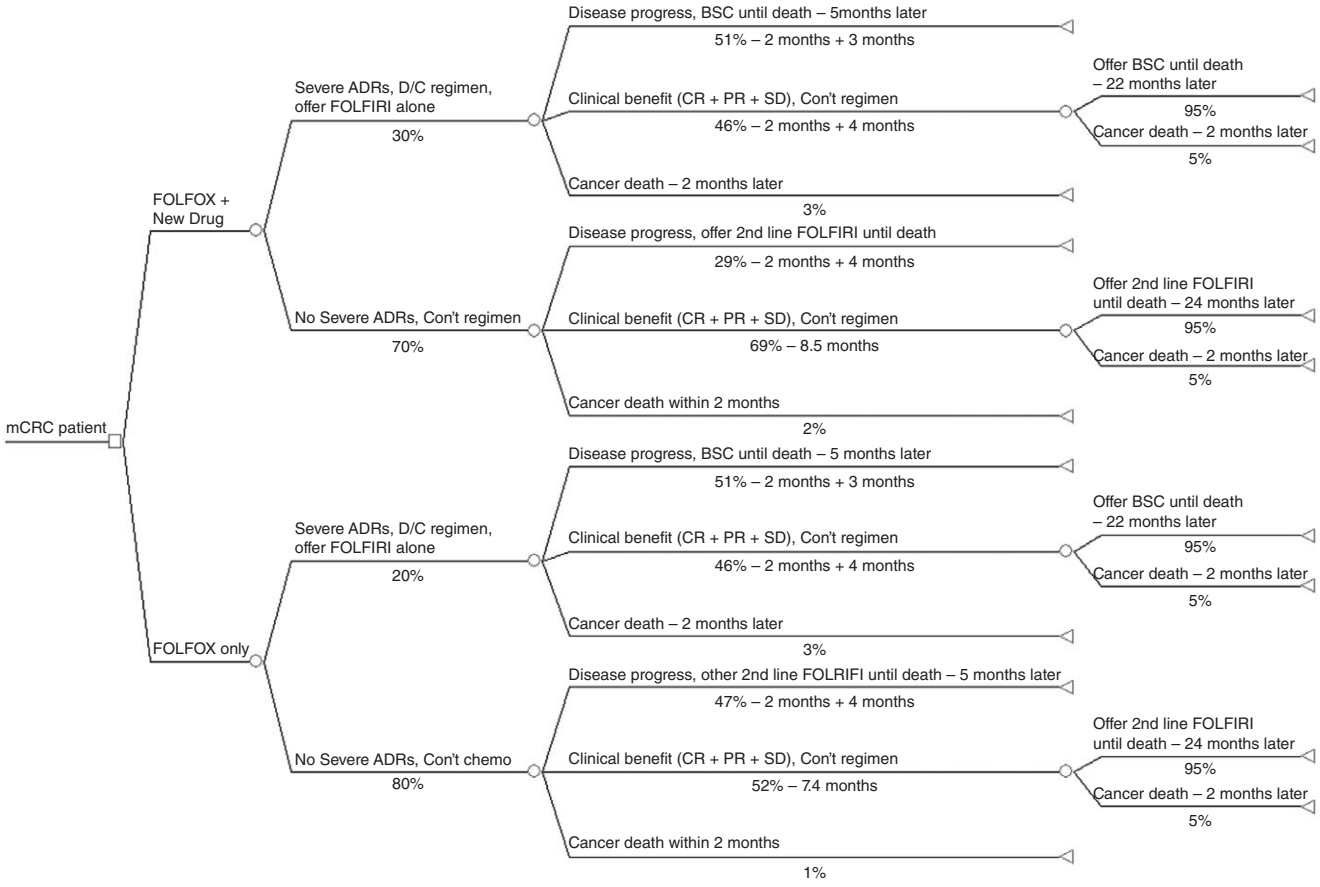

Figure 1 Decision analysis model for the treatment of metastatic colorectal cancer. ADR, adverse drug reaction costs; BSC, best supportive care; CR, complete tumour response; D/C, discontinued; FOLFIRI, irinotecan in combination with infusional 5-fluorouracil; FOLFOX, oxaliplatin in combination with infusional 5-fluorouracil; mCRC, metastatic colorectal cancer; PR, partial response; SD, stable disease.

mCRC. The primary objective of the review was to identify the most up-to-date clinical data for populating the model. Care was taken to avoid inclusion of duplicate publications.

Estimation of treatment costs

The analytic time period for this investigation was from the start of first and second line sequential chemotherapy until disease progression and a Canadian health care system perspective was taken. To estimate the direct overall cost of a cycle of FOLFOX and FOLFIRI, a series of quantitative interviews were conducted with oncology nurses and pharmacists who had experience in managing colorectal cancer patients and in the preparation and administration of infusional 5-fluorouracil, oxaliplatin, irinotecan and bevacizumab in this patient population. Overall, 12 health care professionals from three distinct cancer centres (four from each centre) were interviewed to determine the direct resource requirements for FOLFOX, FOLFIRI and bevacizumab. For each chemotherapy protocol, a standardized data collection form was used to collect such items as drug dosage, materials and pharmacy time required for chemotherapy preparation, prophylactic medication, laboratory and diagnostic tests, physician visits, nursing time to administer treatment and all other relevant hospital resource requirements.

In addition to direct costs for drug acquisition, preparation, administration and monitoring, ancillary health care resources required by these patients were also quantified. These include costs for interventions to manage grade III/IV side effects, palliative care costs such as radiation for bone pain, blood transfusions and recombinant erythropoietin for severe anaemia (in some patients), analgesics for pain control and physician costs. In addition, it was assumed that all patients would receive home health care visits or hospice care. These additional data were obtained from the three colorectal cancer oncologists through a standardized data collection form.

Costs for drugs, materials and other related hospital resources (e.g. laboratory and diagnostic tests) were obtained from the University Health Network, 2010. Physician's fees for service were obtained from the Schedule of Benefits: Physician Services under the Health Insurance Act, Ontario Ministry of Health, 2008. Costs from non-Canadian sources were converted and updated into 2010 Canadian dollars using the consumer price index for health care as reported by Statistics Canada ($CAD1 = $US1, as of June 2010).

Treatment preferences and health state utilities

The health-related quality of life values measured in the analysis were patient preferences for alternative health outcomes, as depicted in the decision analytic model (Fig. 1). In the current study, quality-adjusted life periods were measured as 'healthy months equivalent' for the time spent in each outcome of the decision model using the Time Trade-off technique [24,25]. Healthy month equivalence scores measure patient utilities for a given health state. A lower healthy month equivalence for the total time spent in a given health state suggests poorer quality of life during that time period (e.g. a time period when a cancer progression occurs). The scores in months were then converted to utility measures between 0 and 1, where 0 represented death and 1 was a state of perfect health or optimal quality of life. Gains in healthy month equivalence were also converted into QALYs by dividing by 12 months and then entered into the associated branches of the decision analysis model.

Intuitively, the ideal population for measuring health state utilities and treatment preferences should be cancer patients with the disease in question who are in a position to receive the new treatment. However, it has been recommended in the Canadian Guidelines for Economic Evaluations and by the Panel on Cost-Effectiveness in Health and Medicine of the United States that treatment preferences be measured from members of the general public who are potential candidates of the new medical intervention [11,26]. However based on our experience, members of the general public have difficulty in understanding cancer-related utility questionnaires. As a compromise, a patient surrogate group was used that would provide insight from both the perspective of the patient and members of the general public. There is also evidence in the oncology literature to suggest that nurses are suitable patient surrogates for objective outcomes, and that utility estimates derived from such a sample do not substantially alter the findings of cost utility studies [27,28]. Therefore, a patient surrogate sample consisting of 24 oncology nurses provided utility values for the model. With a sample of 24 respondents, healthy month equivalence was measured with a precision of $\pm$1.0 month, with a 95% probability.

After informed consent was obtained, each participant was interviewed for 30 to 45 minutes by trained local field investigators. Respondents were presented with information on FOLFOX, bevacizumab and FOLFIRI consisting of the methods of administration, efficacy and the side effects reported in the literature. The interview was then continued with a description of the 16 health states and the length of time a patient would live in each health state (Fig. 1). The respondents were then asked how many months of 'optimal health' they considered being equivalent to the time spent in each of the less than optimal health states described in the model. These measures were then used to weigh each branch of the model by the quality of life experienced by a patient living through that time period. An identical process was used for each of the 16 outcomes (Fig. 1).

A standardized questionnaire supported by printed interview tools with graphical displays was used to facilitate the participant's understanding of the Time Trade-off technique. To minimize the framing effect, all pathways were presented in a consistent manner pictorially. Demographic data were also collected from each participant, and consisted of years of oncology and colorectal cancer experience, involvement in the development of systemic treatment guidelines for colorectal cancer, familiarity with the cost of anticancer drugs and family history of colorectal cancer.

Value-based pricing using cost utility analysis

The clinical, economic and respondent utility data were then combined into a cost–utility analysis to estimate a price per dose for the 'new drug' in the first line treatment of mCRC. The base case analysis assumed that the addition of the bevacizumab to standard chemotherapy would provide a survival benefit of 1.4 months (*vide infra*). The primary objective of the analysis was to estimate a price for the 'new drug' using a targeted incremental cost of $US117 000 per QALY gained, which is three times the Canadian per capita GDP [16]. Indirect costs were not included because there was no data available on the association between bevacizumab usage and indirect cost avoidance. Future costs and benefits were not discounted because of the short time periods involved. However, the stability of the baseline results was evaluated by a one-way sensitivity analysis. This consisted of substituting the 95% confidence intervals (CI) for the health state utilities as well as variations in the overall survival benefit and costs of care. Overall survival was increased by approximately two and four times to account for gains that are considered clinically relevant for new drugs in mCRC. Costs of care were varied by $\pm$15% to capture any potential differences across the country.

Results

Two randomized trials were identified that provided the required data for the decision model (Table 1). The first trial evaluated FOLFOX or a clinically similar regimen XELOX (capecitabine plus oxaliplatin) $\pm$bevacizumab in the first line treatment of mCRC [10]. A total of 1401 patients were randomized to receive FOLFOX/XELOX + bevacizumab (n = 699) or FOLFOX/XELOX + placebo (n = 701). The interaction between FOLFOX and XELOX on the primary clinical endpoint was not statistically significant (P = 0.70) thereby justifying the combining of patients who received FOLFOX and XELOX [10]. Median progression free survival was 9.4 months in the bevacizumab group compared to 8.0 months with placebo (Hazard = 0.83; P = 0.023) resulting in a survival gain of 1.4 months (P = 0.077). Overall, 30% of patients in the bevacizumab group required a permanent treatment discontinuation because of adverse events compared to 20% in the control (Table 1). Approximately 2% and 1% of patients died during treatment with bevacizumab and placebo (Table 1).

Data on the safety and efficacy of second line FOLFIRI following first line FOLFOX was obtained from a randomized sequential trial reported by Tournigand *et al*. [22]. Patients were randomized to receive sequential FOLFOX followed by FOLFIRI upon progression or the reverse sequence (Table 1). There was no significant difference in progression free and overall survival (FOLFOX–FOLFIRI = 21.5 vs. FOLFIRI–FOLFOX = 20.6 months; P = 0.99) between the two sequences [22]. With second line FOLFIRI, 51% of patients experienced disease progression for an overall progression free survival of 2.5 months, respectively [22]. Approximately 3% of patients died within the first 60 days of second line FOLFIRI (Table 1).

Table 1 Published randomized trials providing clinical data to populate the economic model

Reference	Treatment arms	Clinical outcomes
Saltz *et al.*, (2008) [10]	FOLFOX/XELOX + bevacizumab	Disease progression = 29% Median PFS = 9.4 months Median duration of response = 8.45 months Overall survival = 21.3 months Treatment discontinuations = 30% Death during treatment = 2% Serious side effects (grade III/IV) = 16% *Specific grade III/IV side effects* Deep vein thrombosis = 8% Diarrhea = 18% Bleeding = 2% Neutropenia = 50%
	FOLFOX/XELOX + placebo	Disease progression = 47% Median PFS = 8.0 months Median duration of response = 7.4 months Overall survival = 19.9 months Treatment discontinuations = 20% Death during treatment = 1% Serious side effects (grade III/IV) = 8% *Specific grade III/IV side effects* Deep vein thrombosis = 5% Diarrhea = 11% Bleeding = 1% Neutropenia = 44%
Tournigand *et al.*, (2004) [23]	Second Line FOLFIRI	Disease progression = 51% Death during treatment = 3% Median PFS = 10.9 months Median number of cycles = 6

PFS, progression free survival; FOLFOX, oxaliplatin in combination with infusional 5-fluorouracil; FOLFIRI, irinotecan in combination with infusional 5-fluorouracil; XELOX, capecitabine plus oxaliplatin.

Estimation of treatment costs

A total of 12 respondents with experience in chemotherapy administration in patients with mCRC were interviewed to estimate the resource utilization. Among the 12 respondents, the median duration of chemotherapy experience in mCRC was 14.6 years (range = 5 to 33 years). Respondents for the interviews were selected from three different cancer centres to ensure a wide range of treatment settings. All 12 respondents had direct experience with FOLFOX, FOLFIRI and bevacizumab.

The resource requirement data for each protocol collected through the case report forms were then combined with the unit cost estimates to determine the cost per cycle. FOLFOX at $CAD2121 had the lowest cost per cycle followed by FOLFIRI at $CAD684 (Table 2). Additional costs required to populate the model which included costs for the management of severe toxicity, administration of the bevacizumab and best supportive care are presented in Table 3. These estimates were then incorporated into the decision model for the subsequent pricing analysis.

Table 2 Mean cost per cycle of FOLFOX and FOLFIRI

Resource item*	FOLFOX ($CAD)	FOLFIRI ($CAD)
Drug acquisition*	1530.00	179.00
Ancillary drugs†	163.10	89.13
Preparation and administration‡	339.19	331.36
Patient monitoring§	88.70	84.42
Protocol start up costs¶	199.07	213.63
Total cost per cycle (95%CI)	2121 (1919–2326)	684 (601–768)

*Assuming a 60-kg patient.
†Includes standard premedication and antimetics.
‡Includes materials, supplies, personnel, chemotherapy unit stays and physician visits.
§Standard laboratory and diagnostic tests.
¶These costs are a one-time cost in order to prepare the patient for the associated chemotherapy protocol. In the case of FOLFOX and FOLFIRI, preparations and materials for infusional 5-fluorouracil made up the bulk of the costs. For the economic analysis, the start-up costs were only applied once over the estimated median number of cycles delivered. Thus avoiding double counting.
FOLFOX, oxaliplatin in combination with infusional 5-fluorouracil; FOLFIRI, irinotecan in combination with infusional 5-fluorouracil.

Health state utility assessments

The second component required for the cost–utility analysis was health state utilities for the time period spent in each of the 16 health states (Fig. 1). Utilities for each outcome were estimated

Table 3 Hospital costs for the treatment of metastatic colorectal cancer in Canada

Recourse item	Public hospitals
FOLFOX chemotherapy*	$CAD2121/cycle
FOLFIRI chemotherapy†	$CAD684/cycle
Cost for a permanent chemotherapy discontinuation because of toxicity‡	$CAD2312
Cost to administer the 'new drug' after FOLFOX chemotherapy	$CAD60.50
Cost of best supportive care§	$CAD1233/month

*Oxaliplatin in combination with infusional 5-fluorouracul. Cost per cycle includes resources for drug administration and routine patient monitoring.

†Irinotecan in combination with infusional 5-fluorouracil.

‡Patients would be admitted for 3 days for the management of side effects and for reassessment. The main toxicities leading to a discontinuation were assumed to be either febrile neutropenia of grade III/IV or diarrhoea.

§After failing two lines of chemotherapy, patients would receive best supportive care on an outpatient basis until death. These resources were obtained from a survey of three medical oncologists and consisted of monthly patient needs such as radiation therapy, blood transfusions, analgesics and home care.

FOLFOX, oxaliplatin in combination with infusional 5-fluorouracil; FOLFIRI, irinotecan in combination with infusional 5-fluorouracil.

from a sample of 24 respondents, consisting of oncology nurses ($n = 12$) and pharmacists ($n = 12$). The sample had a mean age of 41.3 years and an average of 11.1 years of direct oncology experience (range 0–23 years) and all but one had experience in the treatment of colorectal cancer patients. In addition, 20 of 24 (83.3%) respondents had direct clinical experience in the administration and follow-up care associated with FOLFOX (mean years = 4.9) and FOLFIRI (mean years = 4.8) chemotherapy. Furthermore, 83.3% and 58.3% had experience with the newer targeted therapies bevacizumab and cetuximab. Lack of drug cost knowledge could affect treatment preferences. Respondents were asked to state their knowledge of costs for modern oncology drugs. The findings revealed that 91.7% were 'very familiar' or 'somewhat familiar' with the cost of drugs used to treat cancer. The final series of demographic questions focused on respondent's family history of colorectal cancer. The findings revealed that 3 of 24 (12.5%) subjects had a positive family history for colorectal cancer. Therefore, the above data suggests that the respondent sample was well informed about mCRC and able to provide meaningful health state utility estimates.

The health state utilities from the oncology nurses are presented in Table 4. The results suggested that patient utilities were most influenced by the severity of side effects, the speed of disease progression and the risk of rapid cancer death. The health states with the lowest utilities (i.e. branches 4, 8, 12 and 16 of the model – Fig. 1) were those where first line therapy had to be stopped because of severe toxicity, and the patient then had an early progression during second line treatment followed by rapid cancer death. It was also interesting to note that in all of the related scenarios, branches that included treatment with the 'new drug' had comparable health state utilities to those where chemotherapy alone was given (Table 4). The interpretation is that respondents were more concerned with achieving a disease response than the inconvenience and the added risk of toxicity with the 'new drug'. Therefore, they were willing to endure added toxicity from the addition of the 'new drug'.

Value-based pricing analysis

The outcomes data from the clinical trial, the estimated costs associated with each treatment and the health state utility estimates were combined for a value-based pricing analysis. The price for one dose of the 'new drug' was then varied until the incremental cost-effectiveness ratio reached a threshold of $CAD117 000 per QALY gained. Using this approach from the public health care system perspective, the base case analysis suggested that a price per dose of $CAD830 would be considered cost-effective for Canada according to the WHO criteria [13–15].

A series of one-way sensitivity analyses were then conducted using the upper 95% CI for the health state utilities, variations in treatment costs and overall survival benefit. When the costs of chemotherapy, best supportive care and side effects management were varied by $\pm 15\%$, the impact on the base case finding was negligible (Table 5). The two biggest factors to impact the base case findings were the health state utilities associated with the 'new drug' and the overall survival gain. The price rose to $CAD1560 per dose when the upper 95% CI of the health state utilities for the new drug were applied to the model. Increasing the overall survival benefit from 1 to 3 and then 6 months allowed the drug price to increase to $CAD2180 and $CAD3430 while providing the same cost per QALY.

Bevacizumab is available in Canada and the price is approximately $CAD2250 per dose (7.5 mg kg^{-1} for a 60 kg patient at a price of $CAD5.00 mg kg^{-1}) for an average mCRC patient. A sensitivity analysis was conducted where the current price of bevacizumab was applied to the model. The results revealed that the incremental cost per QALY gained would be $CAD224 000, well above the $CAD117 000 WHO recommended threshold. In summary, the sensitivity analyses suggested that a price of approximately $CAD830 per dose for a 'new drug' that would prolong patient survival by 1.4 months would be considered cost-effective in Canada using the WHO criteria for value. This price could be adjusted upwards if a new drug was able to enhance patient quality of life or extend survival to 3 or 6 months.

Discussion

In many countries around the world, health care costs have been rising beyond the rate of inflation [29,30]. The main components of health care expenditures are costs for physicians, hospital services and pharmaceuticals. Among these three, the latter is an identifiable and easy source for initial cost containment initiatives. This has certainly been the case in many European countries, as they struggle to contain rising health care costs. In Spain and Greece, the respective governments recently legislated price cuts of up to 23% of branded products [31,32]. Annual drug expenditures in Spain were approximately 12.5 billion euros in 2009, a 4.4% increase from the previous year [32]. Therefore, it was projected that these price cuts would save the national health care system 1.3 billion euros [32]. France has also announced price cuts for both branded and generic products [33]. However, more con-

Table 4 Health state utilities derived using the Time Trade-off technique

Sixteen health outcomes evaluated in the decision model	Time in health state* (months)	Utility estimate† [mean (95% CI)]
FOLFOX + 'new drug' → Folfiri → BSC until death		
Branch #1: Stopped FOLFOX + the 'new drug' after 2 cycles due to side effects and was then treated with FOLFIRI for 4 cycles. There was disease progression. The patient received BSC and died 6 months later.	10	0.61 (0.54–0.68)
Branch #2: Stopped FOLFOX + the 'new drug' after 2 cycles due to side effects and was then treated with FOLFIRI. There was a response to FOLFIRI and the patient went on to receive 8 cycles. Upon progression, the patient received BSC and died 22 months later.	28	0.63 (0.55–0.72)
Branch #3: Stopped FOLFOX + the 'new drug' after 2 cycles due to side effects and was then treated with FOLFIRI. There was a response to FOLFIRI and the patient went on to receive 8 cycles. Upon progression, the patient received BSC and died 2 months later.	8	0.65 (0.57–0.73)
Branch #4: Stopped FOLFOX + the 'new drug' after 2 cycles due to side effects and was then treated with FOLFIRI for 2 cycles. However, the patient died due to cancer progression within the first 2 months.	4	0.47 (0.37–0.88)
Branch #5: Tolerated side effects but had disease progression after 4 cycles of FOLFOX + the 'new drug'. The patient was then treated with FOLFIRI for 4 cycles but the disease did not respond. The patient received BSC and died 2 months later.	6	0.61 (0.51–0.72)
Branch #6: Tolerated side effects and responded FOLFOX + the 'new drug'. The patient went on to receive a total of 17 cycles of first line therapy. Upon progression, the patient went on to receive 6 cycles of FOLFIRI. Upon progression, the patient received BSC and died 21 months later.	29	0.72 (0.63–0.81)
Branch #7: Tolerated side effects and responded FOLFOX + the 'new drug'. The patient went on to receive a total of 17 cycles of first line therapy. Upon progression, the patient went on to receive 2 cycles of FOLFIRI but died 2 months later.	11	0.69 (0.62–0.76)
Branch #8: Tolerated side effects and but had disease progression after 2 cycles of FOLFOX + the 'new drug'. The patient died due to the cancer one month later.	2	0.44 (0.32–0.56)
FOLFOX → FOLFIRI → BSC until death		
Branch #9: Stopped FOLFOX after 2 cycles due to side effects and was then treated with FOLFIRI for 4 cycles. There was disease progression. The patient received BSC and died 6 months later.	10	0.64 (0.57–0.70)
Branch #10: Stopped FOLFOX after 2 cycles due to side effects and was then treated with FOLFIRI. There was a response to FOLFIRI and the patient went on to receive 8 cycles. Upon progression, the patient received BSC and died 22 months later.	28	0.63 (0.55–0.72)
Branch #11: Stopped FOLFOX after 2 cycles due to side effects and was then treated with FOLFIRI. There was a response to FOLFIRI and the patient went on to receive 8 cycles. Upon progression, the patient received BSC and died 2 months later.	8	0.69 (0.62–0.76)
Branch #12: Stopped FOLFOX after 2 cycles due to side effects and was then treated with FOLFIRI for 2 cycles. However, the patient died due to cancer progression within the first 2 months.	4	0.49 (0.38–0.60)
Branch #13: Tolerated side effects but had disease progression after 4 cycles of FOLFOX. The patient was then treated with FOLFIRI for 4 cycles but the disease did not respond. The patient received BSC and died 2 months later.	6	0.62 (0.51–0.72)
Branch #14: Tolerated side effects and responded FOLFOX. The patient went on to receive a total of 15 cycles of first line therapy. Upon progression, the patient went on to receive 6 cycles of FOLFIRI. Upon progression, the patient was offered BSC and died 21 months later.	32	0.68 (0.56–0.80)
Branch #15: Tolerated side effects and responded FOLFOX. The patient went on to receive a total of 15 cycles of first line therapy. Upon progression, the patient went on to receive 2 cycles of FOLFIRI but died 2 months later.	11	0.71 (0.64–0.78)
Branch #16: Tolerated side effects and but had disease progression after 2 cycles of FOLFOX. The patient died due to cancer progression one month later.	2	0.44 (0.32–0.56)

*As presented in each branch of the decision analysis model.

†A quality of life score for a health state between 0 and 1, with 0 = death and 1 = optimal health.

FOLFOX, oxaliplatin in combination with infusional 5-fluorouracil; FOLFIRI, irinotecan in combination with infusional 5-fluorouracil; BSC, best supportive care.

cerning to the pharmaceutical industry is that Germany and the UK plan to introduce a value-based drug pricing scheme where the final price will be linked to the clinical and economic value that the drug offers to society [34,35].

In the UK for instance, there is legislation that regulates profit but not prices. It is not clear what the new scheme will look like, but new product pricing will likely be based on the therapeutic value that it brings to patients and the National Health Service because part of the proposal was to reform NICE and move to a system of value-based pricing [35]. If administered by NICE, it is likely that this new pricing scheme will revolve around the incremental cost per QALY where the current value-based threshold is £30 000 per QALY

Table 5 Sensitivity analysis on the unit price for the 'new drug'

Sensitivity manoeuvre*	Price per dose ($CAD)
Base case	830
Upper 95% CI of health state utilities for chemotherapy + the 'new drug'	1560
Changing cost of FOLFOX chemotherapy by ±15%	785–875
Changing cost of FOLFIRI chemotherapy by ±15%	825–835
Changing cost of BSC cost by ±15%	783–877
Changing cost of ADR cost by ±15%	784–877
Changing survival benefit of the 'new drug' from 1.4 to 3 months	2180
Changing survival benefit of the 'new drug' from 1.4 to 6 months	3430

*For a target threshold of $CAD117 000 per QALY when the new drug is added to FOLFOX chemotherapy.
FOLFOX, oxaliplatin in combination with infusional 5-fluorouracul; FOLFIRI, irinotecan in combination with infusional 5-fluorouracul; BSC, best supportive care; ADR, adverse drug reaction costs.

gained, which is equivalent to approximately $US50 000 [36]. This latter threshold for value, which was based on a 1982 valuation, is now equivalent to approximately $US197 000 per QALY in 2007 US dollars (after a 5.5% annual adjustment in health care inflation) [13]. However, the $US50 000 threshold continues to be used and quoted in the PE literature. If the new value-based pricing scheme proposed by the UK government will revolve around the use of PE modelling and a cost per QALY gained, a more up to date value threshold will need to be identified.

To provide insight on alternative value thresholds, we used the criteria for value recommended by the WHO. The advantage of using the proposed WHO threshold is that the wealth of an individual country is taken into consideration. Therefore, the price for the same drug would be proportionally less in lower income countries compared to wealthier nations. In this study, we assessed the feasibility of our proposed value-based pricing scheme to estimate a price for bevacizumab, a drug that provides a 1.4-month survival benefit when added to chemotherapy in the first line treatment of mCRC.

The primary analysis was conducted from the Canadian public health care system perspective using the WHO criteria for cost-effectiveness. In the base case analysis and in most of the scenarios evaluated, a price of approximately $CAD830 per dose was suggested by the data as being cost-effective. If the drug were able to improve patient quality of life above the standard of care or survival from 1.4 to 3 months, the drug price could increase to $CAD1560 and $CAD2180 and still be considered cost-effective. These findings indicate that the two most important factors driving the cost-effectiveness of any new cancer drug is its ability to significantly improve quality and quantity of life. Therefore, these should be the primary and secondary end points of randomized trials of new cancer agents because they are the two main drivers for optimizing drug price.

What is interesting to note is that the outcomes generated in this study are approximately 60% lower than the current price of bevacizumab in Canada (i.e. $CAD2250 per dose). Had a value-based pricing scheme using the WHO value thresholds been applied to this agent, a substantially lower price would have been proposed by government payers. Such a price would have at least been the starting point for negotiations between public payers and the manufacturer. This would be preferable to government mandated price cuts that are currently ongoing in many European countries. Notwithstanding, a price less than $CAD1000 per dose may be untenable for newer anticancer drugs currently under investigation because research and development (R&D) costs for bringing a product to market now exceed $CAD800 million [37]. Therefore, it is unlikely that a value-based pricing scheme will be able to mandate such large price reductions without affecting investment into R&D.

There are a number of limitations in the application of this technique that have to be discussed. Our modelling exercise was theoretical using simple decision analysis and applied to a drug that is already comerically available. For the proposed methodology to be viable, complete data from randomized trials on a drug by drug basis is required to conduct more robust economic modelling such as Markov processes. mCRC patients who have KRAS wild-type tumours would be offered EGFR inhibitors (e.g. cetuximab) following first line chemotherapy [38]. However, the inclusion of these agents would have unnecessarily complicated the model and would not have altered the final results. Many of the newer cancer drugs such as bevacizumab, cetuximab and panitumumab that have been introduced into clinical practice for mCRC have not demonstrated a significant improvement in patient quality of life and their survival benefit has been less than 3 months [20,39,40]. For our modelling strategy to provide drug prices that are commercially viable for the manufacturer, a new drug must demonstrate either an improvement in quality of life over the standard of care or a survival of sufficient magnitude (i.e. at least 3 months).

Conclusions

The intent of our analysis was to provide a systematic process that would make important cancer drugs available at prices that are considered to be cost-effective. This does not necessarily mean that annual drug expenditures will be contained. True therapeutic innovation requires an investment by society. Therefore, increased spending for innovative drugs should be expected and planned for by formulary committees. The use of the WHO criteria for setting value thresholds is feasible, but it does not necessarily ensure the commercial viability of the product in the reference country. Therefore, the final threshold used for value-based pricing should have input from all of the key stakeholders.

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Using Pharmacoeconomic Modeling to Determine a Value-Based Price of New Pharmaceuticals in Malaysia

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ABSTRACT

Background: Decision analysis (DA) is commonly used to perform economic evaluations of new pharmaceuticals. Using multiples of Malaysia's per capita 2010 GDP as the threshold for economic value as suggested by the World Health Organization (WHO), DA was used to estimate a price per dose for bevacizumab in Malaysia, a drug that provides a 1.4 month survival benefit in metastatic colorectal cancer (mCRC).

Methods: A decision model was developed to simulate progression free and overall survival in mCRC patients receiving chemotherapy with and without bevacizumab. Costs for chemotherapy and side effects management were obtained from both public and private hospitals in Malaysia. Utility estimates measured as QALYs were determined by interviewing 24 oncology nurses using the Time Trade-Off technique. The price per dose was then estimated using a target threshold of $44,400 per quality-adjusted life year gained, which is three times the Malaysian per capita GDP.

Results: A cost effective price for bevacizumab could not be reached because of the short survival benefit provided. If the drug were able to improve survival from 1.4 to 3 or 6 months, then the price per dose could be $U.S.567 and $U.S.1,258 and be considered cost effective according to the WHO criteria.

Conclusions: The use of decision modelling for estimating drug price is a powerful technique to ensure value for money. Such information can be of value to both drug manufacturers and formulary committees because it would facilitate negotiations for value-based pricing in a given jurisdiction.

Key Words: drug pricing, cost analysis, chemotherapy, value

INTRODUCTION

The rapid growth of healthcare expenditures has led to increased interest in economic evaluations of healthcare programmes.[1] This is particularly true for pharmaceuticals, which constitute a substantial portion of the healthcare budget.[2] The basic premise of pharmacoeconomic evaluations is to compare the costs and consequences of alternative pharmaceutical interventions and determine which treatment offers the best value for money.[3] There are several methods available to evaluate economic efficiency of health care interventions.[3,4] All of the approaches measure costs in monetary terms, but differ in the way that consequences are evaluated.

Decision analysis modelling is a systematic process to assess appropriate courses of action in the presence of multiple uncertainties.[5] It is one of the most commonly used methods for conducting pharmacoeconomic evaluations (PE) and the outcomes are typically presented as the incremental cost per quality-adjusted life year (QALY) gained. This is then compared against the value threshold set by national formulary committees. As an illustration, the National Institute of Clinical Excellence (NICE) of the United Kingdom has established the threshold for drug coverage at £30,000 per QALY gained.[6] In the Netherlands, the unofficial threshold is €18,000 per QALY.[7] However, these thresholds for economic value do not reflect the wealth of the nation.

To address this, the World Health Organization (WHO) has proposed to use multiples of a country's per capita gross domestic product (GDP).[8,9] Based on the WHO criteria, products more than three times the GDP would be cost ineffective.[8,9] Using

Malaysia as an illustration (i.e. per capita GDP for 2010 = $U.S.14,800), the threshold for cost effectiveness of new drugs would be $U.S.44,400 per QALY.[10]

Most PE are conducted with an established product price to estimate the cost per QALY gained. However, PE analyses can also be very informative to determine a drug price given recommended thresholds for economic value. To illustrate one application of PE for this purpose, we used decision analysis modeling to estimate a price for a cancer drug in Malaysia using the WHO criteria for cost effectiveness. The drug selected as the case study was bevacizumab, an agent that provides a 1.4 month survival gain when added to first line chemotherapy in patients with metastatic colorectal cancer (mCRC).[11] Bevacizumab was chosen because it has a high acquisition cost and its economic value has been questioned in recent PE studies.[12,13]

METHODS

Economic Model

mCRC was chosen for this analysis because the sequential use of specific chemotherapy regimens is well established. In patients with mCRC, randomized trials have demonstrated that irinotecan (FOLFIRI) or oxaliplatin (FOLFOX) in combination with infusional 5-fluorouracul (5-FU) and leucovorin are highly active and superior to the previous standard of 5-FU/leucovorin alone.[14,15] Data from a large randomized trial also verified that sequential schedules of FOLFOX and FOLFIRI (or the reverse order) are equally effective and have thus emerged as the first and second line standard of care for patients with mCRC.[16] Clinical practice guidelines also recommend the addition of an antivascular endothelial growth factor (VEGF) such as bevacizumab at some point during chemotherapy for mCRC.[17] FOLFOX, FOLFIRI and bevacizumab are all available in Malaysia.

The two most commonly used methods to model the clinical and economic consequences of cancer therapy are decision trees and Markov modelling. The former method is most commonly used in situations where uncertainly arises once over a period of time. However in cases where events occur repeatedly, Markov processes are better able to capture the uncertainties that are faced iteratively.[18] However, one of the disadvantages of Markov modelling is their need for a high level of detailed data. To construct a Markov model of multiple cycles of FOLFOX and FOLFIRI, disease progression and toxicity data would be required for each cycle of chemotherapy. Unfortunately, such data was not available from the published clinical trials. Since only

aggregate data were available (i.e. median number of cycle of chemotherapy), a decision tree approach was used for the current study.

A decision model for the sequential treatment of mCRC with FOLFOX (± an anti-VEGF) followed by FOLFIRI upon disease progression was developed with the DATA software (Treeage Software Inc.) (Figure 1). The analytic timeframe was from the first cycle of FOLFOX chemotherapy until death and a Malaysian health care system perspective (both public and private) was taken. The primary outcome for measuring successful initial therapy was clinical benefit, defined as complete tumour response (CR), partial response (PR) or stable disease (SD) based on the Response Evaluation Criteria in Solid Tumors [*RECIST*]). Three clinical oncologists, each with experience in treating colorectal cancer, evaluated the face and content validity of the model.

The model began at the decision node (square) where the first line treatment choice would be either FOLFOX + "the new drug (bevacizumab)" or FOLFOX alone (Figure 1). During the first two cycles of chemotherapy, patients would be assessed for intolerable toxicity. For those patients with severe toxicity, first line therapy would be discontinued in its entirety and second line FOLFIRI would be offered until disease progression. Upon progression, all patients would receive best supportive care until death. In contrast, patients who did not experience severe toxicity from first line FOLFOX (± "the new drug") would continue receiving treatment until disease progression. They would then be offered second line FOLFIRI alone and bevacizumab would be discontinued. Upon progression, all patients would receive best supportive care until death (Figure 1). Epidermal growth factor receptor (EGFR) inhibitors such as cetuximab in mCRC patients with KRAS wild type tumours were not considered because we did not want to

over complicate the modeling. Furthermore, such agents would be available to both treatments options in the model, so their inclusion would not impact on the final results.

Clinical Data

The clinical data required to populate the model consisted of early treatment discontinuations because of toxicity, achievement of clinical benefit (CR+PR+SD), duration of clinical benefit, risk of cancer related death during active treatment and number of chemotherapy cycles administered. These data were obtained through a literature search of randomized trials evaluating FOLFOX (± bevacizumab) in the first line setting and second line FOLFIRI in the treatment of mCRC. Two randomized trials were identified that provided the required data for the decision model (Table 1). The first trial evaluated FOLFOX or a clinically similar regimen XELOX (capecitabine plus oxaliplatin) ± bevacizumab in the first line treatment of mCRC.[11] A total of 1,401 patients were randomized to receive FOLFOX/XELOX + bevacizumab (n=699) or FOLFOX/XELOX + placebo (n=701). The interaction between FOLFOX and XELOX on the primary clinical endpoint was not statistically significant (p=0.70) thereby justifying the decision to combine patients who received FOLFOX and XELOX. Median progression free survival was 9.4 months in the bevacizumab group compared to 8.0 months with placebo (HR=0.83; p=0.023) resulting in a 1.4 month survival benefit.[11] Overall, 30% of patients in the bevacizumab group required a permanent treatment discontinuation because of adverse events compared to 20% in the control (Table 1). Approximately 2% and 1% of patients died during treatment with bevacizumab and placebo (Table 1).

Data on the safety and efficacy of second line FOLFIRI following first line FOLFOX was obtained from a randomized sequential trial reported by Tournigand et al., (2004), Patients were randomized to receive sequential FOLFOX followed by FOLFIRI upon progression or the reverse sequence (Table 1). There was no significant difference in progression free and overall survival (FOLFOX – FOLFIRI = 21.5 vs. FOLFIRI – FOLFOX = 20.6 mon; p=0.99) between the two sequences.[16] With second line FOLFIRI, 51% of patients experienced disease progression for an overall progression free survival of 2.5 months respectively.[16] Approximately 3% of patients died within the first 60 days of second line FOLFIRI (Table 1).

Estimation of Treatment Costs

Malaysia's healthcare system is composed of a public and private sector. Physicians are required to complete three years of service in public hospitals throughout the nation, ensuring there is adequate coverage for the general population. With respect to drug access, patients treated under the private system typically have access to a greater selection of therapies than those managed under the public system. However, drug prices and costs for hospital resources tend to be higher in private than in public hospitals. As results, an analysis was performed for patients treated under the public and private systems.

The duration of investigation ran from the start of first and second line sequential chemotherapy therapy until death. Health care resources and costs for anticancer drugs, materials, patient monitoring and other related hospital resources (e.g. laboratory, diagnostic tests and best supportive care) were obtained from two private

and two public health care institutions using a standardized data collection form. The costs collected in the study were in Malaysian Ringgit (MYR) and then converted to $US as per the currency conversion prevailing in 2010 (conversion factor 1$US = 3.2 MYR, as of September, 2010).

Patient Preferences for Alternative Health States

Quality adjusted life years or QALYs are a way of measuring the impact of disease on a patient. They include both the quality and the quantity of life lived and are calculated by multiplying the survival gain by the overall utility benefit of one therapy over another. The health-related quality of life (QOL) values measured in the analysis were patient preferences for alternative health outcomes, as depicted in the decision analysis model. In the current study, quality-adjusted progression free periods were measured as "healthy months equivalent" for the time spent in each outcome of the decision model using the Time Trade-Off (TTO) technique.[19] The scores in months were then converted to utility measures between 0 and 1, where 0 represented death and 1 was a state of perfect health or optimal quality of life.

The TTO technique is a preference based approach designed to measure respondent's preferences and QOL for alternative health states.[19] After background information is presented on a particular health state (e.g. a cancer that is not responding to treatment) and the time period within that state, respondents are asked to trade length of life in the poorer health state for a lesser period of time in a state of optimal health and QOL. As an illustration, a respondent may prefer to live 4 months of optimal health rather than the 12 months confined to a wheel chair. Under this scenario, the

utility associated with being in a wheel chair for 12 months would be 0.33 (i.e. 4 / 12) on a scale between 0 and 1, where 0 represents death and 1 is a state of optimal quality of life. In the economic model, all of the possible outcomes were valued in this way and then used to weigh the time spent in each health state in terms of QOL.

Intuitively, the ideal population for measuring health state utilities and treatment preferences should be cancer patients with the disease in question who are in a position to receive the new treatment. However, it has been recommended in the Canadian Guidelines for Economic Evaluations and by the Panel on Cost-Effectiveness in Health and Medicine of the United States that treatment preferences be measured from members of the general public who are potential candidates of the new medical intervention.[5,20] As a compromise in this study, a patient surrogate group was used that would provide insight from both the perspective of the patient and members of the general public because the latter sample often has difficulty in understanding utility questionnaires. There is also evidence in the oncology literature suggesting that nurses are suitable patient surrogates for objective outcomes, and that utility estimates derived from such a sample do not substantially alter the findings of cost utility studies.[21,22] Therefore, a convenience sample consisting of 24 oncology nurses provided utility values for the model. With a sample of 24 respondents, healthy month equivalence was measured with a precision of $\pm$ 1.0 month, with a 95% probability.

After informed consent was obtained, each participant was interviewed for 30 to 45 minutes by trained local field investigators. Respondents were presented with information on FOLFOX, bevacizumab and FOLFIRI consisting of the methods of administration, efficacy and the side effects reported in the literature. Bevacizumab was

not identified by name but simply referred to as the “new drug”. The interview was then continued with a description of the 16 health states and the length of time a patient would live in each health state (Figure 1). The respondents were then asked how many months of "optimal health" they considered being equivalent to the time spent in each of the less than optimal health states described in the model. These measures were then used to weigh each branch of the model by the QOL experienced by a patient living through that time period. An identical process was used for each of the 16 outcomes (Figure 1). The mean “healthy month equivalence” score for each outcome was then divided by 12 months to estimate the number of QALYs associated with that health state.

A standardized questionnaire supported by printed interview tools with graphical displays was used to facilitate the participant’s understanding of the Time Trade-off technique. To minimize the framing effect, all pathways were presented in a consistent manner pictorially. Demographic data were also collected from each participant, and consisted of years of oncology and colorectal cancer experience, involvement in the development of systemic treatment guidelines for colorectal cancer, familiarity with the cost of anticancer drugs and family history of colorectal cancer.

Cost Utility Analysis

The clinical, economic and respondent preference data were then combined into a cost-utility analysis of bevacizumab to identify a price per dose that would be considered cost effective according to the WHO criteria.[8,9] The base case analysis assumed that the addition of the bevacizumab to standard chemotherapy would provide

a survival benefit of 1.4 months. The primary objective of the analysis was to estimate an appropriate price for the bevacizumab by using the target benchmark cost of $U.S.44,400 per QALY gained, which is three times the 2010 Malaysian per capita GDP. Indirect costs were not included because there was no data available on the association between bevacizumab usage and indirect cost avoidance. Future costs and benefits were not discounted because of the short time periods involved. However, the stability of the baseline results was evaluated by a comprehensive sensitivity analysis. This consisted of substituting the 95% confidence intervals (CI) for the health-state utilities as well as variations in the overall survival benefit, costs of care and the target threshold for economic value in Malaysia. Costs of care were varied by ± 15% to capture any potential differences across the country. Individual analyses were conducted for patients treated in public and private hospitals.

RESULTS

Clinical outcomes data and costs used to populate the model are presented in Tables 1 and 2. The economic data revealed that expenses for chemotherapy, side effect management and best supportive care are lower in the public than the private health care system in Malaysia. This may be a reflection of a slightly lower level of care offered to patients in public hospitals and of the ability of the private sector to mark up the cost of goods and health services.

The second component required for the cost-utility analysis was health state utilities for the time period spent in each of the 16 health states (Figure 1). Utilities for each outcome were estimated from a sample of 24 oncology nurses who consented to

participate in the study. There were 14 respondents from public hospitals and the remainder were from private institutions. The sample had an average of 3.4 years of direct oncology experience (range 2 – 8 years) and all had experience in the treatment of colorectal cancer patients. In addition, all respondents had direct clinical experience in the administration and follow up care associated with FOLFOX (mean years = 2.2) and 92% had experience with FOLFIRI (mean years = 1.9) chemotherapy. Furthermore, 22 of 24 (92%) had experience with the newer targeted therapies bevacizumab and cetuximab. Lack of knowledge about the cost of drugs could affect treatment preferences. Respondents were asked to state their knowledge of costs for modern oncology drugs. The findings revealed that 100% were “very familiar” or “somewhat familiar” with the cost of drugs used to treat cancer. The final series of demographic questions focused on respondent’s family history of colorectal cancer. The data revealed that only one of the 24 subjects had a positive family history for colorectal cancer.

The health state utilities from the oncology nurses are presented in Table 3. The results suggested that patient utilities were influenced by the severity of drug toxicity, the likelihood of achieving a response to chemotherapy and the risk of rapid cancer death. The health states with the lowest utilities (i.e. branches 11 and 16 of the model – Figure 1) were those where first line therapy had to be stopped because of severe toxicity, the patient then had an early progression during second line treatment followed by a rapid cancer death. It was also interesting to note that in all of the related scenarios, comparative branches that included treatment with the “new drug” tended to have lower health state utilities (Table 3). This is likely related to the additional side

effects that would occur with the addition of an anti-VEGF agent like bevacizumab to chemotherapy (Table 1).

Cost Utility Analysis for the Public and Private Hospital Systems

The outcomes data from the clinical trial, the estimated costs associated with each treatment and the health state utility estimates were combined into the cost-utility analysis. The price for one dose of bevacizumab was then varied until the incremental cost-effectiveness ratio reached a threshold of $U.S.44,400 per QALY gained. Using this approach from the public health care system perspective, the base case analysis suggested that a cost per dose that would achieve cost effectiveness according to the WHO criteria could not be reached because bevacizumab simply did not provide enough of a survival benefit in mCRC patients (Table 4). Similar results were also identified when the analysis was undertaken from the perspective of private hospitals.

A series of one-way sensitivity analyses were then conducted using the upper 95%CI for the health state utilities, variations in treatment costs and the targeted cost per QALY threshold. Identical results as in the base case analysis for both public and private hospitals were achieved. A price per dose that would make bevacizumab cost effective could not be realized. This was primarily driven by the modest survival benefit offered by bevacizumab in mCRC patients.

The only situation where a cost effective price per dose was identified occurred when the survival gain was increased to 3 and 6 months. When the survival benefit of bevacizumab was increased from 1.4 to 3 months, the cost per dose for public and private hospitals was estimated to be $U.S.567 and $U.S.490 respectively. When the

survival gain was increased to 6 months, the price per dose of bevacizumab could increase further to $U.S.1,258 and $U.S.1,182 in both public and private institutions and be considered cost effective according to the WHO criteria.[8,9] Therefore, the single biggest factor controlling the cost effectiveness of bevacizumab is the drug's ability to increase overall survival.

Bevacizumab is available in Malaysia and its purchase price is approximately $U.S.1,800 per dose (5 mg/kg) for an average 60 kg mCRC patient. A sensitivity analysis was conducted where the current price of bevacizumab was applied to the model. The results revealed that the incremental cost per QALY gained would be greater than $U.S.200,000 for both public and private institutions. When a $U.S.50,000 cost per QALY threshold was used instead of the WHO criteria, a cost effective price per dose could also not be achieved. In summary, the sensitivity analyses suggested that bevacizumab is not a cost effective drug in Malaysia according to the WHO criteria. In order to achieve cost effectiveness, drug performance in terms of survival gain in mCRC patient will need to improve and the price would have to be reduced to between $U.S.500 to $U.S.1,300.

DISCUSSION

Decision analysis modeling is a powerful simulation technique widely used to perform cost-effectiveness evaluations of new drugs. In such studies, the health services researcher develops a decision model comparing the new therapy to the current standard, incorporates into the analysis the costs and consequences of the two alternatives and then estimates the incremental cost per QALY gained with the new intervention. If the cost per QALY is below a predetermined threshold, the conclusion is that the new treatment is cost effective and should be added to a hospital or national formulary.

Decision analysis is a useful tool that can also be used to estimate any unknown in the analysis. The unknown in most published studies has been the incremental cost per QALY gained. However, decision analysis can also be applied in the context of pricing a new drug before it is introduced to the market. In this study, the latter process was used to estimate the cost of bevacizumab, a drug that provides a 1.4 month survival benefit when added to chemotherapy in the first line treatment of mCRC.[11]

The analysis was conducted from both the Malaysian public and private health care system perspective using the WHO criteria for cost effectiveness. In the base case analysis and in most of the scenarios evaluated, a cost per dose resulting in cost effectiveness could not be identified because a 1.4 months survival gain was inadequate. A final price was only realized when the survival gain from bevacizumab was artificially increased to at least three months. When the current Malaysian price per dose (i.e. $U.S.2,622) for bevacizumab was evaluated, the drug was not considered to be cost effective according to the WHO criteria.

The findings of this study suggest that the WHO criteria for cost effectiveness can be applied to a country like Malaysia for estimating an appropriate price which may be more affordable to the national health care system and patients. Furthermore, our results suggest that bevacizumab has been priced excessively high in Malaysia for the 1.4 month survival benefit that it provides to mCRC patients. For the drug to become cost effective, the price would have to be reduced and a new treatment algorithm would need to be identified that would increase survival to at least 3 months.

There are a number of limitations in the application of this technique that need to be addressed. Given the lack of data by cycle of chemotherapy, we constructed a decision tree instead of a Markov model to simulate the clinical and economic consequences of chemotherapy for mCRC. The latter would have been preferable given its ability to incorporate the element of time. For the proposed methodology to be viable, complete data from randomized trials on a drug by drug basis is required. This is not always the case. One of the limitations of using the per capita GDP for value based pricing is that it represents a national average and does not consider income dispersion. Our study measured health state utilities from a sample of oncology nurses. However, the external validity of our findings would have been enhanced if we had also included patients, family members and members of the general public. For our modeling strategy to be applied, a new drug must demonstrate either an improvement in QOL over the standard of care or a survival of sufficient magnitude to identify a final price point for cost effectiveness. In the case of bevacizumab, the drug simply did not provide enough of a survival benefit to identify a price that would be considered cost effective. Lastly, indirect costs such as time off work secondary may be relevant in this

setting, but were not considered in this analysis because there was a lack of such data in the metastatic colorectal cancer literature. Future modelling should consider their inclusion.

CONCLUSIONS

The current paper presents a systematic process to estimate drug cost based on pre-determined thresholds for societal value. The advantages of this technique are that it is relatively straightforward to perform, transparent and the decision model can be easily applied to other jurisdictions using local cost data. Such information can be of value to both drug manufacturers and formulary committees because it would facilitate negotiations for optimal pricing in a given jurisdiction.

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LIST OF TABLES

Table 1: Published randomized trials providing clinical data to populate the economic model.

Reference	Treatment Arms	Clinical Outcomes
Saltz et al., (2008)	FOLFOX/XELOX + bevacizumab	Disease progression = 29% Median PFS = 9.4 mon Median duration of response =8.45 mon Overall survival = 21.3 mon Treatment discontinuations = 30% Death during treatment = 2% Serious side effects (grade III/IV) = 16% <u>Specific Grade III/IV Side Effects</u> Deep vein thrombosis = 8% Diarrhea = 18% Bleeding = 2% Neutropenia = 50%
	FOLFOX/XELOX + placebo	Disease progression = 47% Median PFS = 8.0 mon Median duration of response =7.4 mon Overall survival = 19.9 mon Treatment discontinuations = 20% Death during treatment = 1% Serious side effects (grade III/IV) = 8% <u>Specific Grade III/IV Side Effects</u> Deep vein thrombosis = 5% Diarrhea = 11% Bleeding = 1% Neutropenia = 44%
Tournigand et al., (2004)	Second Line FOLFIRI	Disease progression = 51% Death during treatment = 3% Median PFS = 10.9 mon Median number of cycles= 6

Abbreviations: PFS = progression free survival, OS = overall survival, FOLFOX = oxaliplatin in combination with infusional 5-fluorouracul, FOLFIRI = irinotecan in combination with infusional 5-fluorouracul.

Table 2: Hospital costs for the treatment of metastatic colorectal cancer in Malaysia.

Recourse Item	Public Hospitals	Private Hospitals
FOLFOX chemotherapy[a]	$U.S.998 / cycle	$U.S.1047 / cycle
FOLFIRI chemotherapy[b]	$ U.S.1395 / cycle	$ U.S.1489 / cycle
Cost for a permanent chemotherapy discontinuation because of toxicity[c]	$ U.S.111.60	$ U.S.241.80
Cost to administer the "new drug" after FOLFOX chemotherapy	$ U.S.18.60	$ U.S.40.30
Cost of best supportive care[d]	$ U.S.156/month	$ U.S.338/month

[a]Oxaliplatin in combination with infusional 5-fluorouracul. Cost per cycle includes resources for drug administration and routine patient monitoring. In the hospitals that provided data for this study, patients are admitted for two days to receive the chemotherapy.

[b]Irinotecan in combination with infusional 5-fluorouracul.

[c]Patients would be admitted for 3 days for the management of side effects and for reassessment.

[d]After failing two lines of chemotherapy, patients would receive best supportive care on an outpatient basis until death.

Table 3. Health state utilities derived using the Time Trade-Off technique.

Sixteen Health Outcomes Evaluated in the Decision Model	Time in Health State[a]	Utility Estimate[b] [mean (95%CI)]
FOLFOX + "new drug" → Folfiri → BSC until death		
Branch #1: Stopped FOLFOX + the "new drug" after 2 cycles due to side effects and was then treated with FOLFIRI for 4 cycles. There was disease progression. The patient received BSC and died 6 months later.	10 months	0.74 (0.65 - 0.83)
Branch #2: Stopped FOLFOX + the "new drug" after 2 cycles due to side effects and was then treated with FOLFIRI. There was a response to FOLFIRI and the patient went on to receive 8 cycles. Upon progression, the patient received BSC and died 22 months later.	28 months	0.80 (0.73 - 0.87)
Branch #3: Stopped FOLFOX + the "new drug" after 2 cycles due to side effects and was then treated with FOLFIRI. There was a response to FOLFIRI and the patient went on to receive 8 cycles. Upon progression, the patient received BSC and died 2 months later.	8 months	0.67 (0.61 - 0.73)
Branch #4: Stopped FOLFOX + the "new drug" after 2 cycles due to side effects and was then treated with FOLFIRI for 2 cycles. However, the patient died due to cancer progression within the first 2 months.	4 months	0.74 (0.65 - 0.84)
Branch #5: Tolerated side effects but had disease progression after 4 cycles of FOLFOX + the "new drug". The patient was then treated with FOLFIRI for 4 cycles but the disease did not respond. The patient received BSC and died 2 months later.	6 months	0.82 (0.76 - 0.89)
Branch #6: Tolerated side effects and responded FOLFOX + the "new drug". The patient went on to receive a total of 17 cycles of first line therapy. Upon progression, the patient went on to receive 6 cycles of FOLFIRI. Upon progression, the patient received BSC and died 21 months later.	29 months	0.81 (0.77 - 0.86)
Branch #7: Tolerated side effects and responded FOLFOX + the "new drug". The patient went on to receive a total of 17 cycles of first line therapy. Upon progression, the patient went on to receive 2 cycles of FOLFIRI but died 2 months later.	11 months	0.83 (0.79 - 0.87)
Branch #8: Tolerated side effects and but had disease progression after 2 cycles of FOLFOX + the "new drug". The patient died due to the cancerone month later.	2 months	0.75 (0.63 - 0.86)

Table 3. Continued…

FOLFOX → Folfiri → BSC until death		
Branch #9: Stopped FOLFOX after 2 cycles due to side effects and was then treated with FOLFIRI for 4 cycles. There was disease progression. The patient received BSC and died 6 months later.	10 months	0.82 (0.75 - 0.82)
Branch #10: Stopped FOLFOX after 2 cycles due to side effects and was then treated with FOLFIRI. There was a response to FOLFIRI and the patient went on to receive 8 cycles. Upon progression, the patient received BSC and died 22 months later.	28 months	0.81 (0.76 - 0.86)
Branch #11: Stopped FOLFOX after 2 cycles due to side effects and was then treated with FOLFIRI. There was a response to FOLFIRI and the patient went on to receive 8 cycles. Upon progression, the patient received BSC and died 2 months later.	8 months	0.72 (0.66 - 0.79)
Branch #12: Stopped FOLFOX after 2 cycles due to side effects and was then treated with FOLFIRI for 2 cycles. However, the patient died due to cancer progression within the first 2 months.	4 months	0.75 (0.66 - 0.84)
Branch #13: Tolerated side effects but had disease progression after 4 cycles of FOLFOX. The patient was then treated with FOLFIRI for 4 cycles but the disease did not respond. The patient received BSC and died 2 months later.	6 months	0.84 (0.76 - 0.92)
Branch #14: Tolerated side effects and responded FOLFOX. The patient went on to receive a total of 15 cycles of first line therapy. Upon progression, the patient went on to receive 6 cycles of FOLFIRI. Upon progression, the patient was offered BSC and died 21 months later.	32 months	0.91 (0.88 - 0.94)
Branch #15: Tolerated side effects and responded FOLFOX. The patient went on to receive a total of 15 cycles of first line therapy. Upon progression, the patient went on to receive 2 cycles of FOLFIRI but died 2 months later.	11 months	0.84 (0.79 - 0.90)
Branch #16: Tolerated side effects and but had disease progression after 2 cycles of FOLFOX. The patient died due to cancer progression one month later.	2 months	0.75 (0.63 - 0.86)

[a]As presented in each branch of the decision model. [b]A quality of life score for a health state between 0 and 1, with 0 = death and 1 = optimal health. Abbreviations: FOLFOX = Oxaliplatin + infusional 5-FU. FOLFIRI = Irinotecan + infusional 5-FU, BSC = best supportive care.

Table 4. Sensitivity analysis on the cost per dose of the "new drug".

Sensitivity Analysis[1]	Public Hospitals	Private Hospitals
Base case	Not reached	Not reached
Upper 95%CI of health state utilities for chemotherapy + the "new drug"	Not reached	Not reached
Changing cost of FOLFOX chemotherapy by ± 15%	Not reached	Not reached
Changing cost of FOLFIRI chemotherapy by ± 15%	Not reached	Not reached
Changing cost of BSC cost by ± 15%	Not reached	Not reached
Changing cost of ADR cost by ± 15%	Not reached	Not reached
Changing survival benefit of the "new drug" from 1.4 to 3 months	$U.S.567	$U.S.490
Changing survival benefit of the "new drug" from 1.4 to 6 month	$U.S.1,258	$U.S.1,182
Using the current cost of bevacizumab ($U.S.1,800 per dose) in Malaysia	Not cost effective	Not cost effective
Setting the threshold for cost effectiveness at $U.S.50,000 per QALY gained	Not reached	Not reached

Abbreviations: FOLFOX = Oxaliplatin in combination with infusional 5-fluorouracul. FOLFIRI = Irinotecan in combination with infusional 5-fluorouracul. BSC = best supportive care, ADR = adverse drug reaction costs.

[1]For a target threshold of $U.S.44,400 per QALY when the new drug is added to FOLFOX chemotherapy.

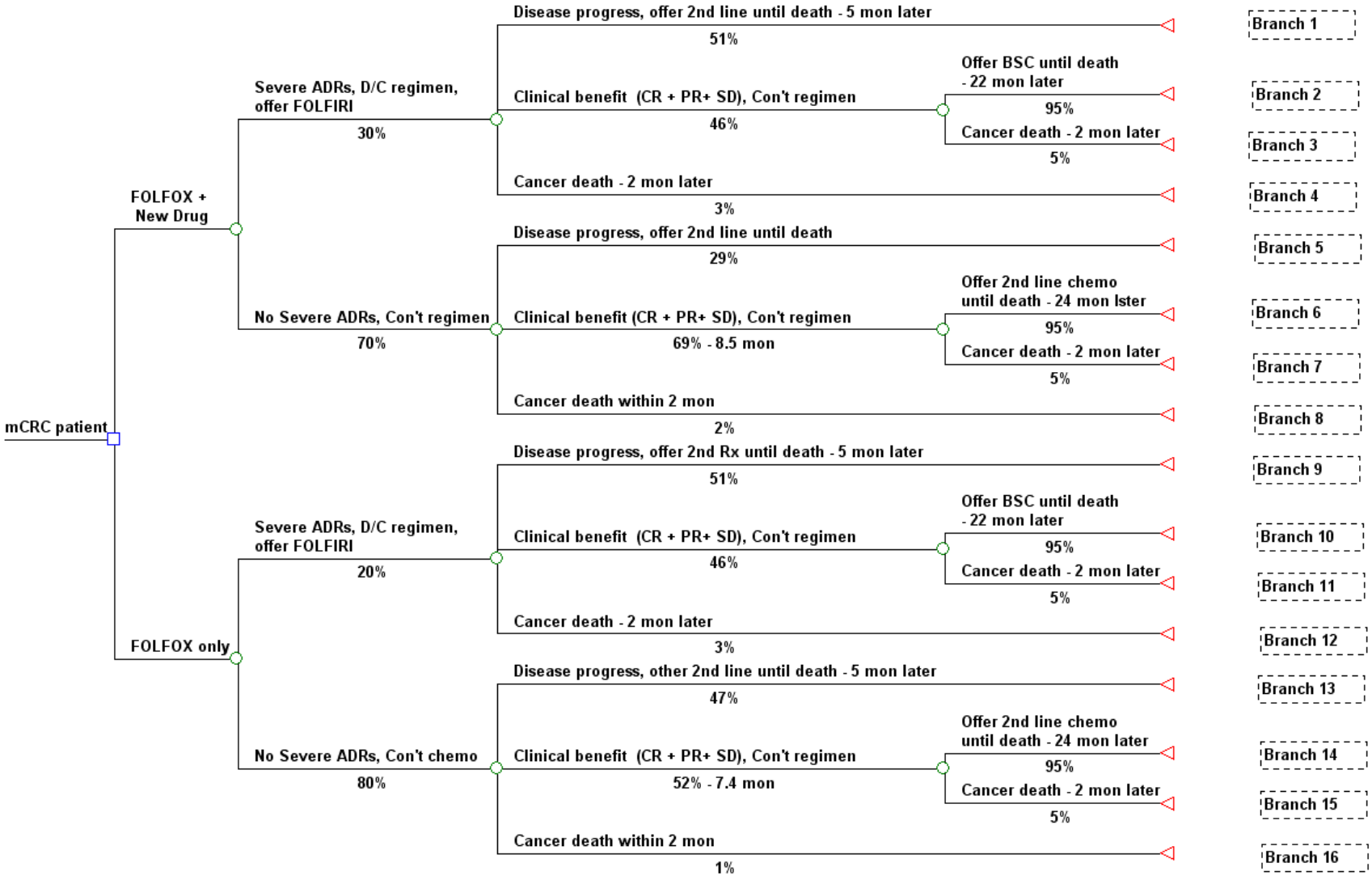

Figure 1. Decision analysis model for the treatment of metastatic colorectal cancer.

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Using Measures of Societal Value and Economic Modeling to Estimate Prices for Cancer Drugs in South Africa

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The authors of this paper have no conflict of interest to declare

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ABSTRACT

Background: One of the major barriers against patient access to new cancer drugs has been price. We present a novel approach to estimate a value based price for new cancer drugs that considers the clinical benefits of the product and the wealth of a nation. To demonstrate its application, pharmacoeconomic (PE) modeling was used to estimate a value based South African price for bevacizumab, a drug that improves survival in metastatic colorectal cancer (mCRC) patients by 1.4 months. The threshold used for economic value used was 3 times the South African per capita gross domestic product (GDP), as recommended by the World Health Organization (WHO).

Methods: A PE model was developed to simulate the outcomes in mCRC patients receiving chemotherapy ± bevacizumab. Utility estimates were determined by interviewing 16 oncology nurses involved in the care of mCRC patients. A price per dose of bevacizumab was then estimated using a target threshold of R219,000 per quality adjusted life year (QALY) gained, which is 3 times the South African per capita GDP.

Results: A cost effective price for bevacizumab could not be reached because of the short survival benefit provided by the drug. If the drug were able to improve survival from 1.4 to 3 or 6 months, then the price per dose could be R400 and R1,780 and be considered cost effective in South Africa according to the WHO criteria.

Conclusions: A value based pricing approach using PE modelling and the WHO criteria for economic value is feasible for South Africa.

Key Words: drug pricing, South Africa, cost analysis, chemotherapy, value

INTRODUCTION

Cancer is a global problem with 7.4 million deaths per year, which is approximately 13% of all cause mortality.[1] The populations of many countries around the world are ageing and cancer is more prevalent in older people. Therefore, cancer clinics can also expect an increase in the number of patients seeking treatment. In one study, Wilking and Jonsson estimated a 10% increase in the number of new diagnoses in 25 European countries from 2002 to 2006.[2,3] Encouragingly, these same investigators also reported stability in the number of deaths over the same time period.[2,4] Similar findings have also been reported by the Surveillance Epidemiology and End Results (SEER) of the United States.[5]

For many years, the backbone of cancer treatment has been the use of cytotoxic agents such as anthracyclines, alkylating agents, taxanes and platinum analogues.[6] One characteristic of traditional chemotherapy is its non-specificity to the target. As a result, side effects such as neutropenia, anemia, thrombocytopenia, alopecia and decreased renal function are common.[6] Over the past decade, there has been an emergence of new anticancer agents that are more specific to the target. These new compounds which include agents such as imatinib, rituximab, cetuximab and trastuzumab are collectively known as “targeted therapies”.[7-10] In contrast to traditional chemotherapy which affects both healthy and malignant cells, targeted agents are specific to the latter. Therefore, they tend to be better tolerated than chemotherapy and the side effects described above are less common. In addition, at least part of the stabilization in overall cancer mortality has been attributed to the availability of these newer targeted drugs.[2,4]

The new targeted drugs have taken patient care forward towards more personalized care. However, despite their effectiveness and improved safety profile, not all cancer patients in South Africa have access to them. One of the single biggest barriers to drug access is the high cost of these new agents. In one editorial published in the Journal of the National Cancer Institute of the United States, the annual cost for an average 60 kg patient for the targeted therapies erlotinib, sorafenib, bevacizumab and cetuximab was estimated to be $U.S.15,752 (R109,400), $U.S.34,373 (R238,700), $U.S.80,352 (R558,000) and $U.S.90,816 (R630,600) respectively.[10] These costs would be prohibitively high for most non-insured patients in South Africa. Even in wealthier countries with socialized health care systems, such drugs have either been rejected for reimbursement by national health care agencies or patient access has been delayed or limited following initial regulatory approval.[11,12] Therefore, both public and private payers need to make decisions about which drugs provide the greatest economic value.

Pharmacoeconomics (PE) is an analytical technique that compares the costs and benefits of alternative pharmaceutical interventions to determine which treatment offers the best value for limited resources. There are several methods available to evaluate economic efficiency and these include cost minimization, cost benefit and cost effectiveness analysis.[13] With respect to oncology drugs, cost utility analysis is the preferred method because it considers cost, overall survival and quality of life differences between two competing therapies.[13] Quality adjusted life years or QALYs are a way of measuring the impact of new treatments for cancer. They include both the quantity and quality of life experienced by patients during treatment with alternative

options. Therefore, the outcomes of cost utility studies are reported as an incremental cost per QALY gained when a new drug is used over a lower cost alternative.

PE evaluations of new drugs provide an important component to the overall process of formulary decision making. However, they may have an additional and perhaps more valuable role in estimating or negotiating a drug price based on societal value thresholds. PE has been used in this role for a few cancer drugs assessed by the National Institute of Clinical Excellence (NICE) of the United Kingdom, which is a national body that assesses the cost effectiveness of new drugs. NICE was able to secure price reductions from manufacturers for erlotinib, lenalidomide and sunitinib based on cost effectiveness.[14] However, what has not been extensively examined was the estimation of drug price before a drug receives regulatory approval.

One of the outstanding issues in estimating a value based price for new cancer drugs is in establishing the value cut off. The World Health Organization (WHO) has proposed to use multiples of a country's per capita gross domestic product (GDP) to establish thresholds for economic value.[12,15,16] Products less than or equal to the per capita GDP would be considered very cost effective, one to three times would be cost effective and more than three times would be cost ineffective.[12] Using South Africa as an illustration (i.e. per capita GDP = $US 10,000 or R73,000) the three time threshold for cost effectiveness of new anticancer drugs would be approximately $U.S.30,000 (R210,000) per QALY gained.[17]

The use of thresholds based on per capita GDP in combination with PE modeling to establish a value-based price for cancer drugs is novel because it incorporates product attributes such as disease response, survival, quality of life improvements and impact

on health care resource use. To illustrate its application, PE modelling was used to estimate a value-based price for bevacizumab, a commercially available drug that provides a survival benefit to patients with metastatic colorectal cancer (mCRC) when added to first line chemotherapy.[18] Bevacizumab was chosen because its economic value questioned in recent PE studies.[19,20] The analysis was conducted from a South African public health care scheme perspective because our objective was to identify a pricing strategy for the country that would potentially improve drug access by making them more affordable to patients and government payers.

METHODS

Modeling the Pharmacoeconomic Outcomes of mCRC

A decision model for the management of mCRC was developed with the DATA software (Treeage Software Inc., Williamstown, MA, USA). The timeframe was from the first cycle of first line chemotherapy until death. In many countries including South Africa, the addition of oxaliplatin to infusional 5-fluorouracil (FOLFOX) is considered a standard of care for the first line treatment of mCRC.[21] If disease progression or treatment related toxicity develops, then irinotecan with infusional 5-fluorouracil (FOLFIRI) is a recommended second line treatment.[21,22] There is also data from a large randomized trial to suggest that safety and efficacy with sequential schedules of FOLFOX and FOLFIRI (or the reverse order) are equally effective for the first and second line treatment of mCRC.[23] Lastly, clinical practice guidelines recommend the addition of bevacizumab at some point during chemotherapy for mCRC.[24]

Using these recommended standards of care, a PE model was developed to simulate the management of mCRC with FOLFOX (± bevacizumab) followed by FOLFIRI upon disease progression or the discontinuation of first line therapy because of intolerable toxicity (Figure 1). The primary endpoint of the model was the achievement of successful therapy defined as complete tumour response (CR), partial response (PR) or stable disease (SD). However, all outcomes of the PE model resulted in eventual death, which is the unfortunate reality for patients with mCRC. The face and content validity of the model was verified by three clinical oncologists who had experience in the treatment of mCRC.

The PE model began at the choice node where a first line therapeutic decision between FOLFOX + “the new drug (bevacizumab)” or FOLFOX alone would have to be made (Figure 1). At the completion of the first two cycles of chemotherapy, patients would be evaluated for intolerable toxicity. In situations of severe toxicity, the initial first line regimen would be permanently stopped and second line FOLFIRI would be offered until disease progression or treatment related death. Upon disease progression, best supportive care would be offered to all patients until eventual death. In patients who tolerate first line FOLFOX (± “the new drug”), treatment would be continued until disease progression. Second line FOLFIRI would then be offered but the new drug would be discontinued. Upon progression following second line FOLFIRI, best supportive care would be available to all patients until death (Figure 1). Epidermal growth factor receptor (EGFR) inhibitors such as cetuximab in mCRC patients with KRAS wild type tumours were not considered in the model because we did not want to unnecessarily complicate the analysis. Notwithstanding, such agents would be available

to both treatment options following a first line progression, so their inclusion would not affect the final results.

Clinical Data

The clinical data to populate the economic model were obtained from a literature search. A search of Medline, Embase and the Cochrane databases was performed from 2000 through 2010 for human clinical studies involving FOLFOX, FOLFIRI and bevacizumab as first and second line therapy in mCRC. The objective of the review was to identify the most up-to-date clinical data which included tumour response, treatment discontinuations because of severe side effects, progression free and overall survival.

Estimation of Treatment Costs

The economic model began from the first cycle of FOLFOX chemotherapy (± the "new drug (bevacizumab)", followed by second line sequential chemotherapy until disease progression and eventual death. Costs for anticancer drugs, materials for drug delivery, patient monitoring and other related hospital resources (e.g. laboratory and diagnostic tests) were obtained from Wilgers Oncology Center in Pretoria. Palliative care costs for terminally ill cancer patients were obtained from the South African palliative care literature.[25] All costs in the current study were reported in 2010 South African Rand. Costs from previous years were converted into 2010 estimates using the South African consumer price index.

Health State Utilities

Health state utilities are scores between 0 and 1, where 0 represents death and 1 is a state of perfect health or optimal quality of life. In economic evaluations, they are used to adjust the survival benefit of a new drug by the quality of life experienced by a patient during that time period. So a cancer drug that improves survival but is associated with severe toxicity would have a reduced quality adjusted survival period. In the current study, the Time Trade-off technique was used to measure the utility for each of the health states described in the PE model (Figure 1).[26] The quality adjusted life periods were measured as "healthy months equivalent" for the time spent in each outcome of the decision model (Figure 1).[27] The scores in months were then converted to utility measures and applied to each of the respective branches of the economic model.

There is currently some debate in the health economic literature as to which population should provide health state utility estimates. The Canadian Guidelines for Economic Evaluations and the Panel on Cost-Effectiveness in Health and Medicine of the United States recommend that treatment preferences be measured from members of the general public who are potential candidates of the new medical intervention.[13,28] However it has been our experience that members of the general public have difficulty understanding cancer related utility questionnaires. As an alternative, we used oncology nurses as a patient surrogate sample to provide estimates for the health state utilities required by the model. Such a sample is reasonable because they are members of the general public and have a good understanding of the treatments and their side effects that are under investigation. There is also evidence in the oncology

literature to suggest that nurses are suitable patient surrogates for objective outcomes, and that utility estimates derived from such a sample do not substantially alter the findings of cost utility studies.[29,30] Therefore, a patient surrogate sample consisting of 16 oncology nurses provided utility values for the model. With a sample of 16 respondents, healthy month equivalence was measured with a precision of ± 1.5 month, with a 95% probability.

After informed consent was obtained, a local investigator interviewed each participant. The interviewer presented each respondent with information on FOLFOX, bevacizumab and FOLFIRI. This included method of administration, treatment efficacy in terms of tumour response, progression free and overall survival as well as the major toxicities reported in the literature. The interviewer then presented a detailed description of the 16 health state as depicted in the model and the length of time a patient would live in each of the health states (Figure 1). To apply the Time Trade-off technique, respondents were then asked how many lesser months of "optimal health" they considered being equivalent to the time spent in each of the less than optimal health states described in the model. Hence, they are trading length of life in a poorer health state for a lesser period of time in a state of optimal quality of life. This is the “trade off” component of the health state utility assessment. The final health state utilities were then used to weigh each branch of the model by the quality of life experienced by a patient living through that time period. An identical process was used for each of the 16 outcomes (Figure 1). A standardized questionnaire supported by printed interview tools with graphical displays was used to facilitate the participant’s

understanding of the Time Trade-off technique. To minimize the framing effect, all pathways were presented in a consistent manner pictorially.

Estimating a Value Based Price for new Cancer Drugs in South Africa

A cost utility analysis was undertaken to estimate a value based price for the "new drug" in the first line treatment of mCRC in South Africa. The base case analysis assumed that the addition of the "new drug (bevacizumab)" to first line oxaliplatin-based chemotherapy would provide a survival benefit of 1.4 months as reported in the literature.[31] The main outcome of the analysis was to estimate a price per dose for the "new drug" using an incremental cost of R219,000 per QALY gained, which is three times the South Africa per capita GDP.[17] Secondary to the short time periods involved, future costs and benefits were not discounted. However, the base case results were evaluated for uncertainty by a series of one-way sensitivity analyses. This consisted of applying variations in the survival benefit, costs of care and substituting the 95% confidence intervals (CIs) for the health-state utilities. Specifically, the survival gain was increased to 3 and 6 months from the base case of 1.4 months. Costs were changed by ±15% to account for possible variations across South Africa for both private and public health care schemes.

RESULTS

Upon review of the oncology trial literature, two key studies were identified and provided the clinical data to populate the model.[23,31] Data on the sequential use of first line FOLFOX followed by second line FOLFIRI were provided in a randomized trial reported by Tournigand et al.[23] In that study, patients were randomized to receive sequential FOLFOX followed by FOLFIRI upon progression or the reverse sequence. There was no significant difference in progression free and overall survival (FOLFOX – FOLFIRI = 21.5 vs. FOLFIRI – FOLFOX = 20.6 months; p=0.99) between the two sequences.[28] With second line FOLFIRI, 51% of patients experienced disease progression for an overall progression free survival of 2.5 months respectively.[28] Approximately 3% of patients died within the first 60 days of second line FOLFIRI.

The clinical data for the addition of bevacizumab to first line FOLFOX were provided from a randomized trial reported by Saltz et al.[31] In that study, patients were randomized to receive FOLFOX or a clinically similar regimen XELOX (capecitabine plus oxaliplatin) ± bevacizumab (every two weeks with FOLFOX and every 3 weeks with XELOX) in the first line treatment of mCRC.[31] A total of 1,401 patients were randomized to receive FOLFOX/XELOX + bevacizumab (n=699) or FOLFOX/XELOX + placebo (n=701). A 9.4 month median progression free survival was reported in the bevacizumab group compared to 8.0 months with placebo (HR=0.83; p=0.023). Patients in the bevacizumab group also experienced a 1.4 month improvement in survival (HR = 0.89, p = 0.077). Overall, 30% of patients in the bevacizumab group required a permanent treatment discontinuation because of adverse events compared to 20% in the control.

Estimation of Treatment Costs

Using unit cost estimates obtained from the Wilgers Oncology Center in Pretoria, the cost per cycle of FOLFOX was estimated to be R12,040. However before the first cycle of FOLFOX, the protocol start up costs were estimated to be approximately R1,227 (Table 1). The costs per cycle for FOLFIRI were slightly less at R9,985 with the associated start up costs being R1,398. Additional costs required to populate the model which included costs for the management of severe toxicity, administration of the "new drug" and best supportive care are presented in Table 2. These estimates were then incorporated into the PE model for the subsequent pricing analysis.

Health State Utility Assessments

To fully populate the model, health state utilities for the time period spent in each of the 16 health outcomes were required for the analysis (Figure 1). The utility estimates were measured in a sample of 16 oncology nurses. The sample had a mean age of 47.3 years, an average of 14.8 years of direct oncology experience (range 2.5 – 27 years) and all had experience in the treatment of colorectal cancer patients. In addition, all respondents had direct clinical experience in the preparation/administration and follow up care associated with FOLFOX (mean = 6.6 years), FOLFIRI (mean = 6.5 years) chemotherapy and the newer targeted therapies bevacizumab (mean = 5.5 years) and cetuximab (mean = 4.2 years) which are used in mCRC. In addition, 13 of 16 (81.2%) respondents had been involved in the development of systemic treatment guidelines for mCRC within the last two years. Respondents were then asked to state their knowledge of costs for modern oncology drugs because this could affect their

health state utilities. The findings revealed that 100% were “very familiar” with the high cost of the newer drugs used to treat cancer. Therefore, the oncology nurses who provided information for the assessment of health state utilities associated with mCRC were a well informed sample.

The health state utilities from the respondents are presented in Table 3. Considering that utilities are anchored between 0 and 1, where 0 represents death and 1 is a state of perfect health or optimal quality of life, all of the health states depicted in the model had estimates below 0.5 suggesting that patients with mCRC who are receiving chemotherapy have a poor quality of life during treatment. The branches with the highest utilities (i.e. branches 8 and 16) were those where the patient initially tolerated the treatment, but had a rapid cancer death with 2 months of starting therapy. The interpretation of this finding is that in cases of terminal disease, respondents may not be averse to a rapid death that would avoid prolonged pain and suffering.

Value Based Pricing Analysis

The clinical, health state utility and cost data were then applied to the model to derive a value based price for South Africa using R219,000 per QALY gained as the threshold for cost effectiveness. For a 1.4 month survival benefit when added to FOLFOX chemotherapy, a final price for bevacizumab that would be considered cost effective in South Africa could not be identified. The major factor behind this finding was that the 1.4 month survival gain was too small to overcome the value threshold.

The investigation was continued with a one way sensitivity evaluation on the key value drivers. These consisted of using the upper 95% CI of the health state utilities,

variations (± 15%) in the cost of chemotherapy, best supportive care and the management of side effects from anticancer therapy. The results indicated that despite reasonable variations in the above parameters, a final price that would be considered cost effective could not be identified. The sensitivity analysis was continued with variations in the overall survival gain offered by the "new drug". When the overall survival gain was changed to 3 and 6 months respectively, a price per dose considered to be cost effective by the WHO criteria was identified. If the "new drug" were able to provide a 3 or 6 month benefit in survival, it could be priced at R400 and R1,780 and be considered cost effective in South Africa. The current price per dose of bevacizumab in South Africa is approximately R10,216 (5 mg/mg for a 60 kg patient). At this price, our analysis indicated that bevacizumab is not cost effective using the WHO value criteria and is well beyond the R219,000 value threshold (Table 4). To summarize, the only major factor that would affect the economic value of a "new drug" for mCRC would be its ability to improve overall survival by at least 3 months.

DISCUSSION

With a per capita GDP of only R73,000, the South African government faces the challenge of making modern cancer drugs available to its citizens. To address this important issue, strategies need to be identified that will increase patient access, but at the same time, ensure a reasonable return on research and development cost to the innovating company. Without such a return, new drug discovery may be compromised or the pharmaceutical industry will simply not launch new products in South Africa. To reduce drug costs, several European governments such as Greece, Spain and France have recently mandated price cuts of up to 23% for branded products.[32,33,34] We believe that this is not a correct policy because it is not based on cost effectiveness analysis nor does it consider the value that a new drug brings to society. There are many examples in the medical literature where new drugs have saved lives and reduced overall health care costs.[35] Therefore, a scientifically sound and systematic process for estimating a value based drug price is recommended over draconian measures such as government mandated price cuts.

In the current study, we provide such an approach. Using principles of pharmacoeconomic analysis and value thresholds recommended by the WHO that consider the wealth of a nation, we were able to demonstrate its application in estimating a value based price for bevacizumab in mCRC. The findings suggested that any new drug in mCRC would need to provide at least a 3 month survival benefit for a value based price to be derived. Taking bevacizumab, which provides only a 1.4 month survival gain as an example, a value based price could not be identified. This finding suggests that at its current price and with the modest 1.4 month survival benefit,

bevacizumab is not cost effective in South Africa and is in fact excessively priced. Therefore our approach is sound and can be applied to all future cancer drugs to estimate a value based price prior to launch in South Africa. Even though the estimated price should not be seen as final, it can be the starting point for committed negotiations between the manufacturer and public/private payers.

Value-based drug pricing will likely have a major role to play in Europe over the next few years. The new government of the UK recently announced its intent to revise the current drug pricing scheme and move towards a value based approach that will be delivered by NICE on behalf of the National Health Service.[36] Specifics of this new system have yet to be announced, however previous initiatives by NICE would suggest that value estimations involving cost per QALY gained coupled with comprehensive PE models would drive new product pricing. The UK has established a threshold for drug coverage at £30,000 per QALY gained (equivalence to approximately $U.S.50,000).[37] In many other jurisdictions, a $U.S.50,000 cost per QALY threshold has been used; which was based on a 1982 valuation and is now equivalent to approximately $U.S.197,000 per QALY in 2007 U.S. dollars (after a 5.5% annual adjustment in health care inflation).[12] However, the $U.S.50,000 threshold continues to be used and quoted in the pharmacoeconomic literature. Therefore, it is possible that the new value based pricing scheme proposed by the UK government will revolve around the use of PE modeling and current value thresholds even though they are outdated.

There are several limitations in our study and in our proposed approach that need to be addressed. For the proposed methodology to be viable, complete data from randomized trials on a drug by drug basis is required. One of the limitations of using the

per capita GDP for value based pricing is that it represents a national average and does not consider income dispersion. Moving forward, it would be relevant to identify a threshold for value based pricing that incorporates both income dispersion and the per capita GDP. Many of the newer cancer drugs have not demonstrated a significant improvement in patient quality of life (QOL) and their survival benefit has been less than 3 months.[31,38,39] For our modeling strategy to be applied, a new drug must demonstrate either an improvement in QOL over the standard of care or a survival of sufficient magnitude to identify a final price point for cost effectiveness. Oncology nurses and pharmacists were used as patient surrogates in the utility assessments. Even though respondents had an average of 14.8 years cancer experience and 100% also had experience with FOLFOX and FOLFIRI chemotherapy as well as the the newer targeted therapies, patients would have been preferable to surrogates. Lastly, indirect costs such as time off work secondary may be relevant in this setting, but were not considered in this analysis. Future modeling should consider their inclusion.

CONCLUSIONS

Improving patient access to new cancer drugs is an important objective of the South African government. In this study, we present a novel approach to estimating a value based drug price that can be the starting point for negotiations. The ultimate outcome of these discussions between the key stakeholders is to identify a final drug price that would simultaneously reflect what the South African government can pay and provide a reasonable return on investment by the innovating company.

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Table 1. Mean cost per cycle of FOLFOX and FOLFIRI.

Resource Item[a]	**FOLFOX**	**FOLFIRI**
Drug acquisition[a]	R9,129	R7,572
Ancillary drugs[b]	R961	R483
Preparation and administration[c]	R1,572	R859
Patient monitoring[d]	R378	R771
Protocol start up costs[e]	R1,227	R1,398
Total cost per cycle	**R12,040**	**R9,685**

[a]Assuming a 60 kg patient with a body surface area of 1.6 m^2.

[b]Includes standard premedication such as loperamide and antiemetics such as ondansetron and dexamethasone.

[c]Includes materials, supplies, personnel, chemotherapy unit stays and physician visits.

[d]Standard laboratory and diagnostic tests.

[e]These costs are a one-time cost in order to prepare the patient for the associated chemotherapy protocol. In the case of FOLFOX and FOLFIRI, preparations and materials for infusional 5-fluorouracil made up the bulk of the costs. For the economic analysis, the start up costs were only applied once over the estimated median number of cycles delivered. Thus avoiding double counting.

Table 2. Hospital costs for the treatment of metastatic colorectal cancer in South Africa.

Recourse Item	Hospital Cost
FOLFOX chemotherapy[a]	R12,040 / cycle
FOLFIRI chemotherapy[b]	R9,685 / cycle
Cost for a permanent chemotherapy discontinuation because of toxicity[c]	R19,800
Cost to administer the "new drug" after FOLFOX chemotherapy	R440
Cost of best supportive care[d]	R869 / month

[a]Oxaliplatin in combination with infusional 5-fluorouracul. Cost per cycle includes resources for drug administration and routine patient monitoring.

[b]Irinotecan in combination with infusional 5-fluorouracil.

[c]Patients would be admitted for 3 days for the management of side effects and for reassessment. The principle side effects that would lead to the discontinuation of therapy would be febrile neutropenia and grade III/IV diarrhea.

[d]From Uys and Hensher (2002)[25]. The 2002 estimate was converted in 2010 South Africa Rand using the consumer price index.

Table 3. Health state utilities derived using the Time Trade-Off technique.

Sixteen Health Outcomes Evaluated in the Decision Model	Time in Health State[a]	Utility Estimate[b] [mean (SD)]
FOLFOX + "new drug" → Folfiri → BSC until death		
Branch #1: Stopped FOLFOX + the "new drug" after 2 cycles due to side effects and was then treated with FOLFIRI for 4 cycles. There was disease progression. The patient received BSC and died 6 months later.	10 months	0.29 (0.14)
Branch #2: Stopped FOLFOX + the "new drug" after 2 cycles due to side effects and was then treated with FOLFIRI. There was a response to FOLFIRI and the patient went on to receive 8 cycles. Upon progression, the patient received BSC and died 22 months later.	28 months	0.21 (0.16)
Branch #3: Stopped FOLFOX + the "new drug" after 2 cycles due to side effects and was then treated with FOLFIRI. There was a response to FOLFIRI and the patient went on to receive 8 cycles. Upon progression, the patient received BSC and died 2 months later.	8 months	0.28 (0.11)
Branch #4: Stopped FOLFOX + the "new drug" after 2 cycles due to side effects and was then treated with FOLFIRI for 2 cycles. However, the patient died due to cancer progression within the first 2 months.	4 months	0.34 (0.21)
Branch #5: Tolerated side effects but had disease progression after 4 cycles of FOLFOX + the "new drug". The patient was then treated with FOLFIRI for 4 cycles but the disease did not respond. The patient received BSC and died 2 months later.	6 months	0.26 (0.13)
Branch #6: Tolerated side effects and responded FOLFOX + the "new drug". The patient went on to receive a total of 17 cycles of first line therapy. Upon progression, the patient went on to receive 6 cycles of FOLFIRI. Upon progression, the patient received BSC and died 21 months later.	29 months	0.19 (0.21)
Branch #7: Tolerated side effects and responded FOLFOX + the "new drug". The patient went on to receive a total of 17 cycles of first line therapy. Upon progression, the patient went on to receive 2 cycles of FOLFIRI but died 2 months later.	11 months	0.28 (0.17)
Branch #8: Tolerated side effects and but had disease progression after 2 cycles of FOLFOX + the "new drug". The patient died due to the cancer one month later.	2 months	0.39 (0.20)

Table 3. Continued…

FOLFOX → FOLFIRI → BSC until death		
Branch #9: Stopped FOLFOX after 2 cycles due to side effects and was then treated with FOLFIRI for 4 cycles. There was disease progression. The patient received BSC and died 6 months later.	10 months	0.26 (0.11)
Branch #10: Stopped FOLFOX after 2 cycles due to side effects and was then treated with FOLFIRI. There was a response to FOLFIRI and the patient went on to receive 8 cycles. Upon progression, the patient received BSC and died 22 months later.	28 months	0.20 (0.16)
Branch #11: Stopped FOLFOX after 2 cycles due to side effects and was then treated with FOLFIRI. There was a response to FOLFIRI and the patient went on to receive 8 cycles. Upon progression, the patient received BSC and died 2 months later.	8 months	0.24 (0.06)
Branch #12: Stopped FOLFOX after 2 cycles due to side effects and was then treated with FOLFIRI for 2 cycles. However, the patient died due to cancer progression within the first 2 months.	4 months	0.34 (0.22)
Branch #13: Tolerated side effects but had disease progression after 4 cycles of FOLFOX. The patient was then treated with FOLFIRI for 4 cycles but the disease did not respond. The patient received BSC and died 2 months later.	6 months	0.20 (0.09)
Branch #14: Tolerated side effects and responded FOLFOX. The patient went on to receive a total of 15 cycles of first line therapy. Upon progression, the patient went on to receive 6 cycles of FOLFIRI. Upon progression, the patient was offered BSC and died 21 months later.	32 months	0.19 (0.19)
Branch #15: Tolerated side effects and responded FOLFOX. The patient went on to receive a total of 15 cycles of first line therapy. Upon progression, the patient went on to receive 2 cycles of FOLFIRI but died 2 months later.	11 months	0.21 (0.11)
Branch #16: Tolerated side effects and but had disease progression after 2 cycles of FOLFOX. The patient died due to cancer progression one month later.	2 months	0.38 (0.20)

[a]As presented in each branch of the decision analysis model. [b]A quality of life score for a health state between 0 and 1, with 0 = death and 1 = optimal health. Abbreviations: FOLFOX = oxaliplatin+ infusional 5-FU. FOLFIRI = irinotecan + infusional 5-FU, BSC = best supportive care

Table 4. Sensitivity analysis on the unit price for the "new drug"

Sensitivity Manoeuvre[1]	**Price per Dose**
Base case	Not reached
Upper 95% CI of health state utilities for chemotherapy + the "new drug"	Not reached
Changing cost of FOLFOX chemotherapy by ± 15%	Not reached
Changing cost of FOLFIRI chemotherapy by ± 15%	Not reached
Changing cost of BSC cost by ± 15%	Not reached
Changing cost of ADR cost by ± 15%	Not reached
Changing survival benefit of the "new drug" from 1.4 to 3 months	R400
Changing survival benefit of the "new drug" from 1.4 to 6 months	R1,780
Using the current price of bevacizumab (R10,216) in South Africa	Not cost effective

Abbreviations: FOLFOX = Oxaliplatin in combination with infusional 5-fluorouracul. FOLFIRI = Irinotecan in combination with infusional 5-fluorouracul. BSC = best supportive care, ADR = adverse drug reaction.

[1]For a target threshold of R219,000 per QALY when the new drug is added to FOLFOX chemotherapy.

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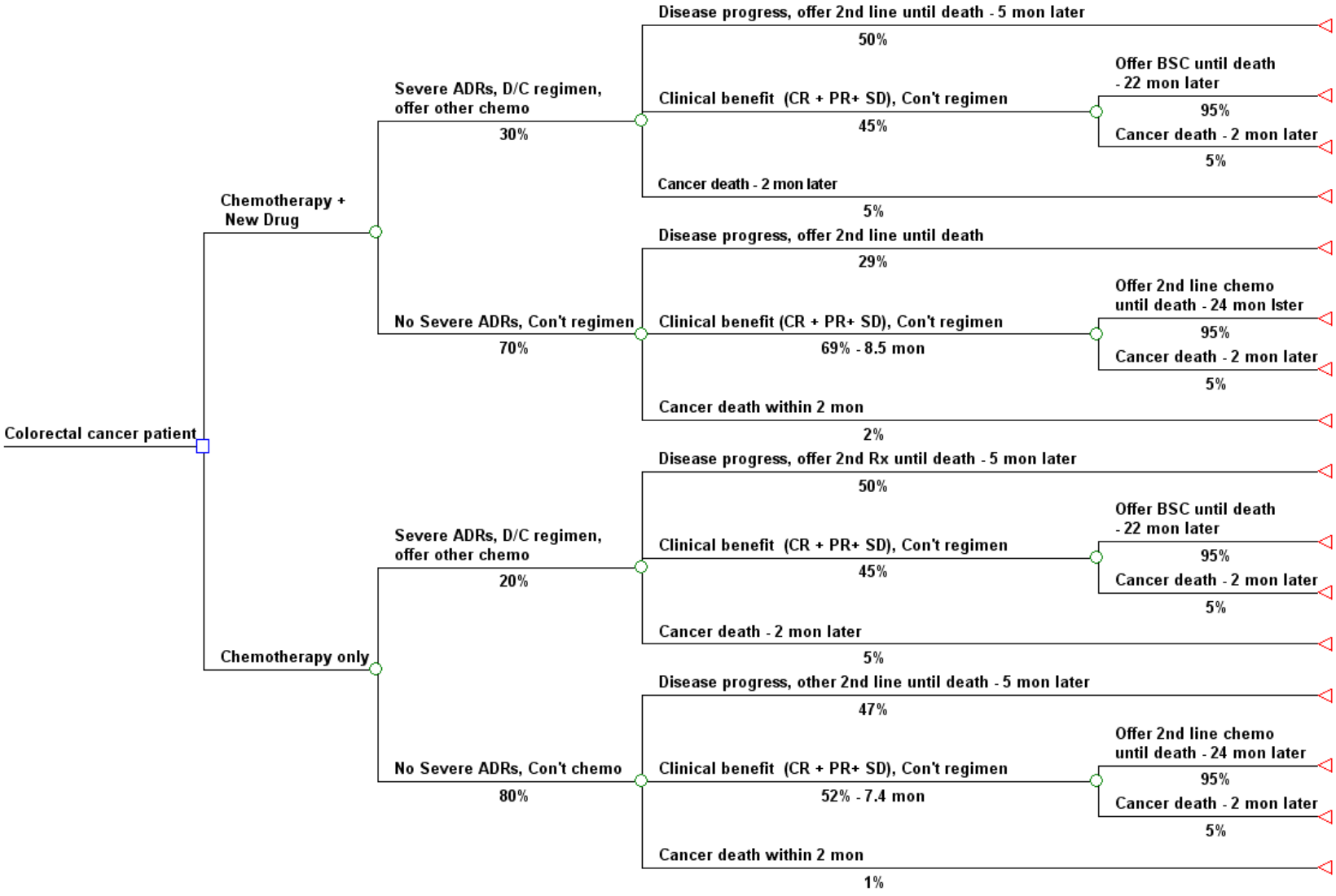

Figure 1. Decision analysis model for the treatment of metastatic colorectal cancer.

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The development of a value based pricing index for new drugs in metastatic colorectal cancer

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ABSTRACT

Background: Worldwide, prices for cancer drugs have been under downward pressure where several governments have mandated price cuts of branded products. A better alternative to government mandated price cuts would be to estimate a final price based on drug performance, cost effectiveness and a country's ability to pay. We developed a global pricing index for new cancer drugs in patients with metastatic colorectal cancer (mCRC) that encompasses all of these attributes.

Methods: A pharmacoeconomic model was developed to simulate mCRC patients receiving chemotherapy plus a 'new drug' that improves survival by 1.4, 3 and 6 months, respectively. Cost and utility data were obtained from cancer centres and oncology nurses ($n = 112$) in Canada, Spain, India, South Africa and Malaysia. Multivariable analysis was then used to develop the pricing index, which considers survival benefit, per capita GDP and income dispersion (as measured by the Gini coefficient) as predictor variables.

Results: Higher survival benefits were associated with elevated drug prices, especially in higher income countries such as Canada. For Argentina with a per capita GDP of $15,000 and a Gini coefficient of 51, the index estimated that for a drug which provides a 4 month survival benefit in mCRC, the value based price would be $US 630 per dose. In contrast, the same drug in a wealthier country like Norway (per capita GDP=$50,000) could command a price of $US 2,775 per dose.

Conclusions: The application of this index to estimate a price based on cost effectiveness and the wealth of a nation would be important for opening dialogue between the key stakeholders and a better alternative to government mandated price cuts.

1. Introduction

The cost of health care has been growing rapidly over the past decade.[1] There are several contributing factors such as an ageing population, a more aggressive treatment culture and the availability of more effective drugs that have replaced medical procedures previously requiring hospitalisation.[2–4] One of the most identifiable parts of increased health care costs has been pharmaceuticals. Using oncology drugs as an illustration, it was reported from 1993 to 2004, total sales for oncology drugs in Europe alone increased seven times from €840 to €6170 million.[5] Similar trends have also been reported in the United States where cancer drug expenditures increased from $3 billion in 1997 to $11 billion in 2004.[6]

Rising drug costs have now become a global concern as institutionalised health care systems struggle to offer modern

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treatments within limited budgets. Combined with the global economic recession, many governments have responded by mandating cuts in branded pharmaceuticals of up to 30%.[7–9] However, government mandated price cuts may not serve the patient in the long term because they would deter innovative pharmaceutical companies from making large investments into research and development. Without such investment, new drug discovery would be compromised. In the end, manufacturers should be rewarded for innovation because new drugs have been a major contributor towards improved patient outcomes and reduced health care costs.[4,5]

A better and more systematic alternative to government mandated price cuts is the establishment of a drug price based on performance during randomised trials and the total value that it brings to society. Such value based pricing schemes have been proposed in several countries.[10,11] As an illustration, the new government of the United Kingdom (UK) recently announced its intent to revise the current free drug pricing scheme and move towards a value based approach.[11] Specifics of this new system have yet to be announced nor is it known who will administer it. However, previous drug pricing initiatives by the National Institute of Clinical Excellence (NICE) would suggest that value thresholds involving the cost per quality adjusted life year (QALY) gained coupled with comprehensive pharmacoeconomic (PE) models would likely play a central role in the new product pricing system.

The application of value based drug price estimation requires the establishment of a threshold for societal value where drugs at or below this level would be reimbursed by publicly funded health care systems. As an illustration, the National Health Service (NHS) of the UK has established a threshold for drug coverage at £30,000 per QALY gained.[12] In the Netherlands, the unofficial threshold is €18,000 per QALY.[5] One of the challenges in the use of such thresholds is that the wealth of an individual country is not considered. To address this, the World Health Organization (WHO) has proposed to use multiples of a country's per capita gross domestic product (GDP) to establish thresholds for economic value.[13,14] Based on the WHO criteria, products less than or equal three times the per capita GDP would be considered cost effective.[13]

What would be of interest to all the key stakeholders would be the development of a drug pricing index that is linked to both product performance and value thresholds that also consider the wealth of a nation. In this study, we describe the development of such an index that can be applied to new therapies indicated for the treatment of metastatic colorectal cancer (mCRC).

2. Methods

2.1. Modeling the pharmacoeconomic outcomes of mCRC

mCRC was chosen because several new anticancer agents have been approved in this disease site but their high cost has led to their outright refusal for reimbursement by government payers.[15,16] The development of a pricing index for new drugs in mCRC began with the construction of a PE model. The model was designed to simulate the clinical and economic outcomes in patients receiving standard chemotherapy with the addition of a 'new drug' that provides a survival increment between 1.4 and 6 months. Details of the model's development, validation and its population are described elsewhere.[17] Briefly, the timeframe was from the first cycle of first line chemotherapy until death. The current standard of care for the first line treatment of mCRC is oxaliplatin in combination with infusional 5-fluorouracil (FOLFOX).[18,19] In patients who have disease progression or intolerable toxicity, second line irinotecan in combination with infusional 5-fluorouracil (FOLFIRI) is a recommended treatment.[18] Therefore, the model began with FOLFOX (± the 'new drug') followed by FOLFIRI upon disease progression or the discontinuation of first line therapy because of intolerable toxicity. The clinical data required to populate the model were obtained from the oncology literature.[19,20] The drug that provided the point estimates for the incremental benefits quantified by the pricing index was bevacizumab, an agent that targets the vascular endothelial growth factor (VEGF) and is associated with a 1.4 month survival benefit in mCRC.[20]

2.2. Multinational data collection

The intent of this study was to develop a pricing index that could be used across many countries to estimate a value based price for new drugs in patients with mCRC. The PE model had to be populated with cost and utility data in order to generate the cost effectiveness pricing outputs required to develop the pricing index. The required data were collected in cancer centres from Canada, Spain, South Africa, Malaysia and India. The selection of these countries provided a per capita GDP ranging from $3100 to $39,000 (Table 1).

2.3. Estimation of treatment costs

For each country, costs for anticancer drugs, materials for drug delivery, patient monitoring, other related hospital resources (e.g. laboratory and diagnostic tests) as well as palliative care costs for terminally ill cancer patients were collected from local cancer centres and from the international oncology literature.[17,21–24] All costs and outputs in the current study were reported in 2010 US dollars.

2.4. Health state utilities

Health state utilities are scores between 0 and 1, where 0 represents death and 1 is a state of perfect health or optimal quality of life. In economic evaluations, they are used to adjust the survival benefit of a new drug by the quality of life experienced by a patient during that time period. In the current study, quality-adjusted life periods were measured as 'healthy months equivalent' for the time spent in each outcome of the PE, model using the Time Trade-off technique[17,25,26] Utilities for the various outcomes in the PE model (16 in total) were obtained from a sample of oncology nurses and pharmacists (total $n = 112$) involved in the treatment of mCRC patients in each of the respective countries.[17,21–24]

2.5. Estimating a value based price for each country

Using the country specific cost and utility data, a cost utility analysis was performed to estimate a value based price for

Table 1 – Description of reference countries.

Country	Population	GDP per capita[a,b] ($US)	Gini coefficent[c]	Health care system
Canada	33 million	$39,000	32.6	Public only
Spain	45 million	$35,000	34.7	Public-private mix
Malaysia	28 million	$14,800	49.2	Public-private mix
South Africa	49 million	$10,000	57.8	Public-private mix
India	1.1 billion	$3100	36.8	Public-private mix

[a] The World Fact Book. Central Intelligence Agency 2010. https://www.cia.gov/library/publications/the-world-factbook/rankorder/2004rank.html. Accessed November 18, 2010.
[b] The cost per QALY value threshold was three times the per capita GDP for that country.
[c] The Gini coefficient is a measure of income dispersion. A value of 0 represents absolute equality, and a value of 100 is absolute inequality.[28]

the 'new drug' in the first line treatment of mCRC. The base case analysis assumed that the addition of the 'new drug' to first line oxaliplatin-based chemotherapy would provide a survival benefit of 1.4 months as reported in the literature for bevacizumab.[20] The main outcome of the analysis was to estimate a price per dose for the 'new drug' using an incremental cost per QALY gained threshold, which was three times the respective countries' per capita GDP (Table 1). The survival gain was then increased to approximately 3 and 6 months from the base case of 1.4 months to determine how the price points would change for each country. Such a procedure provided 15 data points for the subsequent multivariable analysis.

2.6. Statistical considerations

After application of the PE model towards a cost utility analysis, the evaluation in each country provided three price points for the 'new drug' that were linked to the associated gains in survival. A multivariable regression analysis, which was adjusted for clustering on the variable 'country', was then conducted with 'drug price' as the dependent variable and survival gain, per capita GDP and the Gini coefficient, which is a measure of income dispersion (a value of 0 represents absolute equality, and 100 is absolute inequality) as independent variables.[27,28] Given our small sample size consisting of only 15 price points in total from the five countries, non-parametric bootstrapping was applied. Resampled data (1000 iterations) were used to generate bootstrap estimates of the regression coefficients of the multivariable model. All of the statistical analyses were performed using Stata, release 11.0 (Stata Corp., College Station, Texas, USA).

3. Results

Economic and health state utility data were collected in five countries with populations ranging from 28 million to 1.1 billion (Table 1). All countries with the exception of Canada had health care systems consisting of a mix of public and private. In Canada, the health care system is entirely public and there are no private hospitals. Among the five countries, the per capita GDP ranged from $3100 to $39,000. Such a range would encompass approximately 140 countries worldwide.[27]

The value based price points for a 'new drug' providing a **1.4, 3 and 6 month survival benefit in mCRC determined in the cost utility analyses are described in Table 2. A clear relationship was seen where countries with a higher per capita** GDP were associated with a higher value based drug price for each of the three survival periods. It was interesting to note that in the lower income countries (i.e. Malaysia, South Africa and India), a drug price considered cost effective by the WHO criteria could not be achieved with only a 1.4 month survival benefit. For a price point to be reached in these countries, at least a 3 month survival increment would be needed by a new oncology product indicated for mCRC. The other relationship noted in the data was that the incremental survival benefit was the major driver for a premium drug price. If a new drug for mCRC was able to increase survival by 6 months, then a price per dose exceeding $2,900 could be charged in high income countries such as Canada and Spain. This price point can be extended to all countries of the European Union where the overall per capita GDP is approximately $32,000.[27] Therefore, new drug products with the ability to improve survival by 6 months should be able to command a premium price in wealthier countries and still be considered cost effective according to the WHO criteria.

3.1. Development of a value based pricing index for mCRC

Using the price points for the three levels of survival described in Table 2, a main effects multivariable analysis was undertaken to develop a pricing index for new drugs in mCRC. The three independent variables added to the model were survival gains in months, per capita GDP and the Gini coefficient for the respective country. The results of the analysis

Table 2 – Value based price points for absolute survival benefits in the five countries.

Country[a,b]	1.4 month survival[d]	3 months survival	6 months survival
Canada	$830	$2180	$3430
Spain	$465	$1145	$2905
Malaysia[c]	0.0	$567	$1258
South Africa[c]	0.0	$57.00	$254
India[c]	0.0	$98.00	$253

[a] All currencies are in 2010 US dollars.
[b] Point estimates for each of the five countries were reported in Ref.[17,21–24]
[c] In these countries, a cost effective price could not be found because a 1.4 month survival was simply too short.
[d] The survival benefit reported for bevacizumab from the Saltz et al. trial.[20]

are presented in Table 3. Overall, the three independent variables accounted for 83% of the variability in the dependent variable 'price' as indicated by the adjusted R^2 statistic. As suggested before, the single biggest contributor to drug price was the incremental gain in overall survival. For every month of survival benefit, our pricing index indicated that an additional $296 could be added to the final launch price.

A stepwise pricing index was then developed from the point estimates of the regression coefficients and the intercept generated from the analysis. Each of the final regression coefficients evaluated in the model provided a statistical weight for that factor's contribution to the overall price point. The scoring system was then adjusted by adding a constant across all scores to ensure that none of the final scores were below zero. The final product was a pricing algorithm where higher survival benefits are associated with a price premium. The starting point and score assigned to each of the pricing factors is as follows:

- Start at base score of $11,000.
- Multiply the Gini coefficient for that country by $300 and add to base score.
- Subtract the country specific per capita GDP.
- Multiply the drug's survival benefit in months by $6,000 and subtract.
- Add the above scores and then multiply by −5%.

The above pricing index is easy to apply and best illustrated with an example. Suppose there is a new drug for mCRC that has demonstrated a four month survival benefit in a recent randomised trial. What would be a value based price for the drug in a country like Argentina, with a per capita GDP of $15,000 and a Gini coefficient of 51.3? Going through the pricing index, a value based launch price in Argentina for a drug that provides a 4 month survival benefit would be $630 per dose. If the same drug was to be launched in Norway, whose per capita GDP and Gini coefficient is $50,000 and 25 respectively, the price per dose for the same drug would be $2,775. Through the application of our price index, we ensure that the final launch price of a new drug is linked to a country's ability to pay. Therefore, government payers in countries like Argentina and Norway would have a better indication of what a cost effective price should be relative to the survival benefit offered by the drug.

Table 3 – Multivariable regression analysis on the value based price estimates.

Variable[a]	Parameter estimate	SE	95% CI
Intercept	−542	1583	
Survival gain (in months)	296	95	110–482
Per capita GDP	0.051	0.020	0.012–0.089
Gini coefficient[b]	−15.1	26.6	−67–37
Adjusted R^2	0.83		

Abbreviations: GDP, gross domestic product; SE, standard error; CI, confidence interval.

Adjusted R^2 = proportion of variability in the dependent variable that is accounted for by the regression analysis. Dependent variable: Drug price in 2010 $US.

[a] Point estimates and 95% CIs determined by non-parametric bootstrapping.

[b] The Gini coefficient is a measure of income dispersion. A value of 0 represents absolute equality, and a value of 100 is absolute inequality.[28]

4. Discussion

Government mandated cuts of branded drugs do not serve patients in the long term because such actions will only serve as a disincentive for pharmaceutical companies to invest in new drug discovery. A better alternative to such actions would be to set product price based on several factors such as performance under a controlled clinical trial setting, a nation's ability to pay a price premium for exceptional products, how uniformly income is distributed within a given country, and the overall cost effectiveness of the product measured against some reasonable societal value threshold. In the oncology setting, drug performance is best measured by the incremental survival benefit that is offered over the standard of care. Estimating an overall product value threshold is more challenging, but a reasonable starting point is three times the per capita GDP as recommended by the WHO.[13]

In this study, we used a PE model for a hypothetical 'new drug' in mCRC that was populated with cost and utility data from five different countries to develop an index to estimate a value based price.[17,21–24] From the PE model, price points were estimated for survival increments of 1.4, 3 and 6 months using three times the per capita GDP as the target value threshold from each country. Multivariable analysis was then applied on the price points to measure the contribution of survival benefit, per capita GDP and income dispersion on the final price estimate. The coefficients from the multivariable model were then used to develop the final pricing index, which can be used to estimate a value based price for a new drug in mCRC. The index is easy to apply using information that is readily available to national drug formulary committees.

A major advantage of our pricing index is its transparency and the ability to apply it to approximately 140 countries whose per capita GDP falls within the range evaluated in this study. In addition, the index is able to rapidly estimate a value based price using international recommendations for economic value.[13,14] Such an index would also be valuable to manufacturers who are considering launching their products in lower income countries. If they were to launch a critically important product at a high price that is simply out of reach for that country's health care budget, the national government may issue a compulsory licence, which would enable local production of the patented drug. This is possible under the Trade Related Intellectual Property Rights agreement of the World Trade Organisation and has already occurred with some HIV drugs.[29] Alternatively, a value based price estimated with our index could be the starting point for negotiations between government payers and the manufacturer, which could lead to a more affordable launch price for that country.

There are a number of limitations in our study that need to be acknowledged. The intent of our initiative was to develop a tool that can be applied to mCRC drugs for estimating a value

based price that would potentially increase patient access. For the proposed methodology to be applied to other disease sites, complete data from randomised trials on a drug by drug basis will be required to develop disease specific pricing indexes. Our index can only be applied towards new drugs in mCRC and for countries that fall within our range of per capita GDP. Our sample size was small (only five countries) and this may limit the generalisability of our index. In addition, external validation in other countries outside of our GDP range is warranted.

5. Conclusions

The present study describes the development of a global pricing index that can be used to estimate a value based price in different countries for new drugs in mCRC. The application of this index to estimate a cost effective drug price would be a good starting point for opening dialogue between the key stakeholders and a better alternative to governments' mandated price cuts. However, this does not necessarily mean that annual drug expenditures will be contained. True therapeutic innovation requires an investment by society. Ultimately, the final price that is negotiated must create a balance that will reward innovation and maximise patient access to new drugs.

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Con ict of interest statement

None declared.

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Editorial Comment

The pharmacoeconomics of spiralling cancer drug costs – Is there a viable solution?

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The IARC estimates that 27 million new cancer cases will be diagnosed in 2030.[1] This will place massive strain on institutionalised health systems already pressured under the current economic climate. During the decade leading up to 2004 spending on cancer drugs in the EU has increased from 840 to 6170 million euros[2] and in the United States during a similar period (1997–2004) this figure within Medicare rose from $3 billion to $11 billion.[3] The stark and well known fact facing healthcare providers remains that this spending will become unsustainable, and probably already is. The ability to balance, on one hand the rising costs of drugs with short and long term constriction of budgets will define the accessibility of new and effective treatments to patients reliant on publicly funded healthcare.

The reaction thus far to the current economic situation has been mixed. In Spain and France for example government mandated cuts of branded pharmaceutical prices of up to 30% have been implemented. In the United Kingdom, however, pharmaceutical companies are currently free to set their own pricing, although a move to a value based pricing index has been suggested by 2014 that will take into account 'drug efficacy and the potential benefit to society' though measurement of this will be controversial.[4]

Although in the short term the measures briefly described above would decrease budgetary expenditure, in the long term one may argue that the risk is a knock on decrease in investment in the very expensive arena of cancer drug development and innovation. In this issue of the *Journal*, Dranitsaris and colleagues propose a simple to understand and useful alternative to arbitrary government intervention in cancer drug pricing. Simply put, they propose a system of value based pricing based on the performance of the product and the wealth of the nation purchasing the drug.[5] The paradigm they have used to illustrate this is that of metastatic colorectal cancer. The Gross Domestic Product (GDP) in the five countries they have studied to evaluate this index ranges from $3100 to $39,000, and as such if applied more broadly this range would include 140 countries. As an example if a new drug in colorectal cancer has demonstrated a 4 month survival benefit in a recent study, using GDP and Gini coefficients (a measure of distribution of wealth within a nation) the value based launch price in Argentina (per capita GDP $15,000) would be $630 per dose, whereas in Norway (per capita GDP $50,000) this would be $2775.

This proposition is not entirely new and the idea of value based pricing has been suggested in various forms previously.[6] Indeed the demand for such a system, not only within Europe but globally has arisen from the awareness of the need of healthcare systems to annotate value to costly interventions. Last year the debate around 'value' permeated the

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United States healthcare system[7] and cost-effectiveness in healthcare is a pillar of current reforms there. The debate occurred with greater intensity following the FDA approval of Sipuleucel-T (Provenge), a treatment for metastatic prostate cancer that costs $93,000, with therapy deriving a median 4 month increment in overall survival.[8] It is in this context that we should evaluate the value based pricing index proposed by *Dranitsaris* which incorporates not only efficacy measures, but affordability measures too.

What are the potential pitfalls with these variables? There are problems if we are using survival as the sole efficacy measure in cancer patients. In many metastatic cancers, for example breast cancer and colorectal cancer, multiple lines of treatment may be given before a new putative agent and overall survival benefits may be lost or diluted by cross-over, and instead outcome measures that becomes significant may simply be time to progression or even quality of life. The implications here are complex for an outcome measure for pricing. In cases where the effect of single agents on the course of a patients survival is difficult to assess, is it valid to consider other measures such as quality of life as a reasonable outcome for a value based pricing index? This is perhaps one question to be addressed in the debate that will follow between stakeholders. As far as an intrinsic affordability factor is concerned, this will be viewed by many physicians as fair and long overdue. Certainly the ability of a third party to negotiate drug prices is credited with part of the estimated 37% savings in 1 year seen in one in the Medicare Part D Programme.[3] Any ability to negotiate prices is an improvement compared to the system that exists in countries such as the United Kingdom currently. Importantly 'negotiation' in context here is a nebulous term, open to interpretation and lobbying in ways that a *de facto* costing based on the fixed measures of affordability outlined above, is not.

What are the implications of value based pricing for rationing systems already in place? Although the United Kingdom National Institute of Clinical and health Excellence (NICE) has been widely praised for its attempts to address cost effectiveness of interventions, there have been criticisms in its handling of cancer drug rationing. It is a view held by many that the *Quality Adjusted Life Year* (QALY) is a flawed measure of assigning cost effectiveness,[9] and its use in defining a threshold below which a publicly funded healthcare system will pay for a drug has been criticised. Furthermore with this rationing comes debate and the various consultations and processes that are in themselves costly in terms of time, infrastructure and expenditure.[10] Although this infrastructure is changing in the United Kingdom, it follows that if a cancer drug is already costed at launch to allow for efficacy and affordability, then much effort and time would potentially be saved in having to assign these values within organisations in individual nations. This presumably implies patients would have access to drugs quicker than is the case currently, and with less reliance on other measures of cost-effectiveness.

The palatability of this to the pharmaceutical industry, governments, and what this will mean for patients is evolving. It is clear an alternative to the status quo is needed, and stakeholders need to consider the long term sustainability of new innovations. Pharmaceutical companies should have some incentive to spending resources on research and development of new drugs to treat cancer 'better', as opposed to efforts devoted to marketing or prolonging patent lives of existing products with 'me too' formulations. Value based pricing with the integration of affordability as described by *Dranitsaris* and colleagues would seem to be an excellent and necessary starting point for this debate.

Conflict of interest statement

None.

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6.10 Chapter Summary

The intent of this study was to develop a pricing index that could be used across many countries to estimate a value based price for new drugs in patients with mCRC. The PE model had to be populated with cost and utility data in order to generate the cost effectiveness pricing outputs required to develop the pricing index. The required data were collected in cancer centers from Canada, Spain, South Africa, Malaysia and India. The selection of these countries provided a per capita GDP ranging from $3,100 to $39,000 (Table 5.1). Notwithstanding, the inclusion of more countries in the model development phase would have added precision to the final predictive index.

Using the country specific cost and utility data, a cost utility analysis was performed to estimate a value based price for the “new drug” in the first line treatment of mCRC. The base case analysis assumed that the addition of the “new drug” to first line oxaliplatin-based chemotherapy would provide a survival benefit of 1.4 months as reported in the literature for bevacizumab (Saltz et al., 2008). The main outcome of the analysis was to estimate a price per dose for the “new drug” using an incremental cost per QALY gained threshold, which was three times the respective countries’ per capita GDP (Table 5.1). The survival gain was then increased to approximately 3 and 6 months from the base case of 1.4 months to determine how the price points would change for each country. Such a procedure provided 15 data points for the subsequent multivariable analysis.

Table 6.1. Value based price points for absolute survival benefits in the five countries.

Country[1]	1.4 mon survival[3]	3 mon survival	6 mon survival
Canada	$830	$2,180	$3,430
Spain	$465	$1,145	$2,905
Malaysia[2]	0.0	$567	$1,258
South Africa[2]	0.0	$57.00	$254
India[2]	0.0	$98.00	$253

[1]All currencies are in 2010 U.S. dollars. [2]In these countries, a cost effective price could not be found because a 1.4 month survival was simply too short. [3]The survival benefit reported for bevacizumab from the Saltz et al. trial (2008).[20]

After application of the PE model towards a cost utility analysis, the evaluation in each country provided three price points for the "new drug" that were linked to the associated gains in survival. A multivariable regression analysis, which was adjusted for clustering on the variable "country", was then conducted with "drug price" as the dependent variable and survival gain, per capita GDP and the Gini coefficient, which is a measure of income dispersion (a value of 0 represents absolute equality, and 100 is absolute inequality) as independent variables (De Maio, 2007). The unit of analysis was "country". Therefore, country level variables that are associated with a country's ability to pay for high cost cancer drugs were evaluated in the model. Since the level of income dispersion is a relevant factor, it was considered in the model. The Gini coefficient was used for several reasons. It is presented on a standardized linear scale from 0 to 100, there is the availability of data for most countries around the world and lastly, it has been accepted by the WHO as a measure of income dispersion globally (The World Fact Book, 2010).

6.11 Statistical Issues

Given the small sample size consisting of only 15 price points in total from the five countries, nonparametric bootstrapping was applied. Resampled data (1000 iterations) were used to generate bootstrap estimates of the regression coefficients within the multivariable model. The final regression coefficients were of primary importance because their relative magnitude was used to estimate the weighting for each predictor variable in the final pricing algorithm. Standard errors and confidence intervals were of secondary importance because the intent was not to measure the statistical significance between the dependent variable, drug price and the three predictor variables (i.e. survival gain, per capita GDP and the Gini coefficient). To simplify calculations with the pricing algorithm, the regression coefficients were transformed by multiplying each by a constant (in this case -5%, derived by trial and error) and then rounding to the nearest unit value. This would allow the estimation of a drug pricing estimate as guided by a country's per capita GDP, Gini coefficient and survival benefit offered by the new drug.

A simple main effects multivariable linear regression was used to determine the relative magnitude of the final regression coefficients. Interaction effects were not evaluated in the model because the objective was not to perform a subgroup analysis between countries. The linearity assumption was also evaluated in the model through the application of polynomials. The findings suggested that the associations between the dependent variable (i.e. drug price) and the predictor variables (i.e. survival gain, per capita GDP and the Gini coefficient) were indeed linear.

6.12 Conclusions

This chapter described the seven scientific papers that were generated from this research. There is a section on introduction, methods, results and discussion within each paper. Therefore, the intent of this thesis was to conduct high quality research that can be published in peer reviewed journals. This objective has been met.

CHAPTER 7

CONCLUSIONS

7.1 Introduction

Chapter seven summarizes the major findings from the five countries in terms of price points for different gains in overall survival. The chapter describes a multivariate regression model that was built around these price points. The chapter also illustrates how relative weight of the multivariate coefficients were used to develop the final value based pricing index. Lastly, the chapter demonstrates how the index can be applied to estimate a value based price for any new drug in mCRC. The chapter closes by providing recommendations on how the pricing index can be used by formulary committees and the pharmaceutical industry in estimate a launch price for a new drug in a given country.

7.2 The value based pricing index for new drugs in metastatic colorectal cancer

Government mandated cuts of branded drugs do not serve patients in the long term because such actions will only serve as a disincentive for pharmaceutical companies to invest in new drug discovery. A better alternative to such actions would be to set product price based on several factors such as performance under a controlled clinical trial setting, a nation's ability to pay a price premium for exceptional products, how uniformly income is distributed within a given country, and the overall cost effectiveness of the product measured against some reasonable societal value threshold. In the oncology setting, drug performance is best measured by the incremental survival benefit that is offered over the standard of care. Estimating an overall product value threshold

is more challenging, but a reasonable starting point is three times the per capita GDP as recommended by the WHO (Murray et al., 2000; Hillner and Smith, 2009).

In this study, a PE model for a hypothetical "new drug" in mCRC that was populated with cost and utility data from five different countries was used to develop an index to estimate a value based price. From the PE model, price points were estimated for survival increments of 1.4, 3 and 6 months using three times the per capita GDP as the target value threshold from each country. Multivariable analysis was then applied to the price points to measure the contribution of survival benefit, per capita GDP and income dispersion on the final price estimate. The coefficients from the multivariable model were then used to develop the final pricing index, which can be used to estimate a value based price for a new drug in mCRC. The final product was a pricing algorithm where higher survival benefits are associated with a price premium. The starting point and score assigned to each of the pricing factors is as follows:

- *Start at base score of $11,000*
- *Multiply the Gini coefficient for that country by $300 and add to base score*
- *Subtract the country specific per capita GDP*
- *Multiply the drug's survival benefit in months by $6,000 and subtract*
- *Add the above scores and then multiply by - 5%*

The above pricing index is easy to apply and best illustrated with an example. Suppose there is a new drug for mCRC that has demonstrated a four month survival benefit in a recent randomized trial. What would be a value based price for the drug in a country like Argentina, with a per capita GDP of $15,000 and a Gini coefficient of 51.3? Going through the pricing index, a value based launch price in Argentina for a drug that provides a 4 month survival benefit would be $630 per dose. If the same drug

were to be launched in Norway, whose per capita GDP and Gini coefficient is $50,000 and 25 respectively, the price per dose for the same drug would be $2,775 per dose. Through the application of our price index, it is ensured that the final launch price of a new drug is linked to a country's ability to pay as well as income dispersion. Therefore, government payers in countries like Argentina and Norway would then have a better indication of what a cost effective price should be relative to the survival benefit offered by the drug.

7.3 Limitations

There are a number of limitations in pricing index that need to be acknowledged. The intent of our initiative was to develop a tool that can be applied to mCRC drugs for estimating a value based price that would potentially increase patient access. For the proposed methodology to be applied to other disease sites, complete data from randomized trials on a drug by drug basis will be required to develop disease specific pricing indexes. Our index can only be applied towards new drugs in mCRC and for countries that fall within our range of per capita GDP. Our sample size was small (only five countries) and this may limit the generalizability of our index. In addition, external validation in other countries outside of our GDP range is warranted. The original WHO threshold for cost effectiveness (i.e. < 3 times the per capita GDP) was initially developed for global health care programmes (e.g. the use of malaria nets) as opposed to specific treatment interventions. As a result, it has not been fully validated for application to pharmaceuticals. Therefore, additional empirical work is needed to evaluate its appropriateness for evaluating individual treatments. The equal application of a per capita GDP threshold may not be applicable to both rich and poor countries. It

may have been more appropriate to use threshold beyond three times the per capita GDP for less resource rich countries. Future work is needed to test various thresholds based on a countries wealth.

7.4 Summary of major findings

The first key finding in this study was that the WHO criteria for estimating a value based price is feasible and can be applied to a wide variety to countries with unique health care systems. This was demonstrated through the successful PE modeling analyses conducted in the five reference countries. With the pricing information generated from each country specific analysis, an index to estimate a value based price for new drugs in mCRC was developed. The index is easy to apply using data that is readily available to drug formulary committees. With a scientifically based estimate on what a cost effective price for a new drug should be for their country, public payers would be in a more informed position as they enter price negotiations with the manufacturer. Therefore, the second key finding in this study is that the methodological approach used in this thesis can be applied to other cancer sites such as breast and lung cancer in order to develop similar value based pricing indexes. The development of pricing indexes across the major tumour types can empower public payers with better information which could lead to reduced prices for new cancer drugs. Reduced costs for new drugs would mean better patient access, particularly in lower income countries.

A major advantage of the pricing index is its transparency and the ability to apply it to approximately 140 countries whose per capita GDP falls within the range evaluated in this study. In addition, the index is able to rapidly estimate a value based price using international recommendations for economic value (Hillner and Smith, 2009). Such an

index would also be important to manufacturers who are considering launching their products in lower income countries. If they were to launch a critically important product at a high price that is simply out of reach for that country's health care budget, the national government may issue a compulsory license, which would enable local production of the patented drug. This is possible under the Trade Related Intellectual Property Rights agreement of the World Trade Organisation and has already occurred with some HIV drugs (Shashikant, 2005). Alternatively, a value based price estimated with this index could be the starting point for negotiations between government payers and the manufacturer, which could lead to a more affordable launch price for that country.

7.5 Implementation of the Pricing: Practical Considerations

A pricing index has been developed to allow the estimation of drug price based on what a country can afford to pay, national income dispersion and the survival benefit offered by the new treatment over the standard of care. The strength of this index is its transparency and ease of administration. However, there are some practical challenges that would need to be overcome before widespread implementation. As a first step, a partnership between the drug manufacturer and the respective national government would need to be established. The primary objective of the partnership should be to ensure patient access to effective cancer therapies. This partnership should be initiated with a binding agreement where both parties would accept the initial price point estimated by the pricing index. This estimate would then be the starting point for negotiations. If the manufacturer would like to launch the drug at a price beyond the estimated price point, they would need to provide evidence to government negotiators

that a higher price is warranted. Alternatively, the manufacturer may offer a risk sharing program where the higher price would be reimbursed by the government only in cases where the drug meets its primary clinical endpoint. For patients who do not derive clinical benefit from the drug, the manufacturer would reimburse the health care system for the cost of the drug. These are but a few practical suggestions on how the pricing index can be used to initiate a discussion between the manufacturer and all of the key stakeholders. A key factor for making a drug affordable in a given county would be transparency, good will and the willingness for both parties to make price concessions in sufficient supporting evidence is available.

7.6 Conclusions

The present study describes the development of a global pricing index that can be used to estimate a value based price in different countries for new drugs in mCRC. The application of this index to estimate a cost effective drug price would be a good starting point for opening dialogue between the key stakeholders and a better alternative to government mandated price cuts. However, this does not necessarily mean that annual drug expenditures will be contained. True therapeutic innovation requires an investment by society. Ultimately, the final price that is negotiated must create a balance that will reward innovation and maximize patient access to new drugs.

7.7 Recommendations

PE analyses are typically undertaken once a new product receives regulatory approval and the price has been set by the manufacturer. This may not be the optimal use of PE evaluations.

Recommendation # 1

- A potentially more powerful use of PE analysis would be in estimating a drug price using predetermined thresholds of economic value. This would allow a more transparent drug price to be determined.

Before initiating pricing negotiations, drug formulary committees typically do not undertake their own PE studies to determine a final price that would make a new product cost effective for their patient populations.

Recommendation # 2

- In preparation for their pricing negotiations with manufacturers, drug formulary committees should undertake PE modeling analyses using the WHO criteria for economic value to estimate value based prices for all new cancer drugs, particularly the ones where the manufacture will likely request a premium price. With such information, public payers will be in a stronger position to negotiate a better price for their health care system.

There are multiple factors such as overall survival, the cost per QALY gained over the standard of care, income dispersion and a country's ability to pay that can influence the final drug price.

Recommendation # 3

- The pricing index that was developed in the current study can be used to estimate a price for new drugs in mCRC. Formulary committees can use this index to

determine a value based price for new products in mCRC, which will be critical in their price negotiations with manufacturers.

It has been demonstrated in this study that a value based pricing index for new drugs in mCRC can be developed using standard cost utility methodology and internationally recommended thresholds for economic value. However, the index should not be applied to other disease sites.

Recommendation # 4

The methodology used in this study should be applied to develop pricing indexes for new drugs in other important disease sites such as breast, lung and prostate cancer.

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LIST OF APPENDICES

Appendix 1. Survey instrument used for the utility assessment.

Utility Measurement for Targeted Treatments of Metastatic Colorectal

Introduction

Thank respondent for agreeing to participate in the interview. Review the material describing the two treatment options for metastatic colorectal cancer.

Purpose and confidentiality

Explain that:

- The purpose of this is to explore the trade off between length of life versus quality of life whilst being on a new "hypothetical" targeted drug (when combined with the standard of care chemotherapy), taking into account the efficacy and side effect profile of the treatment.
- We are totally independent in this research and would like everybody to be completely honest with their views.
- Anything said will be treated as confidential unless you have given your consent to the contrary.

NOTE TO INTERVIEWER:

Throughout this interview the respondent will be required to imagine that they are a colorectal cancer patient with metastatic disease, about to undergo treatment with chemotherapy, without or without a new "targeted" drug. The purpose of this is to explore the trade off between length of life versus quality of life whilst being on chemotherapy ± a new "targeted" drug, taking into account the efficacy and side effect profile of each treatment (see additional supportive material). There are 16 questions, for each of the various health outcomes.

If the respondent appears to have difficulty understanding what they are being asked then you could use the following example to help explain it to them.

Ask the respondent to imagine themselves being in a wheelchair for 12 months. Then tell them that they have an option of being completely healthy but for a less amount of time. So the question is, *how many of these 12 months of being in a wheelchair would they give up in order to be completely healthy*? Eg. If 9 months being completely healthy is equivalent to 12 months in a wheelchair, then they should answer that they are willing to give up 3 months of their time.

NOTE TO INTERVIEWER:

Check that the respondent has understood the information regarding the cancer treatments before proceeding. If not, take some time to review the information again. Before to review how the chemotherapy is delivered and what the common grade III/IV side effects are.

1. Treatment with FOLFOX chemotherapy + the New Drug

Imagine you are a colorectal cancer patient with metastatic disease and are about to undergo treatment with FOLFOX chemotherapy (see slide #2). This would require coming to the chemotherapy suite every 2 weeks of intravenous therapy. After the FOLFOX chemotherapy, you are also given the New Drug through a one hour infusion (see slide #9 for pathway).

If you could trade length of life for a shorter time with much better quality of life, what lesser number of months in optimal health would you consider equivalent to the 10 months where you received 2 cycles of FOLFOX + the New Drug, and then 4 cycles of FOLFIRI chemotherapy. Note the side effect rates associated with FOLFOX + the New Drug and FOLFIRI (refer to the Tables 1 and 2 for the clinical and side effect information). *Also, use the linear time scale to help their response. For a 10 month survival, only show the scale up to 10 months).*

Outcome # 1 where survival = 10 months: Lesser Months in optimal health: _____

2. Treatment with FOLFOX chemotherapy alone

Imagine you are a colorectal cancer patient with metastatic disease and are about to undergo treatment with FOLFOX chemotherapy (see slide #2). This would require coming to the chemotherapy suite every 2 weeks for intravenous therapy (see slide #9 for pathway).

If you could trade length of life for a shorter time with much better quality of life, what lesser number of months in optimal health would you consider equivalent to the 10 months where you received 2 cycles of FOLFOX alone, and then 4 cycles of FOLFIRI? Be aware of the side effect rates associated with FOLFOX alone and FOLFIRI (refer to the Tables 1 and 2 for the clinical and side effect information). *Also, use the linear time scale to help their response. For a 10 month survival, only show the scale up to 10 months).*

Outcome # 2 where survival = 10 months: Lesser Months in optimal health: _____

3. Treatment with FOLFOX chemotherapy + the New Drug

Imagine you are a colorectal cancer patient with metastatic disease and are about to undergo treatment with FOLFOX chemotherapy (see slide #2). This would require coming to the chemotherapy suite every 2 weeks for intravenous therapy. After the FOLFOX chemotherapy, you are also given the New Drug through a one hour infusion (see slide #10 for pathway).

If you could trade length of life for a shorter time with much better quality of life, what lesser number of months in optimal health would you consider equivalent to the 28 months where you received 2 cycles of FOLFOX + the New Drug, and then the 8 cycles of FOLFIRI? Be aware of the side effect rates associated with FOLFOX + the New Drug and with FOLFIRI (refer to the Tables 1 and 2 for the clinical and side effect information). *Also, use the linear time scale to help their response. For a 28 month survival, only show the scale up to 28 months).*

Outcome # 3 where survival = 28 months: Lesser Months in optimal health: _____

4. Treatment with FOLFOX chemotherapy alone

Imagine you are a colorectal cancer patient with metastatic disease and are about to undergo treatment with FOLFOX chemotherapy (see slide #2). This would require coming to the chemotherapy suite every 2 weeks for intravenous therapy (see slide #10 for pathway).

If you could trade length of life for a shorter time with much better quality of life, what lesser number of months in optimal health would you consider equivalent to the 28 months where you received 2 cycles of FOLFOX alone, then the 8 cycles of FOLFIRI? Be aware of the side effect rates associated with FOLFOX and with FOLFIRI (refer to the Tables 1 and 2 for the

clinical and side effect information). *Also, use the linear time scale to help their response. For a 28 month survival, only show the scale up to 28 months).*

Outcome # 4 where survival = 28 months: Lesser Months in optimal health: _____

5. Treatment with FOLFOX chemotherapy + the New Drug

Imagine you are a colorectal cancer patient with metastatic disease and are about to undergo treatment with FOLFOX chemotherapy (see slide #2). This would require coming to the chemotherapy suite every 2 weeks for intravenous therapy. After the FOLFOX chemotherapy, you are also given the New Drug through a one hour infusion (see slide #12 for pathway).

If you could trade length of life for a shorter time with much better quality of life, what lesser number of months in optimal health would you consider equivalent to the 8 months where you received 2 cycles of FOLFOX + the New Drug, and then the 8 cycles of FOLFIRI? Be aware of the side effect rates associated with FOLFOX + the New Drug and with FOLFIRI (refer to the Tables 1 and 2 for the clinical and side effect information). *Also, use the linear time scale to help their response. For an 8 month survival, only show the scale up to 8 months).*

Outcome # 5 where survival = 8 months: Lesser Months in optimal health: _____

6. Treatment with FOLFOX chemotherapy alone

Imagine you are a colorectal cancer patient with metastatic disease and are about to undergo treatment with FOLFOX chemotherapy (see slide #2). This would require coming to the chemotherapy suite every 2 weeks for intravenous therapy (see slide #12 for pathway).

If you could trade length of life for a shorter time with much better quality of life, what lesser number of months in optimal health would you consider equivalent to the 8 months where you received 2 cycles of FOLFOX alone, and then the 8 cycles of FOLFIRI? Be aware of the side effect rates associated with FOLFOX and with FOLFIRI (refer to the Tables 1 and 2 for the clinical and side effect information). *Also, use the linear time scale to help their response. For an 8 month survival, only show the scale up to 8 months).*

Outcome # 6 where survival = 8 months: Lesser Months in optimal health: _____

7. Treatment with FOLFOX chemotherapy + the New Drug

Imagine you are a colorectal cancer patient with metastatic disease and are about to undergo treatment with FOLFOX chemotherapy (see slide #2). This would require coming to the chemotherapy suite every 2 weeks for intravenous therapy. After the FOLFOX chemotherapy, you are also given the New Drug through a one hour infusion (see slide #12 for pathway).

If you could trade length of life for a shorter time with much better quality of life, what lesser number of months in optimal health would you consider equivalent to the 4 months where you received 2 cycles of FOLFOX + the New Drug, and then 2 cycles of FOLFIRI? Be aware of the side effect rates associated with FOLFOX + the New Drug (refer to the Tables 1 and 2 for the clinical and side effect information). Also, use the linear time scale to help their response. For a 4 month survival, only show the scale up to 4 months).

Outcome # 7 where survival = 4 months: Lesser Months in optimal health: _____

8. Treatment with FOLFOX chemotherapy alone

Imagine you are a colorectal cancer patient with metastatic disease and are about to undergo treatment with FOLFOX chemotherapy (see slide #2). This would require coming to the chemotherapy suite every 2 weeks for intravenous therapy (see slide #12 for pathway).

If you could trade length of life for a shorter time with much better quality of life, what lesser number of months in optimal health would you consider equivalent to the 4 months where you received 2 cycles of FOLFOX alone, and then 2 cycles of FOLFIRI? Be aware of the side effect rates associated with FOLFOX (refer to the Tables 1 and 2 for the clinical and side effect information). Also, use the linear time scale to help their response. *For a 4 month survival, only show the scale up to 4 months).*

Outcome # 8 where survival = 4 months: Lesser Months in optimal health: _____

9. Treatment with FOLFOX chemotherapy + the New Drug

Imagine you are a colorectal cancer patient with metastatic disease and are about to undergo treatment with FOLFOX chemotherapy (see slide #2). This would require coming to the chemotherapy suite every 2 weeks for intravenous therapy. After the FOLFOX chemotherapy, you are also given the New Drug through a one hour infusion (see slide #13 for pathway).

If you could trade length of life for a shorter time with much better quality of life, what lesser number of months in optimal health would you consider equivalent to the 6 months where you received 4 cycles of FOLFOX + the New Drug, then 4 cycles of FOLFIRI? Be aware of the side effect rates associated with FOLFOX + the New Drug and FOLFIRI (refer to the Tables 1 and 2 for the clinical and side effect information). *Also, use the linear time scale to help their response. For a 6 month survival, only show the scale up to 6 months).*

Outcome # 9 where survival = 6 months: Lesser Months in optimal health: _____

10. Treatment with FOLFOX chemotherapy alone

Imagine you are a colorectal cancer patient with metastatic disease and are about to undergo treatment with FOLFOX chemotherapy (see slide #2). This would require coming to the chemotherapy suite every 2 weeks for intravenous therapy (see slide #13 for pathway).

If you could trade length of life for a shorter time with much better quality of life, what lesser number of months in optimal health would you consider equivalent to the 6 months where you received 4 cycles of FOLFOX alone, then 4 cycles of FOLFIRI? Be aware of the side effect rates associated with FOLFOX and FOLFIRI (refer to the Tables 1 and 2 for the clinical and side effect information). *Also, use the linear time scale to help their response. For a 6 month survival, only show the scale up to 6 months).*

Outcome # 10 where survival = 6 months: Lesser Months in optimal health: _____

11. Treatment with FOLFOX chemotherapy + the New Drug

Imagine you are a colorectal cancer patient with metastatic disease and are about to undergo treatment with FOLFOX chemotherapy (see slide #2). This would require coming to the chemotherapy suite every 2 weeks for intravenous therapy. After the FOLFOX chemotherapy, you are also given the New Drug through a one hour infusion (see slide #14 for pathway).

If you could trade length of life for a shorter time with much better quality of life, what lesser number of months in optimal health would you consider equivalent to the 33 months where you received 17 cycles of FOLFOX + the New Drug, then the 6 cycles of FOLFIRI? Be aware of the side effect rates associated with FOLFOX + the New Drug and FOLFIRI (refer to the Tables 1 and 2 for the clinical and side effect information). *Also, use the linear time scale to help their response. For a 33 month survival, only show the scale up to 33 months).*

Outcome # 11 where survival = 33 months: Lesser Months in optimal health: _____

What if Outcome # 11 survival = 39 months: Lesser Months in optimal health: _____

What if Outcome # 11 survival = 28 months: Lesser Months in optimal health: _____

12. Treatment with FOLFOX chemotherapy alone

Imagine you are a colorectal cancer patient with metastatic disease and are about to undergo treatment with FOLFOX chemotherapy (see slide #2). This would require coming to the chemotherapy suite every 2 weeks for intravenous therapy (see slide #14 for pathway).

If you could trade length of life for a shorter time with much better quality of life, what lesser number of months in optimal health would you consider equivalent to the 8 months where you received 15 cycles of FOLFOX alone, then 6 cycles of FOLFIRI? Be aware of the side effect rates associated with FOLFOX and FOLFIRI (refer to the Tables 1 and 2 for the clinical and side effect information). *Also, use the linear time scale to help their response. For a 32 month survival, only show the scale up to 32 months).*

Outcome # 12 where survival = 32 months: Lesser Months in optimal health: _____

13. Treatment with FOLFOX chemotherapy + the New Drug

Imagine you are a colorectal cancer patient with metastatic disease and are about to undergo treatment with FOLFOX chemotherapy (see slide #2). This would require coming to the chemotherapy suite every 2 weeks for intravenous therapy. After the FOLFOX chemotherapy, you are also given the New Drug through a one hour infusion (see slide #15 for pathway).

If you could trade length of life for a shorter time with much better quality of life, what lesser number of months in optimal health would you consider equivalent to the 11 months where you received 17 cycles of FOLFOX + the New Drug, and then 2 cycles of FOLFIRI? Be aware of the side effect rates associated with FOLFOX + the New Drug and FOLFIRI (refer to the Tables 1 and 2 for the clinical and side effect information). *Also, use the linear time scale to help their response. For an 11 month survival, only show the scale up to 11 months).*

Outcome # 13 where survival = 11 months: Lesser Months in optimal health: _____

14. Treatment with FOLFOX chemotherapy alone

Imagine you are a colorectal cancer patient with metastatic disease and are about to undergo treatment with FOLFOX chemotherapy (see slide #2). This would require coming to the chemotherapy suite every 2 weeks for intravenous therapy (see slide #15 for pathway).

If you could trade length of life for a shorter time with much better quality of life, what lesser number of months in optimal health would you consider equivalent to the 10 months where you received 15 cycles of FOLFOX alone, and then 2 cycles of FOLFIRI? Be aware of the side effect rates associated with FOLFOX and FOLFIRI (refer to the Tables 1 and 2 for the clinical and side effect information). *Also, use the linear time scale to help their response. For a 10 month survival, only show the scale up to 10 months).*

Outcome # 12 where survival = 10 months: Lesser Months in optimal health: _____

15. Treatment with FOLFOX chemotherapy + the New Drug

Imagine you are a colorectal cancer patient with metastatic disease and are about to undergo treatment with FOLFOX chemotherapy (see slide #2). This would require coming to the chemotherapy suite every 2 weeks for intravenous therapy. After the FOLFOX chemotherapy, you are also given the New Drug through a one hour infusion (see slide #16 for pathway).

If you could trade length of life for a shorter time with much better quality of life, what lesser number of months in optimal health would you consider equivalent to the 2 months where you received 2 cycles of FOLFOX + the New Drug? Be aware of the side effect rates associated with FOLFOX + the New Drug (refer to the Tables 1 and 2 for the clinical and side effect information). *Also, use the linear time scale to help their response. For a 2 month survival, only show the scale up to 2 months).*

Outcome # 15 where survival = 2 months: Lesser Months in optimal health: _____

16. Treatment with FOLFOX chemotherapy alone

Imagine you are a colorectal cancer patient with metastatic disease and are about to undergo treatment with FOLFOX chemotherapy (see slide #2). This would require coming to the chemotherapy suite every 2 weeks for intravenous therapy (see slide #15 for pathway).

If you could trade length of life for a shorter time with much better quality of life, what lesser number of months in optimal health would you consider equivalent to the 2 months where you received 2 cycles of FOLFOX alone? Be aware of the side effect rates associated with FOLFOX (refer to the Tables 1 and 2 for the clinical and side effect information). *Also, use the linear time scale to help their response. For a 2 month survival, only show the scale up to 2 months).*

Outcome # 16 where survival = 2 months: Lesser Months in optimal health: _____

DEMOGRAPHIC DATA

A. Specify health profession: Nurse □ Pharmacist □

B. How many years of oncology experience do you have?: _____

C. Do you have experience in treating colorectal cancer patients?: YES □ NO □

D. Do you have experience in giving FOLFOX to patients? YES □ NO □

E. If yes, how many years of experience do you have?: _____

F. Do you have experience in giving bevacizumab (Avastin) to patients? YES □ NO □

G. If yes, how many years of experience do you have?: _____

H. Do you have experience in giving cetuximab (Erbitux) to patients? YES □ NO □

I. If yes, how many years of experience do you have?: _____

J. Do you have experience in giving FOLFIRI to patients? YES □ NO □

K. If yes, how many years of experience do you have?: _____

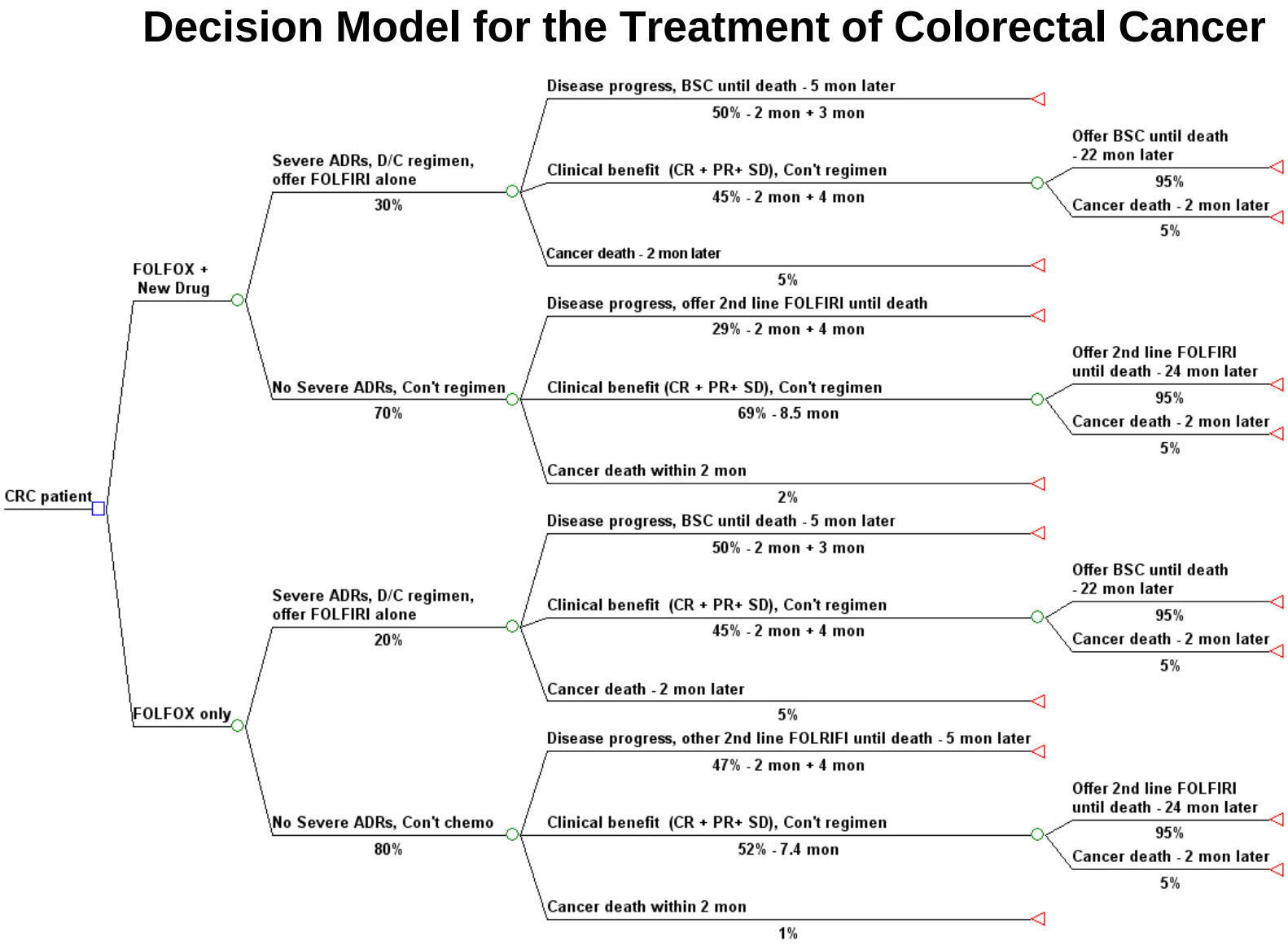
L. In the past 2 years, have you been directly involved in the development of systemic treatment guidelines/criteria for the treatment of colorectal cancer patients? YES □ NO □

M. How familiar would you consider yourself to be with the cost of new cancer drugs?
Very familiar □ Somewhat familiar □ Not familiar □

N. Has anybody in your family ever developed a colorectal cancer? YES □ NO □

O. Respondent year of birth: _____

Appendix 2. Graphical displays was used to facilitate participant's understanding of the Time Trade-off technique.



Treatment of Metastatic Colorectal Cancer

Background Information

- Colorectal cancer is the fourth most common type of cancer world wide.
- The World Health Organization estimated that in 2008, there were 639,000 deaths from colorectal cancer.
- When the cancer spreads to distant sites, chemotherapy is given but the cancer remains incurable.
- The intent of chemotherapy is to prolong life and to enhance patient quality of life.
- The chemotherapy drugs are referred to as a “regimen”. The first regimen given is called “first line”.
- For the regimen to be administered, patients need to visit the cancer clinic every 2 to 3 weeks.
- If patients progresses after the initial chemotherapy, then a second regimen is give (called second line chemotherapy).

First Line Chemotherapy for Advanced Colorectal Cancer

FOLFOX- 4

Oxaliplatin 85 mg/m^2 on day 1
Leucovorin 200 mg/m^2, then 5-fluorouracil 4-00 mg/m^2 bolus and then 600/m^2 of 5- 5-fluorouracil by continuous infusion over 22 hours.

Cycle gets repeated every 2 weeks

Second Line Chemotherapy for Advanced Colorectal Cancer

FOLFIRI

Irinotecan 180 mg/m^2 on day 1
Leucovorin 200 mg/m^2, then 5FU 400 mg/m^2 bolus and then 2.4 g/m^2 of 5FU by continuous infusion over 46 hours.

Cycle gets repeated every 2 weeks

CHEMOTHERAPY BEING GIVEN

A new drug to treat colorectal and other tumours such as lung and breast cancer

- With the use of FOLFOX chemotherapy, which is then followed by FOLFIRI, patients live for an average of 20 months.
- Suppose there is a “hypothetical” new drug that is now available.
- The new drug is not chemotherapy, but a “targeted” therapy that is more specific to the cancer.
- The new drug is given with first line FOLFOX, on the same day of chemotherapy.
- The new drug is administered as a one hour infusion after the chemotherapy is completed. Before the new drug is given, patients receive a 10 mg injection of dexamethasone to prevent infusion reactions.
- Studies have shown that the new drug improves response rates, progression free survival and overall survival when added to chemotherapy.

Table 1. Clinical outcomes when the new drug is added to first line FOLFOX

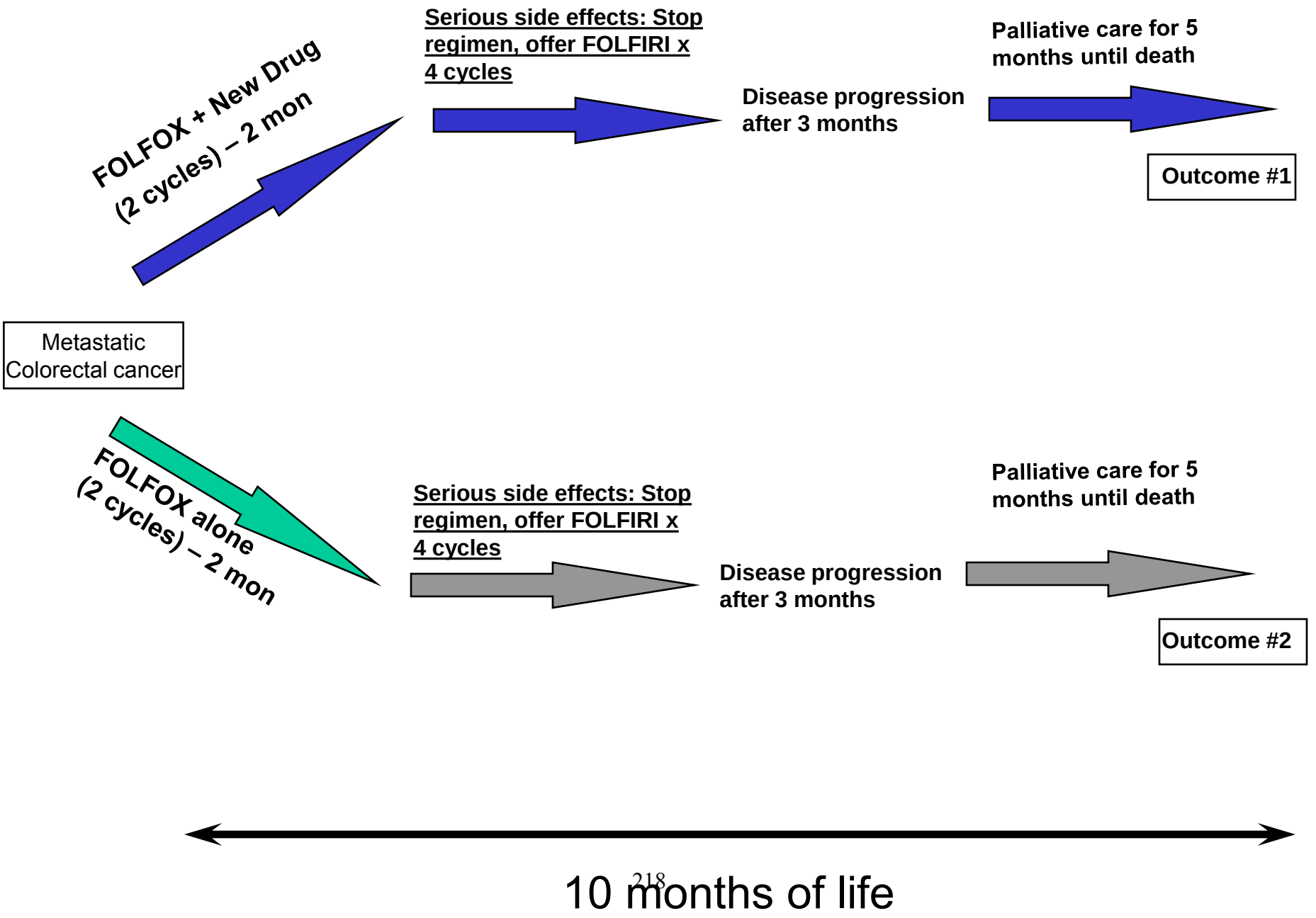
Outcome	FOLFOX	FOLFOX + New Drug
Cancer progression	47%	29%
Average progression free survival	8 months	10 months
Average overall survival	20 months	21 to 26 months

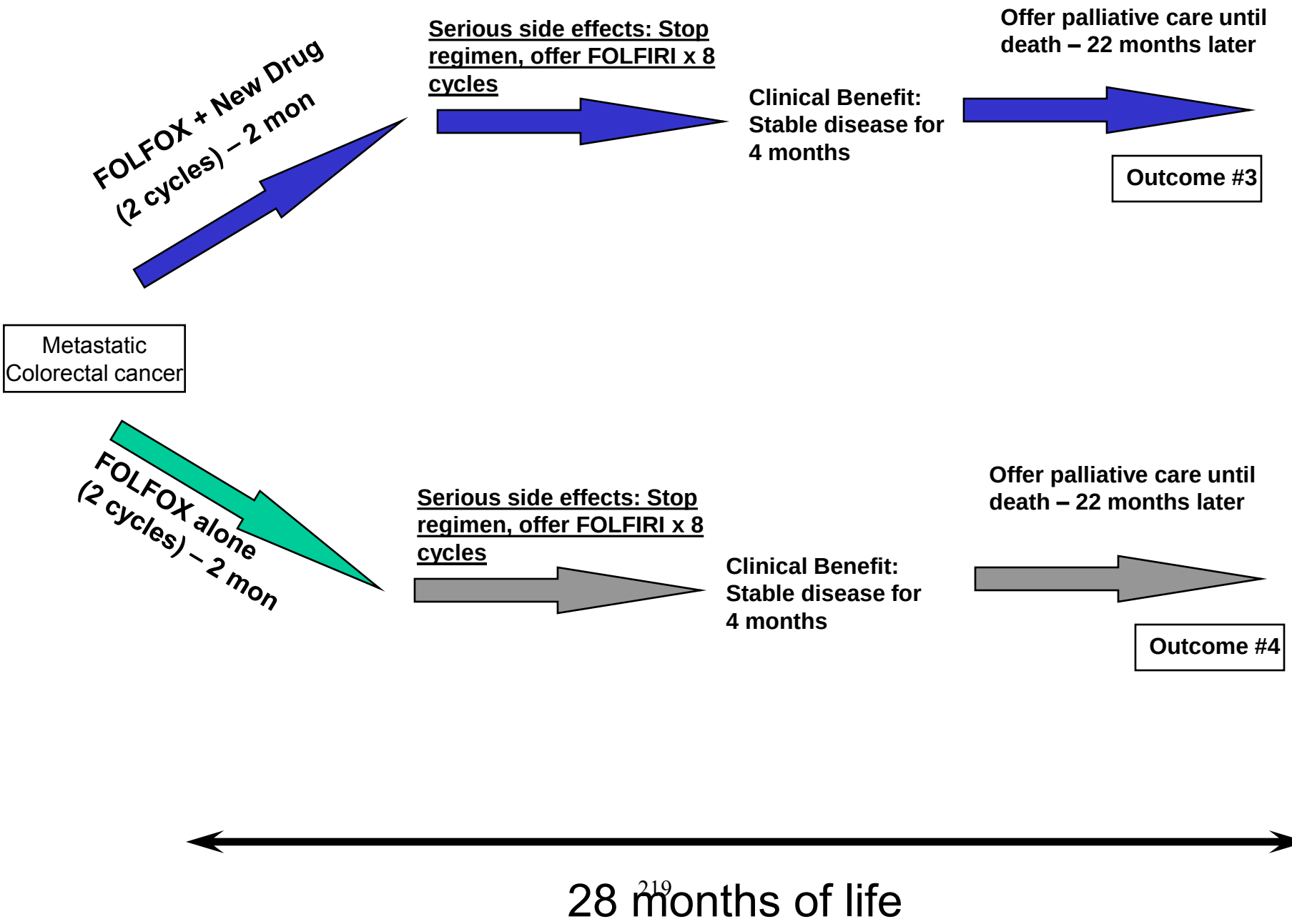
Table 2. Comparison of Side Effects

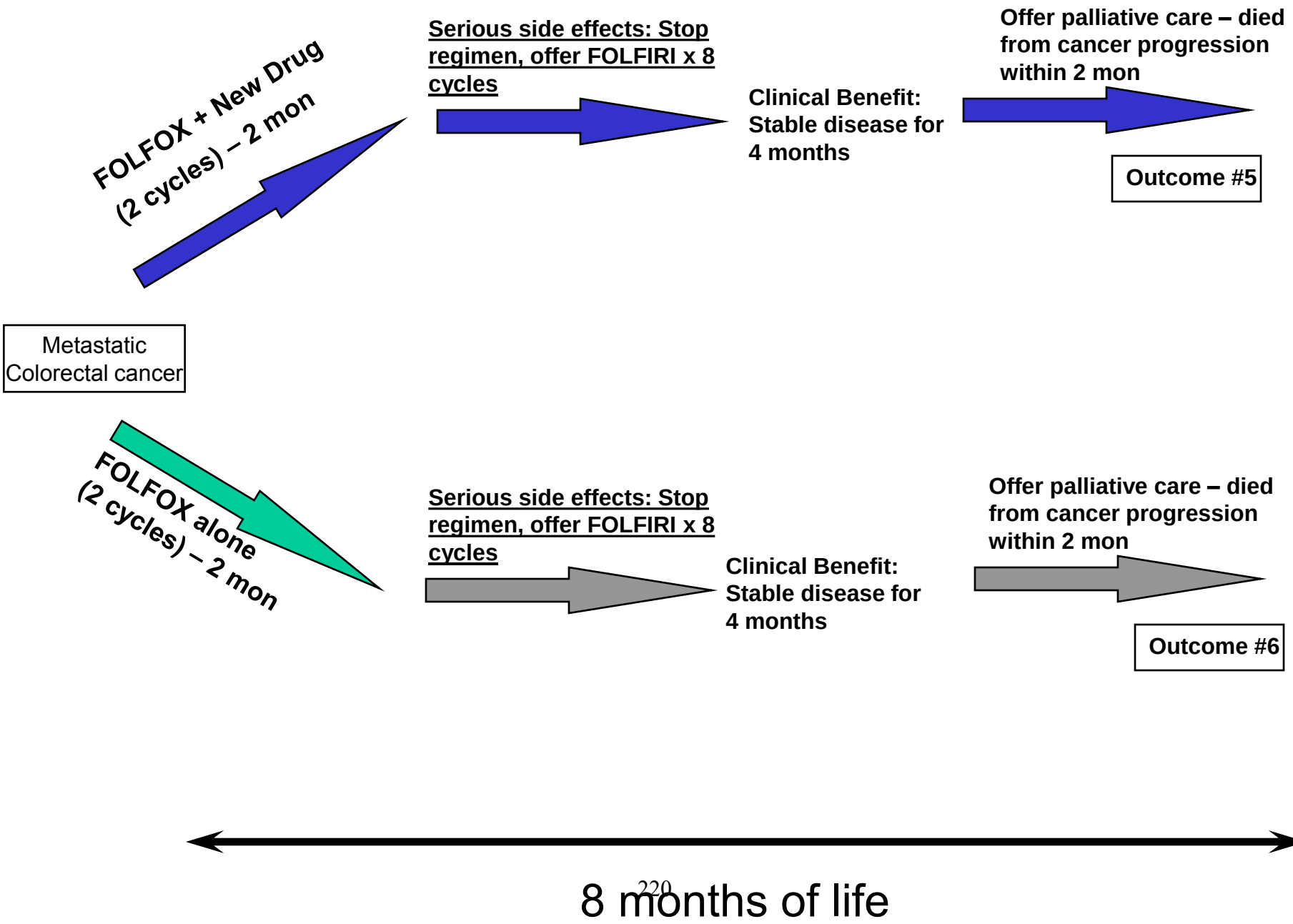
Toxicity	FOLFOX	FOLFOX + New Drug
Side effects leading to the permanent stoppage of treatment	20%	30%
Serious side effects (grade III/IV)	8%	16%
<u>Key Grade III/IV Side Effects</u>		
Deep vein thrombosis	5%	8%
Diarrhea	11%	18%
Bleeding	1%	2%
Neutropenia	44%	50%

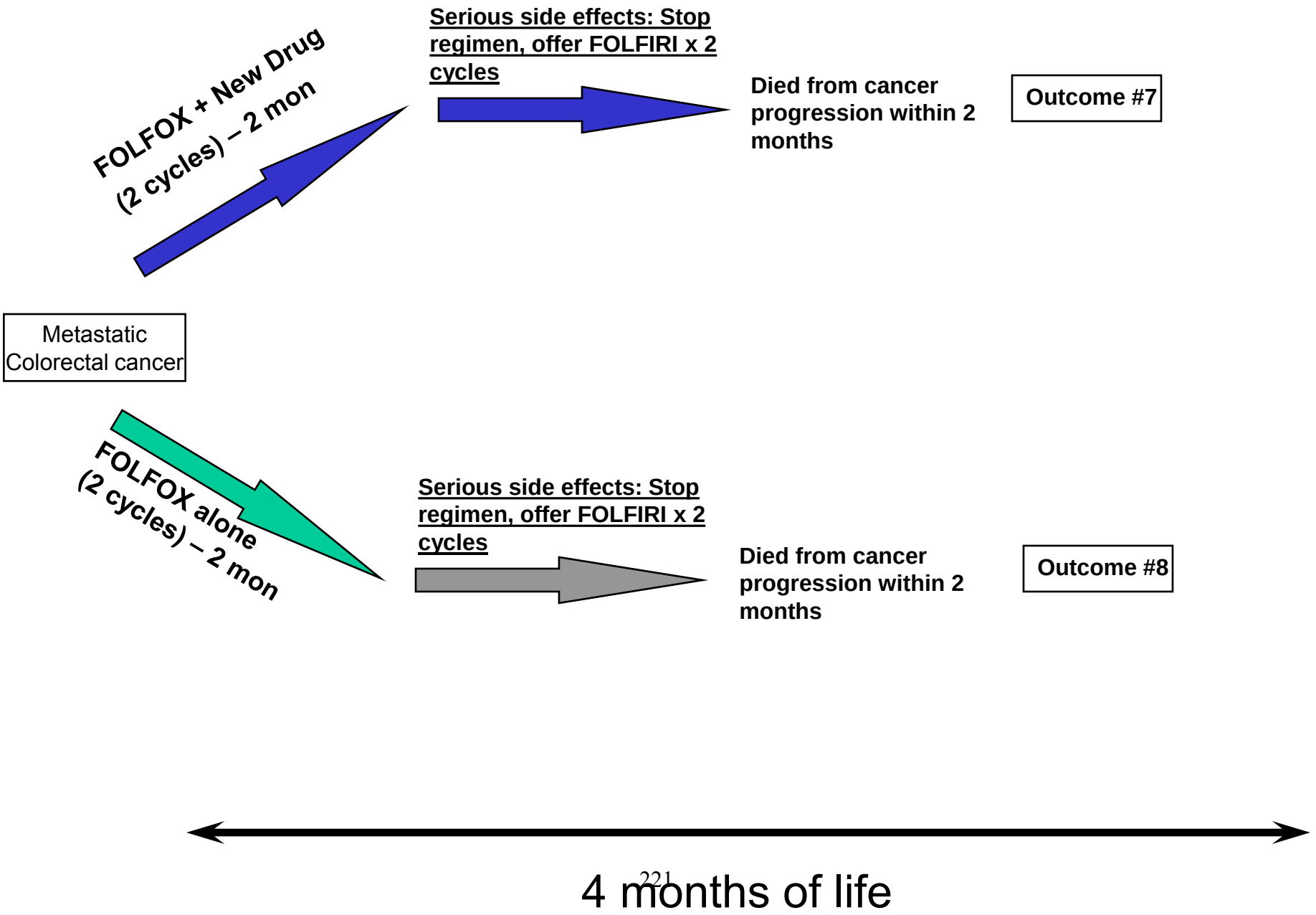
Grade III/IV Toxicity of FOLFIRI

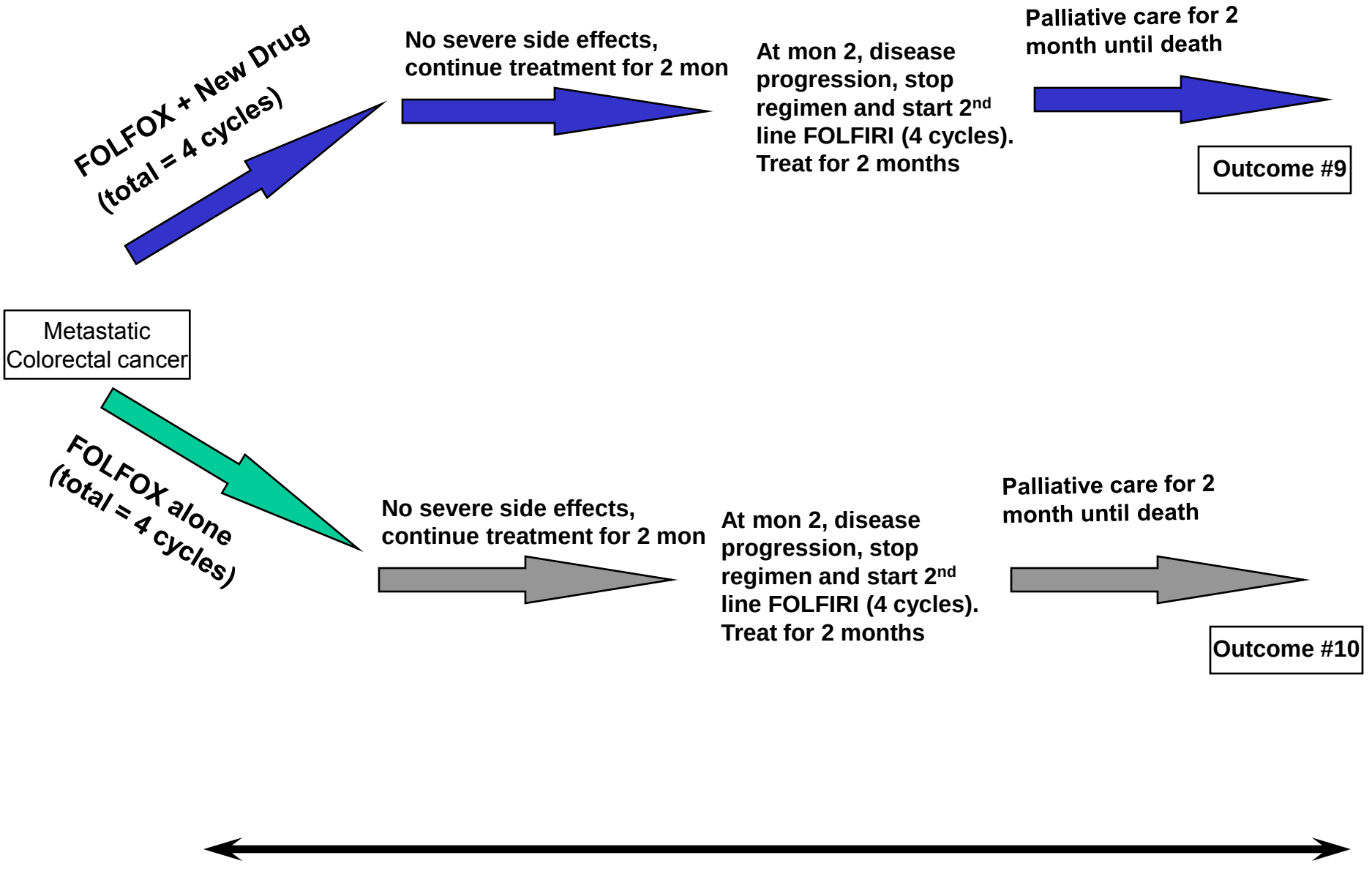
Toxicity	FOLFIRI
Diarrhea	14%
Nausea/vomiting	13%
Sensory neuropathy	0%
Neutropenia	25%
Febrile neutropenia	6%
Stomatitis	10%
Alopecia	24%

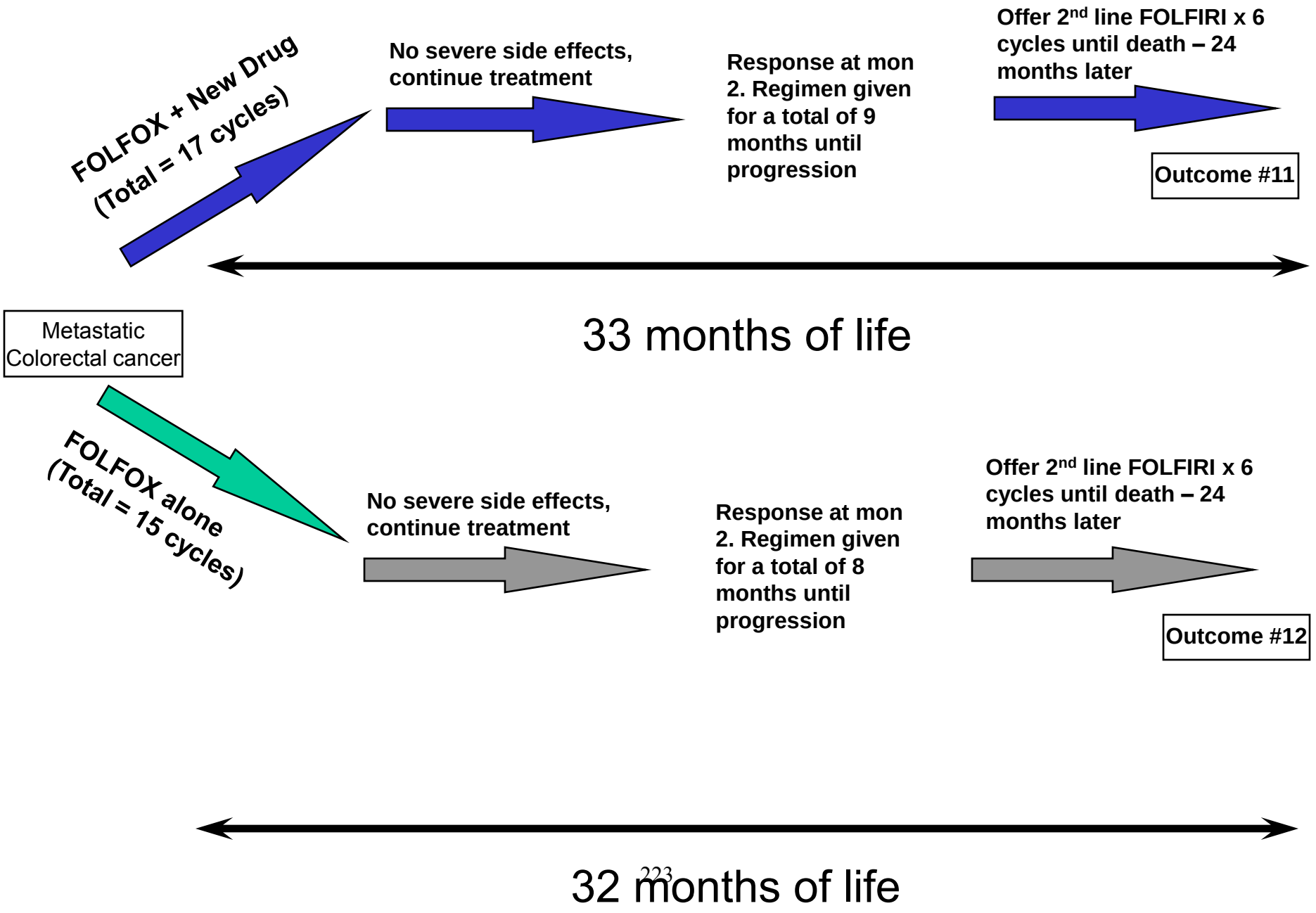

FOLFOX + New Drug
(2 cycles) – 2 mon
Serious side effects: Stop regimen, offer FOLFIRI x 4 cycles
Disease progression after 3 months
Palliative care for 5 months until death
Outcome #1
Metastatic Colorectal cancer
FOLFOX alone
(2 cycles) – 2 mon
Serious side effects: Stop regimen, offer FOLFIRI x 4 cycles
Disease progression after 3 months
Palliative care for 5 months until death
Outcome #2
10 months of life

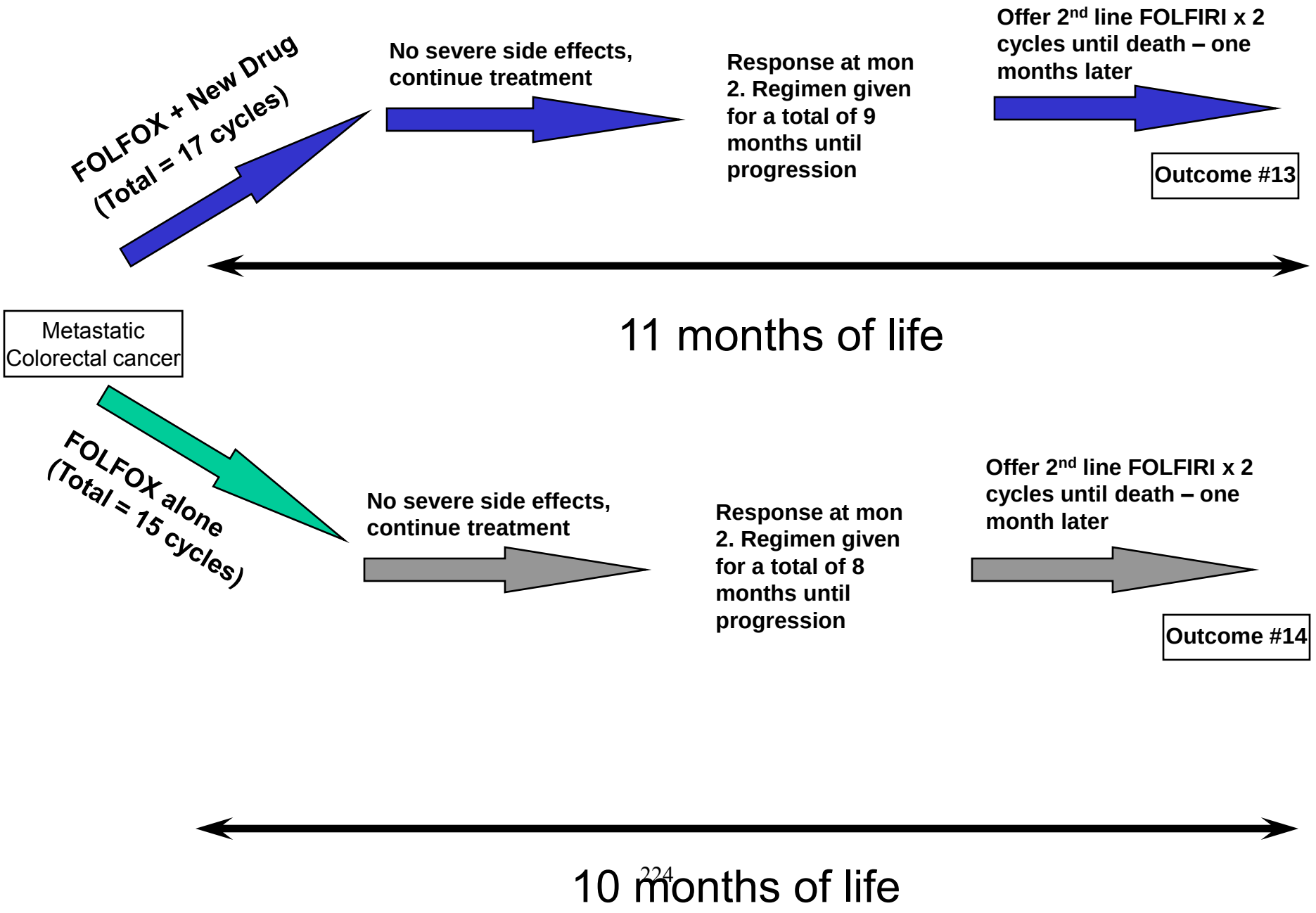

FOLFOX + New Drug
(2 cycles) – 2 mon
Serious side effects: Stop regimen, offer FOLFIRI x 8 cycles
Clinical Benefit: Stable disease for 4 months
Offer palliative care until death – 22 months later
Outcome #3
Metastatic Colorectal cancer
FOLFOX alone
(2 cycles) – 2 mon
Serious side effects: Stop regimen, offer FOLFIRI x 8 cycles
Clinical Benefit: Stable disease for 4 months
Offer palliative care until death – 22 months later
Outcome #4
28 months of life

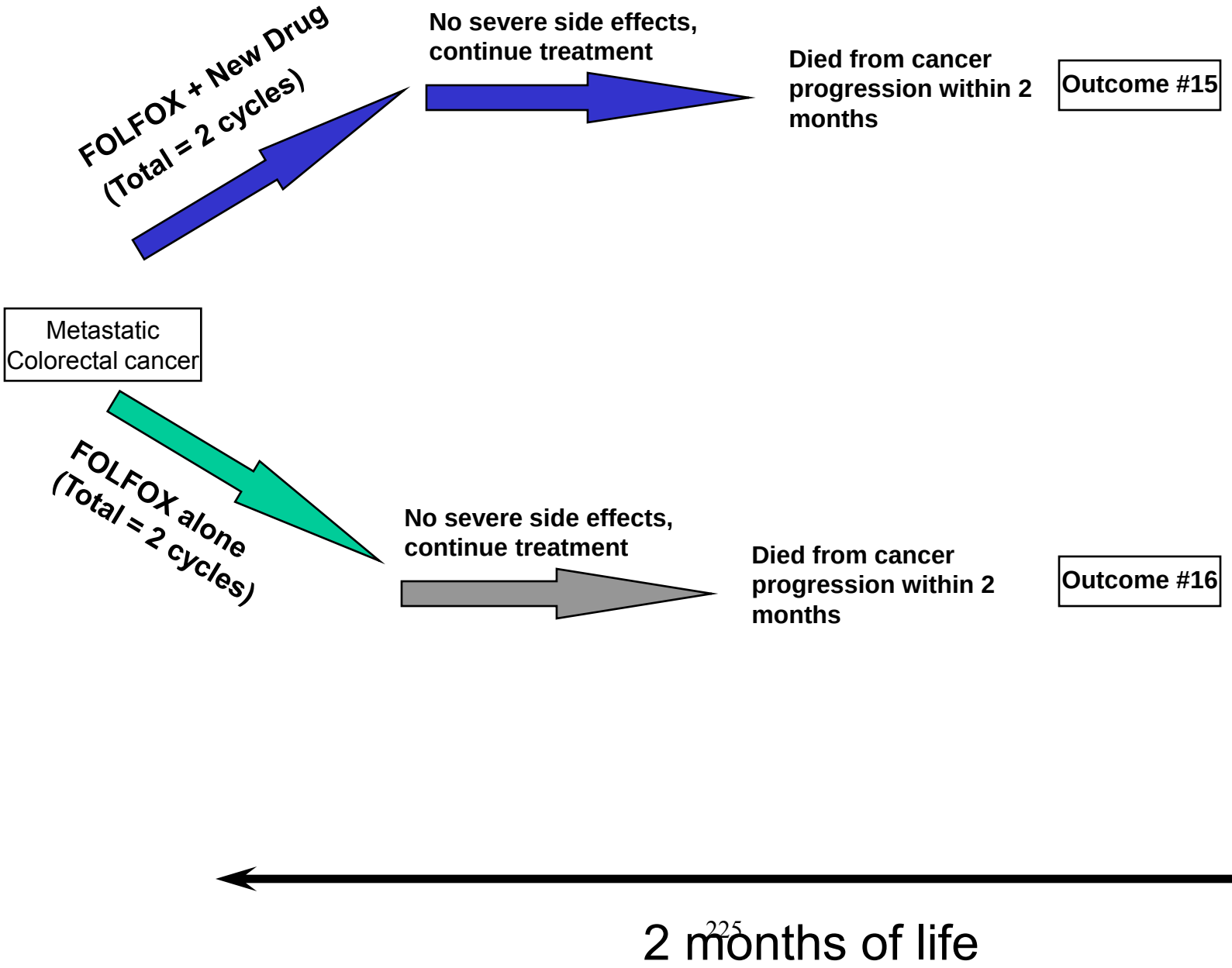

FOLFOX + New Drug
(2 cycles) – 2 mon
Serious side effects: Stop regimen, offer FOLFIRI x 8 cycles
Clinical Benefit: Stable disease for 4 months
Offer palliative care – died from cancer progression within 2 mon
Outcome #5
Metastatic Colorectal cancer
FOLFOX alone
(2 cycles) – 2 mon
Serious side effects: Stop regimen, offer FOLFIRI x 8 cycles
Clinical Benefit: Stable disease for 4 months
Offer palliative care – died from cancer progression within 2 mon
Outcome #6
8 months of life


FOLFOX + New Drug
(2 cycles) – 2 mon
Serious side effects: Stop regimen, offer FOLFIRI x 2 cycles
Died from cancer progression within 2 months
Outcome #7
Metastatic Colorectal cancer
FOLFOX alone
(2 cycles) – 2 mon
Serious side effects: Stop regimen, offer FOLFIRI x 2 cycles
Died from cancer progression within 2 months
Outcome #8
4 months of life

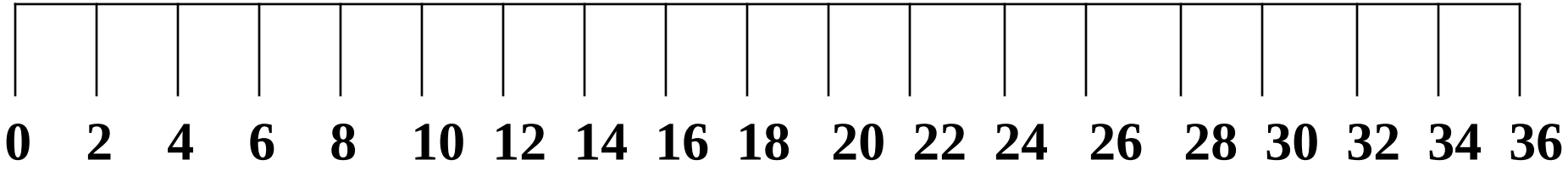

FOLFOX + New Drug
(total = 4 cycles)
No severe side effects,
continue treatment for 2 mon
At mon 2, disease
progression, stop
regimen and start 2nd
line FOLFIRI (4 cycles).
Treat for 2 months
Palliative care for 2
month until death
Outcome #9
Metastatic
Colorectal cancer
FOLFOX alone
(total = 4 cycles)
No severe side effects,
continue treatment for 2 mon
At mon 2, disease
progression, stop
regimen and start 2nd
line FOLFIRI (4 cycles).
Treat for 2 months
Palliative care for 2
month until death
Outcome #10
6 months of life


FOLFOX + New Drug
(Total = 17 cycles)
No severe side effects, continue treatment
Response at mon 2. Regimen given for a total of 9 months until progression
Offer 2nd line FOLFIRI x 6 cycles until death – 24 months later
Outcome #11
33 months of life
Metastatic Colorectal cancer
FOLFOX alone
(Total = 15 cycles)
No severe side effects, continue treatment
Response at mon 2. Regimen given for a total of 8 months until progression
Offer 2nd line FOLFIRI x 6 cycles until death – 24 months later
Outcome #12
32 months of life


FOLFOX + New Drug
(Total = 17 cycles)
No severe side effects, continue treatment
Response at mon 2. Regimen given for a total of 9 months until progression
Offer 2nd line FOLFIRI x 2 cycles until death – one months later
Outcome #13
11 months of life
Metastatic Colorectal cancer
FOLFOX alone
(Total = 15 cycles)
No severe side effects, continue treatment
Response at mon 2. Regimen given for a total of 8 months until progression
Offer 2nd line FOLFIRI x 2 cycles until death – one month later
Outcome #14
10 months of life


FOLFOX + New Drug
(Total = 2 cycles)
No severe side effects,
continue treatment
Died from cancer
progression within 2
months
Outcome #15
Metastatic
Colorectal cancer
FOLFOX alone
(Total = 2 cycles)
No severe side effects,
continue treatment
Died from cancer
progression within 2
months
Outcome #16
2 months of life

Number of Health Months Equivalence



Months*

*For each treatment regimen, only show the respective overall survival for that regimen.

Appendix 3. Author guidelines for journals where the papers were accepted for publication.

Appendix 3A: PHARMACOECONOMICS

Manuscript Format and Style

PharmacoEconomics publishes several categories of review article, each with its own specific focus/format (see Appendix B for types of reviews and their scope) plus original research (see Appendix C for recommended guidelines) and letters to the editor. Authors should specify the article type of their submission.
In general, manuscripts should be prepared and paginated in the following manner:

- A. **Title page**: include title, authors (please also provide forename[s]) and institutions for each author where the work was done (indicating the city), and a condensed running title of not more than 50 characters including spaces.
- B. **Acknowledgments:** See Appendix A, point 4.
- C. **Name and address for correspondence:** Mailing address plus telephone and fax number. An e-mail address should also be supplied, but will not be published without your permission.
- D. **Table of contents**
- E. **Figure captions**
- F. **Abstract**: The abstract should succinctly highlight, in an informative manner, the specific important points addressed in the main body of the text; it should not just describe the general areas covered in the manuscript. The aim is for the abstract to stand alone as a synopsis of the article to accommodate those readers who do not have access to the full article. The journal style is to not cite references in the abstract so as to provide a discrete synopsis of the article. The length can be up to 400-500 words. Authors of original research articles should submit a structured abstract as outlined in Appendix C.
- G. **Text pages:** Text pages must have numbered pages. All review articles must include an introductory section that provides background on the topic and the aim should be clearly stated. If applicable, review articles should include details of the literature search parameters used to locate the material included in the review. The author should specify the databases searched, other sources of articles/data used, search terms and date limits, as well as inclusion/exclusion criteria if relevant. Review articles should finish with a conclusion section putting the area into perspective and pointing the way for future research.

- H. **Footnotes**
- I. **Reference list** (in Vancouver style)
- J. **Tables** (begin each table on a new page)
- K. **Figures** (place each figure in a separate file)
- L. **Supplementary digital content** (place each item in a separate file)

- Please put sections A-J into a single file.
- **Abbreviations and Symbols**

Use SI symbols and recognised abbreviations for units of measurement. The first time an abbreviation appears in the abstract and the text it should be preceded by the full name for which it stands, followed by the abbreviation in parentheses. Generally, abbreviations should be avoided as much as possible, and used only when the full term would make the text unduly cumbersome.

Tables and Figures

Tables and figures help to convey information to the reader. Please make every effort to include such items in your article. Tables can be used, for example, to summarise important points, to compare agents or treatment regimens, or to list information that would otherwise impede the flow of the text. Figures may be schematic diagrams, graphical representations of data, photographs or treatment algorithms. Large numbers of tables and figures and lengthy tables can be problematic in print – these can, however, be published online only as supplemental digital content.

Tables

Tables should be comprehensible without reference to the text, and data given in tables should in general not be duplicated in the text or figures. Any necessary descriptions should appear in the table heading, and abbreviations and footnotes should be placed immediately below the table. Each table should be cited in the text. Please prepare tables in ‘table format', rather than using ‘tab' or ‘indent' commands. Do not format tables using word spaces. Tables should be submit within the Microsoft Word manuscript file; do not submit Excel files for publication.

Appendix 3B: JOURNAL OF EVALUATION IN CLINICAL PRACTICE

Preparation of the Manuscript

Articles are accepted for publication only at the discretion of the Editor and are subject to referee by two experts in the field. A manuscript may consist of a maximum of 5000 words. The first page **must** display: article title; names of all authors, with job title / professional designation; professional and academic qualifications; the name(s) and address(es) of the institution(s) at which the work was carried out (the present addresses of the authors, if different from the above, should appear in a footnote); the name, address, telephone and fax numbers of the author to whom all correspondence and proofs should be sent; a suggested running title of not more than fifty characters, including spaces; and six keywords to aid indexing.

The text should be preceded by a short summary (approximately 250 words and structured, if applicable, according to (i) Rationale, aims and objectives; (ii) Method; (iii) Results; and (iv) Conclusion(s)) and followed by (1) Introduction, (2) Methods (and Materials where appropriate), (3) Results, (4) Discussion, (5) Acknowledgements, (6) References, (7) Figure legends, (8) Tables and (9) Figures. All pages must be numbered consecutively from the title page, and include the acknowledgements, references and figure legends, which should be submitted on separate sheets following the main text. The preferred position of tables and figures in the text should be indicated in the left-hand margin. It is essential that approval for the reproduction or modification of figures and tables published elsewhere is sought and obtained in writing from the authors and publishers prior to submission of papers. The original source must be quoted.

Author material archive policy. Please note that unless specifically requested, **Wiley-Blackwell will dispose of all hardcopy or electronic material submitted two months after publication**. If you require the return of any material submitted, please inform the editorial office or Production Editor as soon as possible if you have not yet done so.

References

These should be in the Vancouver style. References should be numbered sequentially as they occur in the text and identified in the main text by numbers in superscript after the punctuation. The reference list should be prepared on a separate sheet from the main text, and references should be listed numerically. The following are examples of the style. Where there more than ten authors, the first three should be listed followed by et al. If there are ten or fewer authors then all should be listed. Journal titles should not be abbreviated. Do not use opcit. etc.

1. Kassirer, J. P. (1994) Incorporating patients' preferences into medical decisions. *New England Journal of Medicine,* 330(26), 1895-1896.

2. Macklin, R. (1993) Enemies of Patients. How Doctors are Losing Their Power and Patients are Losing their Rights. New York: Oxford University Press.

3. Coote, A. (1996) The democratic deficit. In Sense and Sensibility in Health Care (ed M. Marinker), pp. 173-197. London: BMJ Publishing.

Work that has not been accepted for publication and personal communications should not appear in the reference list, but may be referred to in the text (e.g. A. Author, unpubl. observ.; A.N. Other, pers comm.). The editor and publisher recommend that citation of online published papers and other material should be done via a DOI (digital object identifier), which all repuatable online published material should have - see http://www.doi.org/ for more information. If an author cites anything which

does not have a DOI they run the risk of the cited material not being traceable. It is the authors responsibility to obtain permission from colleagues to include their work as a personal communication. A letter of permission should accompany the manuscript.

Tables

Tables should include only essential data. Each table must be typewritten on a separate sheet and should be numbered consecutively with Arabic numerals, e.g. Table 1, and given a short caption. No vertical rules should be used. Units should appear in parentheses in the column headings and not in the body of the table. All abbreviations should be defined in a footnote.

Appendix 3C: INTERNATIONAL JOURNAL OF TECHNOLOGY ASSESSMENT IN HEALTH CARE

Instructions for Contributors

Preparation of Manuscript
The entire manuscript (in MS Word format), including all notes and references, must be typed, *double-spaced* on 8.5 × 11 inch or A4 page size document, with at least 1-inch (2.54 cm) margins. Manuscript pages should be numbered consecutively. Manuscripts should be arranged as follows: 1) cover sheet with title and short title; 2) abstract and key words; 3) acknowledgments, including source of funding; 4) text; 5) references; 6) tables with titles; and 7) figures, with captions on a separate page. Manuscripts should typically have *no more than 4,000 words*— including the abstract, which should not exceed 250 words.

Abstract ad Key Words
A 100-to 250-word abstract, submitted on a separate page, should *summarize* the objectives of the study or analysis, the article's major arguments and/or results, and its conclusions/recommendations. *Abstracts must be submitted in four sections*: Objectives; Methods; Results; and Conclusions, except where the subject and/or format of the article do not permit. Three to five key words, using terms from the Medical Subject Headings from *Index Medicus*, should follow the abstract.

References
Bibliographic citations in the text should be indicated by numbers in parentheses usually at the end of the sentence after the period. When authors are mentioned in the text, the citation number should immediately follow the name(s) as follows:
In-text citations
"Jones and Smith (7) maintained that. . . " *The reference list must be in alphabetical order* if a work has more than five authors, the first three authors should be listed, followed by et al. Abbreviate journal titles according to the listing in the current *Index Medicus*. ***Book:*** 1. Jones AB, Smith JK. *Computer diagnosis and results.* New York: Penta Publishers; 1998. ***Journal:*** 1. Jones AB, Smith JK. The relationship between health needs, the hospital, and the patient. J Chron Dis. 1995;32:310-312.

Cover Letter
All authors, must attest that 1) each named author contributed to both the conception/design and/or analysis/interpretation of the project and the writing of the paper; 2) each has approved the version being submitted; and 3) the content has not been published nor is being considered for publication elsewhere. In the reference list, do not include material that has been submitted for publication but has not yet been accepted. This material, with its date, should be noted in the text as "unpublished data".

Tables and Figures
Tables and figures should be numbered consecutively. All tables and figures must have a caption and must be cited in the text. Abbreviations in tables and figures should be avoided, except in the case of acronyms already used in the text. Table footnotes appear directly after the table; table references follow the footnotes. Figures must be submitted in Excel, PageMaker, or equivalent.

Appendix 3D: JOURNAL OF ONCOLOGY PHARMACY PRACTICE

Manuscript style
File types
Only electronic files conforming to the journal's guidelines will be accepted. Preferred formats for the text and tables of your manuscript are Word DOC, and tiff or jpeg for figures (ideally figures will use journal colours). Please also refer to additional guideline on submitting artwork [and supplemental files] below.

Journal Style
Journal of Oncology Pharmacy Practice conforms to the SAGE house style. Click here to review guidelines on SAGE UK House Style.

Reference Style
Journal of Oncology Pharmacy Practice adheres to the SAGE Vancouver reference style. Click here to review the guidelines on SAGE Vancouver to ensure your manuscript conforms to this reference style. Abbreviations for titles of periodicals should conform to those used in the latest edition of Index Medicus. References should include authors' last names and initials, article title, journal, volume, page range, and year. Include the city and publisher's name for books. For further information, consult the American Medical Association Manual of Style.

Manuscript Preparation
The text should be double-spaced throughout and with a minimum of 3cm for left and right hand margins and 5cm at head and foot. Text should be standard 10 or 12 point.

Keywords and Abstracts
The title, keywords and abstract are key to ensuring that readers find your article online through online search engines such as Google. Please refer to the information and guidance on how best to title your article, write your abstract and select your keywords by visiting SAGE's Journal Author Gateway Guidelines on How to Help Readers Find Your Article Online.

Corresponding Author Contact details
Provide full contact details for the corresponding author including email, mailing address and telephone numbers. Academic affiliations are required for all co-authors.

Guidelines for submitting artwork, figures and other graphics. For guidance on the preparation of illustrations, pictures and graphs in electronic format, please visit SAGE's Manuscript Submission Guidelines. Images should be supplied as bitmap based files (i.e. with .tiff or .jpeg extension) with a resolution of at least **300 dpi** (dots per inch). Line art should be supplied as vectorbased, separate .eps files (not as .tiff files, and not only inserted in the Word or pdf file), with a resolution of **600 dpi**. Images should be clear, in focus, free of pixilation and not too light or dark. If, together with your accepted article, you submit usable colour figures, these figures will appear in colour online regardless of whether or not these illustrations are reproduced in colour in the printed version. For specifically requested colour reproduction in print, you will receive information regarding the possible costs from

Appendix 3E: EUROPEAN JOURNAL OF HOSPITAL PHARMACY SCIENCE

EJHP Science

In March 2005 EAHP launched a strong platform – EJHP Science – for publication of scientific output from the hospital pharmacy profession and related disciplines.

EJHP Science now makes pharmaceutical innovation and developments in pharmaceutical and biomedical sciences accessible to hospital pharmacists for use in all aspects of their clinical, scientific and professional work.

Mission statement

To provide a strong platform that concentrates the scientific output of the pharmacy profession and related disciplines. This will make pharmaceutical innovation and developments in pharmaceutical and biomedical sciences accessible for hospital pharmacists to use in all aspects of their clinical, scientific and professional work.

Scope and profile

The aim of EJHP Science is to publish high quality research papers, review articles and case studies which will be of interest and relevance to various disciplines within hospital and academic pharmacy. To meet these aims, the scope of the Journal is broad and of relevance to pharmacists working in all areas of hospital pharmacy and interested in research in clinical, technical and social pharmacy as well as pharmaco-epidemiology and pharmaco-economics.

Types of article published

- Case studies
- Clinical pharmacy
- Editorials
- Letters to the Editor
- Original research
- Pharmaco-economics
- Review articles
- Scientific commentary / pharmacy
- Social pharmacy
- Technical pharmacy

Governance

EJHP Science is fully compliant with ICMJE Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

Appendix 3F: MALAYSIAN JOURNAL OF MEDICAL SCIENCES

Preparation of Manuscript
General
• Text: Use subheadings for long articles and double-space all portions of the manuscript.
• Font: Times New Roman/Arial/Cambria, size 12pt, double-spaced, single column.
• Authors should number all of the pages of the manuscript consecutively, beginning with the title page, to facilitate the editorial process.
• Please note that, at the moment, we do not accept Microsoft Word 2007/2010 documents (*.docx). Please use Word's "Save As" option to save your document as (.doc) file type.
Each type of manuscript has its own formats; examples of published manuscript are available on our website. Authors may also consult the provided references—or other similar publications—for tips on preparing a scientific manuscript.
Manuscripts should be organised in the following order:

1. Title page
The title page should be sent as a **separate document** from the main text in ScholarOne Manuscripts. This document will not be available for reviewers as we employ a double-blind review process.
The title page should have the following information:
a. Article title without abbreviations
b. Running title/running head (a short title) of less than 50 characters
c. Authors' names and institutional affiliations: Full names are required; indicate last name with SMALL CAPS. For example, Mohammed Ali JAMALUDDIN.

d. Contact information for correspondence. The name, academic qualification, address, telephone number, fax number, and email address of one of the authors who will be responsible for all communication concerning the manuscript are required.
e. Acknowledgements. Because the title page will not be sent to the reviewers, we recommend this section to be included in the title page.

2. Main document
a. Title
b. Abstract
The length of abstract depends on the type of manuscript submitted. The abstract should state the purpose of the study, a brief description of the procedures employed, main findings and principal conclusions. Abbreviations, footnotes, references, and subheadings should be avoided. For original articles, the abstract format is structured as Background, Methods, Results, and Conclusion. For other articles, the abstract format is unstructured.

c. Keywords
Authors must provide between 4 and 6 keywords that characterise the main topics of the article.

d. Text
The text of observational and experimental articles is usually (but not necessarily) divided into Introduction, Materials (or Subjects) and Methods, Results, Discussion, and Conclusion. A case report is divided into Introduction, Case Report (or Series), and Discussion. Other types of manuscript may be divided into several sections, as seen necessary by the authors.
Long articles may need subheadings within some sections (especially Results and Discussion) to clarify their content. Subheadings representing different hierarchical level must be readily distinguished by readers.

Appendix 3G: EUROPEAN JOURNAL OF CANCER

The *European Journal of Cancer (EJC)* is an international comprehensive oncology journal that publishes original research, editorial comments, review articles and news on experimental oncology, translational oncology, clinical oncology (medical, paediatric, radiation, surgical), and on cancer epidemiology and prevention.

The *EJC* will consider manuscripts prepared according to the guidelines adopted by the International Committee of Medical Journal Editors ('Uniform requirements for manuscripts submitted to biomedical journals', available as a PDF from www.icmje.org). Authors are advised to read these guidelines.

All original research manuscripts submitted to the *EJC* will be evaluated by the journal's Editors. Some manuscripts may be rejected outright following this evaluation. Those manuscripts which are judged as being eligible for consideration by the Editors will be subject to peer-review.

Submission of an article implies that the work described has not been published previously (except in the form of an abstract or as part of a published lecture or academic thesis), that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, without the written consent of the Publisher.

The *EJC* will consider the following types of manuscript for publication:
Editorial comments: Editorial comments are generally invited by the *EJC's* Editorial Team. They are 1,500 words in length with no abstract or keywords.
Original research articles: Original research articles have a limit of 2,500 words and no more than 40 references. Authors are asked to provide a structured abstract and a list of keywords.
Review articles: Review articles have a limit of 3,000 words with an unlimited number of references. Authors are asked to provide an unstructured abstract and a list of keywords.

Author Form: The corresponding author must submit a completed Author Form with their submission. The form must be signed by the corresponding author and uploaded to EES with the manuscript.

Acknowledgements: All contributors who do not meet the criteria for authorship as defined above should be listed in an acknowledgements section. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chair who provided only general support. Authors should disclose whether they had any writing assistance and identify the entity that paid for this assistance.

Randomised Controlled Trials: All randomised controlled trials submitted for publication in the *EJC* should include a completed Consolidated Standards of Reporting Trials (CONSORT) flow chart. Please refer to the CONSORT statement website at http://www.consort-statement.org for more information. The *EJC* has adopted the proposal from the International Committee of Medical Journal Editors (ICMJE) which require, as a condition of consideration for publication of clinical trials, registration in a public trials registry. Trials must register at or before the onset of patient enrolment. The clinical trial registration number should be included at the end of the abstract of the article. For this purpose, a clinical trial is defined as any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Studies designed for other purposes, such as to study

pharmacokinetics or major toxicity (e.g. phase I trials) would be exempt. Further information can be found at www.icmje.org.

Ethics: Work on human beings that is submitted to the *EJC* should comply with the principles laid down in the Declaration of Helsinki; Recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975, the 35th World Medical Assembly, Venice, Italy, October 1983, and the 41st World Medical Assembly, Hong Kong, September 1989. The manuscript should contain a statement that the work has been approved by the appropriate ethical committees related to the institution(s) in which it was performed and that subjects gave informed consent to the work. Studies involving experiments with animals must state that their care was in accordance with institution guidelines. Patients' and volunteers' names, initials, and hospital numbers should not be used.

Conflicts of Interest: At the end of the text, under a subheading "Conflict of interest statement" all authors must disclose any financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding.

Role of the Funding Source: All sources of funding should be declared as an acknowledgement at the end of the text. Authors should declare the role of study sponsors, if any, in the study design, in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. If the study sponsors had no such involvement, the authors should so state.

Format: Please write your text in good English with double line-spacing. Original research manuscripts should be no more than 2,500 words in length, with a maximum of 40 references, and review articles should be no more than 3,000 words in length, with an unlimited number of references. Abstracts should not exceed 250 words in length. Manuscripts may be altered to meet the *EJC's* style.

Manuscripts containing research data generally follow the order: Introduction, Patients (or Materials) and Methods, Results, and Discussion.

Title page. The title page should include a concise but informative title; the authors' names; the department/institution and an address for each author, with a symbol to link authors and their addresses; the name, address, fax and telephone numbers and e-mail address of the author to whom correspondence should be addressed; details of sources of support in the form of grants, equipment, and drugs.

Abstract. The second page should start with the abstract, which should be up to maximum of 250 words and must include the aim of the study, a brief summary of the methods, results and a concluding statement.

Keywords: Include up to 10 key words from the Medical Subject Headings from *Index Medicus*

Text: This should start on the third page and should be divided into the following sections: Introduction, Patients (or Materials) and Methods, Results, and Discussion.

References. References should be listed on a new page. They should be consecutively in superscript in the text. 'Unpublished data' and 'Personal communications' are not allowed. As an alternative, say in the text, for example, '(data not shown)' or '(Dr F.G. Tomlin, Karolinska Institute)'. Accepted but

unpublished papers (but not submitted manuscripts) can be referenced as 'in press'. The format of references should be that of the Vancouver guidelines.

Figure Captions, Tables, Figures and Schemes: Present these, in this order, at the end of the article. They are described in more detail below. High-resolution graphics files must always be provided separate from the main text file (see Preparation of illustrations).

Footnotes. Footnotes should be used sparingly. Number them consecutively throughout the article, using superscript Arabic numbers. Many wordprocessors build footnotes into the text, and this feature may be used. Should this not be the case, indicate the position of footnotes in the text and present the footnotes themselves on a separate sheet at the end of the article. Do not include footnotes in the Reference list.

Tables. Number tables consecutively in accordance with their appearance in the text. Place footnotes to tables below the table body and indicate them with superscript lowercase letters. Avoid vertical rules. Be sparing in the use of tables and ensure that the data presented in tables do not duplicate results described elsewhere in the article.