The Real Option Value of Life And Innovation

Meng Li

A dissertation

submitted in partial fulfillment of the

requirements for the degree of

Doctor of Philosophy

University of Washington

2018

Reading Committee:

Louis Garrison, Chair

Anirban Basu

Caroline Bennette

David Veenstra

Program Authorized to Offer Degree:

Pharmacy

University of Washington

Abstract

The Real Option Value of Life and Innovation

Meng Li

Chair of the Supervisory Committee:
Louis Garrison, Professor Emeritus
Department of Pharmacy

Background: Recent developments in healthcare value assessments have expanded the definition of value for medical technologies. The option value of a life-extending treatment is the opportunity of benefiting from future innovations during the extended life. This concept is particularly important in disease areas where the main goal of treatment is life extension and the rate of innovation is rapid. The objective of this dissertation is two-fold: (1) to examine real-world evidence on option value being considered in treatment decision-making, and (2) to develop a modeling approach for incorporating the real option value of life-extending treatments into cost-effectiveness analysis (CEA).

Methods: In the first study, an interrupted time series analysis was conducted using a large administrative claims database to test whether the utilization of existing treatments changed after the disclosures of the then-investigational drug ipilimumab's phase II and

phase III results among metastatic melanoma patients from 2008 to 2011. A multinomial logistic regression was used to analyze the temporal probability of receiving antineoplastic systemic therapy, surgical resection of metastasis, or both, relative to no treatment, in the first three months following the first metastasis diagnosis. In the second study, I estimated the cost-effectiveness of ipilimumab in two scenarios: a conventional scenario, with a model constructed using the standard methods that rely on efficacy data directly from the phase III trial of ipilimumab, and an option value scenario, that incorporates future hypothetical improvements in mortality for metastatic melanoma due to innovations. I developed two approaches to incorporating option value. The first approach projects mortality improvements based on historical trends from the Surveillance, Epidemiology, and End Results Program registry. The second, alternative approach identifies drugs being studied in clinical trials at the time of ipilimumab's approval on clinicaltrials.gov and estimates their likelihood and timing of approval, and potential efficacy and cost. I accounted for increases in overall cancer treatment cost and unrelated medical cost in the option value scenario.

Results: In the first study, 1,846 metastatic melanoma patients were included. After adjusting for clinical and sociodemographic variables, as well as the underlying time trend, the disclosure of ipilimumab's phase II result was associated with a nearly twofold immediate increase in the probability of receiving surgical resection of metastasis relative to no treatment, which was significant at 5% level. No significant effect was observed in the time trend. No significant effects were found for the announcement of phase III result. In the second study, in the option value scenario, using the SEER approach, the

incremental QALY gained and the incremental cost increased by 6.3% and 3.8%, respectively, while the ICER decreased by 2.4%, compared to the conventional scenario. Using the clinicaltrials.gov approach, the incremental QALY gained and the incremental cost increased by 7.5% and 7.1%, respectively, while the ICER decreased by 0.4%, compared to the conventional scenario.

Conclusion: This dissertation research provided the first empirical evidence of the impact of real option value in cancer treatment decision-making. It was also the first to incorporate option value in an *ex ante* CEA and estimated its potential impact on the cost-effectiveness of a treatment. Findings from this dissertation underscored the importance of accounting for option value when assessing the value of medical technologies.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEDGEMENTS

I would like to express my immense gratitude to my dissertation committee: Lou Garrison, Anirban Basu, Carrie Bennette, Dave Veenstra, and Yvonne Lin, for their guidance and support on this research, as well as their mentorship throughout this journey. You have all taught me how to turn an idea into research, how to think critically, how to communicate effectively, and how to manage and deliver a research project. Particular thanks to Lou Garrison for many enlightening conversations, funny jokes, and most importantly, chocolates, throughout the years.

Special thanks to Ryan Hansen, who guided me through the first two years of my PhD and brought me on many research projects from which I learned a great deal. To my amazing cohort, Mark Bounthavong, Elisabeth Vodicka, Dev Dhanda, and Tracy Yep: thank you for being my cheerleaders for the past five years and for making Seattle feel like home. Heartfelt thanks to faculty members at the CHOICE institute for giving me the opportunities to work with them and learn from them. To my fellow graduate students in the CHOICE institute and at UW: thank you for your friendship, which has made the past five years an enjoyable experience. Above all, many thanks to my family and friends, who have been supporting me every step along the way.

Chapter 1. INTRODUCTION

The past few decades have seen a global transformation in human health unmatched in history. In 1960, global average life expectancy at birth was 52.5 years.[1] Today, the global average has risen to 71.4 years, ranging from 60.0 years in the WHO African Region to 76.8 in the WHO European Region.[2] This remarkable increase in longevity can be partly attributed to advances in medical technologies over the past century. Consider antiretroviral therapy for HIV/AIDS, for example: the treatment has transformed HIV/AIDS from a terminal condition into a manageable chronic disease, and an estimated 14.4 million life years have been gained among adults globally between 1995 and 2009 as a result of it.[3] These public health victories came, however, at the cost of huge increase in healthcare spending. Globally, total expenditure on health as a percentage of gross domestic product (GDP) has grown from 8.5% in 1995 to 10.0% in 2014.[4] In the United States, the world's largest healthcare market, total health expenditure has grown from 13.1% to 17.1% of GDP in the same time period.[4]

Whether this additional spending is "worth it" – how much value it produces in terms of better health outcomes or other benefits – is frequently debated. Over the past few decades, both private and public healthcare institutions have been increasingly looking toward cost-effectiveness analysis (CEA) as they consider complex resource allocation decisions concerning medical technologies. Compared to cost-benefit analysis (CBA) as often practiced in many fields of economics, CEA is preferred by many healthcare decision-makers because it is logically similar to the economic problem of utility maximization but does not require directly placing a dollar value on a health outcome.[5]

The most widely used denominator in CEA in health care – the quality-adjusted life-year (QALY) – combines gains from reduced mortality and reduced morbidity into a single measure thus allowing comparison of different medical technologies for different conditions.

The expected QALYs and costs of a specific, new medical technology on a group of patients over a period of time are often projected using decision-analytic models constructed based on how disease is expected to progress or to be managed.[6] In these models, patients transition among different health states while the amount of time in each health state, the number of QALYs, and costs are tallied to calculate the incremental cost-effectiveness ratio (ICER) or the net monetary benefit (using an estimate of the willingness to pay for a QALY) of the technology. Through Monte Carlo simulations, decision-analytic models can also quantify the uncertainty around the ICER and the net monetary benefit estimates.

Several simplifying modeling assumptions are often made in practice mainly due to methodological issues. For example, conventional CEA models usually assume that technology is fixed throughout the modeling period, and the effects of today's treatment decision on potential treatment options in the future are usually neglected. With the rapid advances in medical technologies in recent years and the adoption of a lifetime horizon by many CEA models, these assumptions can be rather unrealistic. In reality, a patient can switch to new, better treatments when they become available in the future, and if current treatment improves survival, it will increase the patient's chance of seeing those

new treatments. Becker and colleagues were among the first to formally recognize the additional value in taking advantage of current treatment as it may enable patients to live long enough to utilize future cures before they die.[7,8] They argued that this "option value" could be one of the explanations for the high expenditure on terminal care in the United States despite its limited survival and quality-of-life benefits.[7,8]

The concept of option value has received considerable attention in financial economics, where it originated. The theory behind option value—"real options theory"—deals with project appraisal and investment decision-making under uncertainty and is often seen as an alternative approach to the conventional discounted-cash-flow (DCF) method. In the conventional DCF approach to valuing a project, the expected streams of incoming and outgoing cash flows from the investment are estimated, discounted, and summed to give the net present value (NPV), which will then be compared across competing investments. Although this traditional NPV rule is relatively easy to apply, it is built on several unrealistic assumptions. For example, it assumes manager's passive commitment to a certain operating strategy and ignores the potential flexibility to adapt and revise it in response to new information. It views investment decisions in isolation and ignores the possibility that some subsequent investment opportunities are contingent on the initial investment.[9]

Well before the development of real options theory, financial economists recognized that the conventional DCF approach often undervalued investment opportunities, leading to myopic decisions, underinvestment, and eventually, loss of competitive position.[10]

This is because in the actual marketplace, which is characterized by change, uncertainty, and interrelated decisions, the conventional DCF assumptions are often violated. For example, in some cases, management may be able to defer, expand, contract, abandon, or otherwise alter a project at various stages as more information on market conditions and future cash flows becomes available. In other cases, once the prerequisite initial investment is made, management may be able to make subsequent investments if market conditions become favorable. These managerial operating flexibilities – rights, with no obligations to take certain course of action at a later time – are called "real" options. The term "real option" came from the similarity between managerial flexibility for real assets and options for financial assets. Classic examples of financial options include call options and put options. A call option on a financial asset gives the right, with no obligation to acquire the asset by paying a pre-specified price (the exercise price) on or before a given date (maturity). Similarly, a put option gives the right to sell the underlying asset and receive the exercise price. Many real options (e.g., to defer, contract, or abandon a capital investment) occur naturally; others may be planned and built in at some extra cost (e.g., to expand capacity, to default when investment is staged sequentially, or to switch between alternative inputs or outputs).[10]

Over the past two decades, financial economists have explored the basic insight of real options and found that thinking of investments as creating, preserving, and exercising options substantially changed the theory and practice of decision-making about capital investments.[9] For example, an investment that appears uneconomical when viewed in isolation by DCF criteria may, in fact, create options that enable the company to

undertake subsequent investments in the future should market conditions turn favorable. If the return to these subsequent investments is high enough, investors may be willing to accept a low return or even a loss during the initial period. As a result, an increasing number of academics and corporate practitioners have called for an expanded or strategic investment criterion, reflecting both value components: the traditional (static or passive) NPV of direct cash flows and the option value of operating flexibility and strategic interactions.

It is not difficult to see the similarities between making a non-health investment decision and making a decision regarding the treatment of a disease. Both are made under some level of uncertainty and cannot be completely reversed at no cost. Both are made in a constantly changing world where new opportunities for investment or treatment may emerge throughout the time horizon. For example, any treatment that prolongs survival can be viewed as creating options as it opens up opportunities for patients to benefit from future treatments should they become available during the extended life. The current treatment in itself may only have a modest treatment effect, but it can increase the patient's chance of seeing future cures. If the potential health gains from future innovations are large, we may see patients more willingly sacrifice quality of life for survival gains.

Interestingly, research on the willingness to pay (WTP) for a QALY gain may also offer some evidence that people internalize value from creating options when they think about choices for treatment. Several recent contingent valuation studies have found that both

physicians and patients valued QALY gains from life extension higher than those from quality-of-life improvement.[11,12] Most recently, Ryen and Svensson reviewed 24 studies that contained a total of 383 unique estimates of WTP for a QALY. In their analyses, the results indicated that WTP for a QALY was significantly higher when the QALY gain was from life extension as compared to quality-of-life improvements.[13] So far, few efforts have been devoted to understanding this consistent difference in valuation although it can be readily explained by real options theory: the expanded health benefit of a life-extending treatment is the traditional health benefit of this treatment evaluated in isolation *plus* the health benefit from potential future treatments unlocked, and the latter is internalized by people but might not be accounted for in conventional QALY calculations.

Despite the salience of real option value in medical decision-making, it has generally been overlooked in research and policy thus far.[14] Neglecting the options created by a treatment may lead to underestimation of its value in some cases. The grounding of CEA in von Neumann-Morgenstern utility theory and more generally, welfare economics, depends heavily on whether the measure of effectiveness adequately represents preferences.[5] Without considering the full health benefit of a treatment, it is questionable whether resource allocation decisions made based on such cost-effectiveness estimates will consistently improve welfare of the population. There have been calls for using a health outcomes modeling approach for benefit-risk assessment and regulatory approval of new drugs, as well as to support pricing drugs based on their health benefit[15,16]; however, none of these can be achieved without a comprehensive

framework that reflects all of the important components of the value of a treatment.

In this dissertation research, I examined the impact of incorporating value from creating options in health technology assessment. I answered two closely related research questions: (1) is option value considered in real-world treatment decision-making, and (2) how does accounting for option value affect the cost-effectiveness of a treatment. This dissertation research was the first to provide revealed-preference evidence on option value being considered in treatment decision-making, and the first to estimate the option value of a treatment in a CEA.

Reference:

[1] The World Bank. Life expectancy at birth, total (years) http://data.worldbank.org/indicator/SP.DYN.LE00.IN. (accessed July 2, 2016).

[2] World Health Organization. In. WHO 2016. http://www.who.int/gho/mortality_burden_disease/life_tables/situation_trends_text/en/ (accessed July 2, 2016).

[3] Mahy M, Stover J, Stanecki K, Stoneburner R, Tassie J-M. Estimating the impact of antiretroviral therapy: regional and global estimates of life-years gained among adults. Sex Transm Infect 2010;86:ii67-ii71.

[4] The World Bank. Health expenditure, total (% of GDP). World Heal Organ Glob Heal Expend Database 2016.

[5] Garber A, Phelps C. Economic foundations of cost-effectiveness analysis. J Health Econ 1997;16.

[6] Briggs A, Claxton K, Sculpher M. Decision Modelling for Health Economic Evaluation. Oxford University Press; 2006.

[7] Becker B, Murphy K, Philipson T. The Value of Life Near Its End And Terminal Care. Cambridge, MA: 2007.

[8] Philipson TJ, Becker G, Goldman D, Murphy KM. Terminal Care And The Value of Life Near Its End. vol. 1. Cambridge, MA: 2010.

[9] Dixit AK, Pindyck RS. The Options Approach to Capital Investment. Harv Bus Rev 1995.

[10] Trigeorgis L. Real Options: Managerial Flexibility and Strategy in Resource Allocation. The MIT Press; 1996.

[11] Kozminski MA, Neumann PJ, Nadler ES, Jankovic A, Ubel PA. How Long and How Well: Oncologists' Attitudes Toward the Relative Value of Life-Prolonging v. Quality of Life-Enhancing Treatments. Med Decis Mak 2011;31:380–5.

[12] Greenberg D, Hammerman A, Vinker S, Shani A, Yermiahu Y, Neumann PJ. Which is more valuable, longer survival or better quality of life? Israeli oncologists' and family physicians' attitudes toward the relative value of new cancer and congestive heart failure interventions. Value Heal 2013;16:842–7.

[13] Ryen L, Svensson M. The Wilingness to Pay for a Quality Adjusted Life Year: A Review of the Empirical Literature. Health Econ 2015;24:1289–301.

[14] Garrison L, Mestre-Ferrandiz J, Zamora B. The Value of Knowing and Knowing the Value : Improving the Health Technology Assessment of Complementary Diagnostics. 2016.

[15] Garrison LP, Towse A, Bresnahan BW. Assessing a structured, quantitative health outcomes approach to drug risk-benefit analysis. Health Aff 2007;26:684–95.

[16] Bach PB, Pearson SD. Payer and Policy Maker Steps to Support Value-Based Pricing for Drugs. Jama 2015;10021:1–2.

Chapter 2. DO CANCER TREATMENTS HAVE OPTION VALUE? REAL-WORLD EVIDENCE FROM METASTATIC MELANOMA

2.1 ABSTRACT

Background. A change in the expectations about future treatments may change the option value of a current treatment, thereby affecting its utilization.

Methods. We conducted an interrupted time series analysis using a large administrative claims database to test whether the utilization of existing treatments changed after the disclosures of the then-investigational drug ipilimumab's phase II and phase III results among metastatic melanoma patients from 2008 to 2011. We used a multinomial logistic regression to analyze the temporal probability of receiving antineoplastic systemic therapy, surgical resection of metastasis, or both, relative to no treatment, in the first three months following the first metastasis diagnosis.

Results. 1,846 metastatic melanoma patients were included. After adjusting for clinical and sociodemographic variables, as well as the underlying time trend, the disclosure of ipilimumab's phase II result was associated with a nearly twofold immediate increase in the probability of receiving surgical resection of metastasis relative to no treatment, which was significant at 5% level. No significant effect was observed in the time trend. No significant effects were found for the announcement of phase III result.

Conclusion. Our findings in metastatic melanoma provide the first empirical evidence of the impact of option value in cancer treatment decision-making.

2.2 BACKGROUND

The rapid pace of medical innovation and growing healthcare and drug costs have spurred interest in defining and assessing the value of medical technologies. In recent years, there have been a flurry of initiatives in the private sector in the US designed to help patients, physicians, and payers understand the value of therapies and thus make better decisions about their use.[1] Different initiatives have considered different elements underlying value: clinical benefit, toxicity, costs, cost-effectiveness, budget impact, novelty, and others.[1] One of the most commonly used metrics for measuring value in health care is the incremental cost per quality-adjusted life-year (QALY), which is usually estimated using analyses with a time horizon that is much longer than most clinical trials.

In many cases, a longer time horizon is more relevant when it comes to estimating the impacts on patient life expectancy, but it gives rise to questions of whether and how analysts should account for technology advances within the time horizon, especially those related to the disease. Most analyses to date have simply assumed that within the time horizon technologies remain the same in both comparator arms. However, with the rapid advancement of medical technologies today, this assumption could be unrealistic in many instances. For example, consider treatments for metastatic melanoma: the FDA approved eight new molecules from March 2011 to November 2015, averaging one approval every six months. Any treatment that can extend life for at least six months will not only improve survival but also give patients an opportunity to benefit from the drug that will be approved next. Becker and colleagues were among the first to formally recognize this

additional value in taking advantage of current treatment – enabling one to live long enough to utilize future cures before one dies.[2] They argued that the additional value is the "option value" of a treatment, and is additive to the conventional survival and quality-of-life benefits.[2]

The concept of option value has received considerable attention in financial economics, where it originated. In capital investment, option value is the value of managerial flexibilities – rights, with no obligations to take certain course of action in the future – when operating in a financial market full of changes, uncertainty, and interrelated decisions. These rights include deferring, expanding, contracting, abandoning, or altering a project in other ways after it is initiated, as more information about market conditions becomes available. For example, company management may hold a lease on valuable land or resources and can wait to see if changing output prices justify constructing a building or plant. And this "option to defer" is frequently seen in natural resource extraction industries, real estate development, farming, etc.[3] In infrastructure-based or strategic industries, a "growth option" is an early investment (e.g., a lease on undeveloped oil reserves), which is a prerequisite in a chain of interrelated projects that opens up future growth opportunities (production and commercializing of oil).[3] The option-pricing techniques, which were first developed in late 1960s, aim to price the value of managerial flexibilities that had been largely omitted in the conventional net present value approach to capital investment.[4]

In the healthcare value assessment literature, only a few studies have addressed the issue

of option value, and they have estimated, via modeling, the option value of antiretroviral therapies (ART) for treating HIV/AIDS, imatinib for treating chronic myelogenous leukemia, nivolumab for treating metastatic renal cell carcinoma and non-small cell lung cancer, tamoxifen for preventing breast cancer, and watchful waiting for managing abdominal aortic aneurysms.[5–9] In these studies, estimates of option value ranged from 5% to as much as 400% of the conventional value of the treatment. In a contingent valuation study, Smith found that the willingness to pay for the use (valuing a health benefit accruing immediately and with certainty to the respondent) *plus* option value (valuing a health benefit potentially accruing to the respondent but at some point in the future) for a hypothetical treatment was significantly greater than its use value alone (A$7,840 vs. A$5,115, P=0.007).[10]

Despites the insights and impact estimates provided by this small body of literature on option value in health economic evaluation, what has been missing is the answer to the positive economic question: "Is option value considered in real-world decision-making?" The goal of our study was to examine empirical evidence on option value being considered in real-world decision-making. We analyzed the revealed preference of patients, and focused on the type of option value that results from technological advancement and intertemporal decisions.

2.3 METHODS

Theoretical Framework

We assume a representative patient with a chronic disease, who lives for a maximum of two periods ($t = 1, 2$). For simplicity, we assume that at the beginning of the first period, one active treatment for the disease is available. At the beginning of the second period, a new treatment for the chronic disease may be approved and launched. We assume the patient undergoes either one treatment or no treatment in a period. Therefore, the choice set for treatments (D_t) in period one includes the active treatment and no treatment; the choice set in period two includes the active treatment, no treatment, and potentially the new treatment if it is approved and launched. In each period, the patient chooses $d_t \in D_t$ to maximize:

$$EU(d_1, d_2) = s_1(d_1)U_1(d_1) + \delta s_1(d_1)s_{2,d_1}(d_2)U_{2,d_1}(d_2) \quad (1)$$

where $s_1(d_1)$ is the survival and $U_1(d_1)$ the quality of life in period one under the treatment chosen for that period. $s_{2,d_1}(d_2)$ is the conditional survival in period two and $U_{2,d_1}(d_2)$ the quality of life in period two. The conditional survival function and the quality-of-life function in the second period are path-dependent and are influenced by what treatment was used in the previous period (d_1). δ is the discount factor for the second period.

This framework implies that a forward-looking patient will consider treatments, both existing and currently under investigation, in both periods when making treatment decision in period one, in order to maximize lifetime expected utility given lifetime expected income. It differs from a conventional framework by allowing the choice set to

change from period one to period two, and the treatment chosen in the first period to affect not only if a patient will survive to the second period but also the effectiveness of the treatment chosen in the second period, which together creates option value. In a conventional framework, in contrast, no technology advancement or path-dependency is allowed, and the patient chooses only at the beginning of the first period $d_1 \in D_1$ to maximize:

$$EU(d_1) = s_1(d_1)U_1(d_1) + \delta s_1(d_1)s_2(d_1)U_2(d_1) \tag{2}$$

The option value is then the difference between Equation (1) and Equation (2):

$$OV = EU(d_1, d_2) - EU(d_1) = \delta s_1(d_1)[s_{2,d_1}(d_2)U_{2,d_1}(d_2) - s_2(d_1)U_2(d_1)] \tag{3}$$

These three equations indicate that the conventional value of d_1 does not change as D_2 changes; the option value does and therefore the total value. D_2 can be modified by news on R&D progress, such as positive results from phase II and/or phase III clinical trials. For example, if a phase II clinical trial demonstrates that an investigational new drug is more effective than the current standard of care, holding everything else the same, the greater the survival benefit of the current treatment ($s_1(d_1)$), the greater the option value. Similarly, the greater the sequential synergy between the current and the new treatments ($s_{2,d_1}(d_2)U_{2,d_1}(d_2)$), the greater the option value. Holding everything else the same, greater option value will result in higher utilization. In the following case study of metastatic melanoma, we sought to test this hypothesis to provide empirical evidence to

support this new framework that includes option value. In the base case, we assumed that health insurance coverage makes the financial implications of treatments negligible.

Case Study

We selected metastatic melanoma as a case study because of the recent proliferation of novel treatments. Metastatic melanoma has until recently been associated with few effective treatment options and a dismal prognosis. By 2011, five-year survival of patients diagnosed with metastatic melanoma had been less than 20%.[11] The main types of treatment for this group of patients are systemic therapies (chemotherapy, immunotherapy, and combination therapy) and surgical resection of metastasis. Before 2011, dacarbazine, interferon alfa-2b (IFN-α), and aldesleukin (IL-2) were the only FDA-approved agents for metastatic melanoma, and they were each approved in 1975, 1986, and 1992, respectively.[12,13] Dacarbazine monotherapy had been the standard of care for over three decades although its effect on overall survival had never been established in a placebo-controlled clinical trial.[14,15] Before 2011, no other monotherapy or combination therapy was shown to have a significant survival benefit over dacarbazine or placebo.[15,16] Furthermore, these older systemic therapies were associated with variable response rates, lack of durable responses, and toxic side effects.[15,17] Surgical resection of metastasis, by contrast, was shown to be associated with improved long-term overall survival while being well tolerated.[17–19] Reduction of metastasis may also reverse tumor-induced immunosuppression and restore host immune function, which may work in synergy with ipilimumab, an immunotherapy that

activates host immune response to cancer cells.[17,20]

Treatment paradigm for metastatic melanoma changed in March of 2011 with the approval of ipilimumab, a monoclonal antibody that works to activate the immune system by targeting cytotoxic T lymphocyte antigen 4. It was the first FDA-approved agent that demonstrated a significant improvement in overall survival in metastatic melanoma. In a series of phase II studies, the two-year survival rate of metastatic melanoma patients treated with ipilimumab ranged from 30 to 42 percent, compared to 8 to 12 percent among historical controls.[21]. In a phase III study of previously treated patients, ipilimumab improved median overall survival compared with an experimental peptide vaccine gp100 either as a monotherapy or as a combination with gp100 (pooled median survival: 10.1 vs. 6.4 months; hazard ratio (HR): 0.66; P=0.003).[22,23] The timeline for ipilimumab's clinical testing and approval is illustrated in **Figure 2.1**.

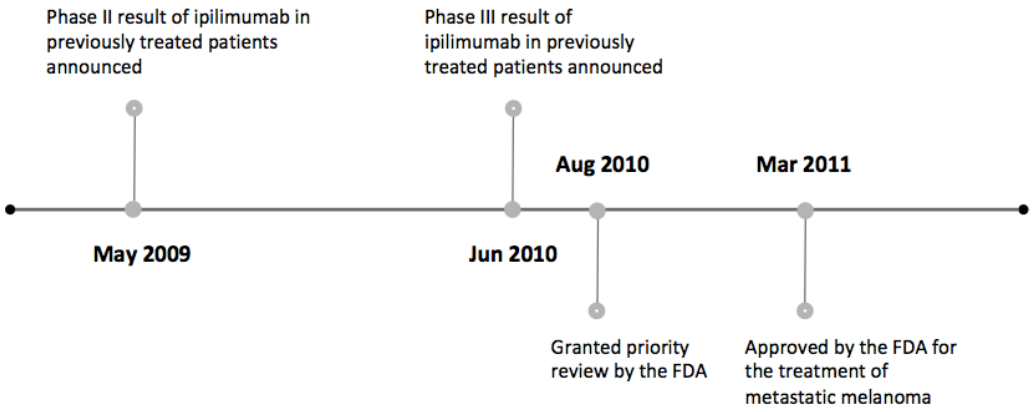

Figure 2.1: Timeline for ipilimumab's clinical testing and approval

In this case, the two announcements made by BMS, in 2009 and 2010, may have significantly altered metastatic melanoma patients' expectations about their choice set of treatments in the future, which now included ipilimumab, in addition to surgical resection, older systemic therapies, and no treatment. Surgical resection of metastasis in the first period may increase the likelihood of surviving to the second period, compared to no treatment, thus creating greater option value. Therefore, in anticipation of ipilimumab's approval, we may see greater utilization of surgical resection of metastasis by metastatic melanoma patients, compared to no treatment. For systemic therapy, the direction of change of utilization would be less clear, as it does not improve survival compared to no treatment.

Data Source

The study population were identified from the Truven Health Analytics MarketScan® databases (commercial and Medicare supplemental). These databases, consisting of fully adjudicated and paid claims, capture individual-level key demographic variables, diagnoses, procedures, and expenditures across inpatient, outpatient, and prescription drug services. The databases contain 170 million de-identified patients from large employers, health plans, and government and public organizations. The Medicare Supplemental Databases contain Medicare-eligible retirees with employer-provided Medicare Supplemental plans.

Study Design and Population

This study employed an interrupted time series design to analyze the utilization of antineoplastic systemic therapy and surgical resection of metastasis among incident metastatic melanoma patients from January 2008 to March 2011. We identified monthly cohorts of metastatic melanoma patients using the following criteria: (1) had at least two International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes of secondary malignant neoplasm (196.xx, 197.xx, and 198.xx) separated by a minimum of 30 days between January 2008 and January 2011 (identification period); (2) had at least two ICD-9 diagnosis codes of melanoma (172.xx) separated by a minimum of 30 days within 365 days prior to the first metastasis diagnosis (baseline period); (3) had no ICD-9 diagnosis code of cancer other than melanoma (140.xx–165.xx, 170.xx-171.xx, 174.xx–195.xx, 200.xx–208.xx) in the baseline period; (4) were at least 18 years old on the day of the first metastasis diagnosis; and (5) were continuously enrolled in the one-year baseline period and at least three months after the first metastasis diagnosis. The follow-up period for an individual was three months after the first metastasis diagnosis.

Dependent and Independent Variables

We used ICD-9 procedure codes, Current Procedural Terminology (CPT) codes, and therapeutic class from the Redbook to identify antineoplastic chemotherapies and immunotherapies received by the study population in the follow-up period. We used ICD-9 procedure codes and CPT codes to identify surgeries for tumor excision, resection, ablation, and destruction. We excluded surgeries that removed the entire organ (e.g.,

mastectomy) as well as surgeries that were not related to the treatment of cancer. The dependent variable in this analysis was a categorical variable that indicated whether an individual patient used systemic therapy, surgery, both, or neither, within three months after their first metastasis diagnosis. The two policy interventions were the disclosure of ipilimumab's phase II result on May 31, 2009, and the disclosures of its phase III result on June 5, 2010. Independent variables included the two disclosures, calendar time of first metastasis diagnosis centered at phase II disclosure, interactions between disclosures and time, age, baseline Charlson Comorbidity Index (CCI), number of distant metastasis sites at diagnosis, region (northeast, north central, south, and west), partially or fully capitated health plan, and the distance between patient and the nearest ipilimumab clinical trial center. The last variable was used to account for participation in ipilimumab's clinical trial, with the assumption that the farther away a patient was from the nearest clinical trial center, the less likely that patient participated in ipilimumab's clinical trial. We used the ZIP Code Tabulation Area Distance Database of the National Bureau of Economic Research to calculate the distance between two zip codes.[24]

Statistical Analysis

We used a multinomial logistic regression to estimate the effects of ipilimumab's phase II and phase III disclosures on the likelihood of using surgical resection, systemic therapy, or both, within the first three months after the first metastasis diagnosis, relative to no treatment. We specified the model as follows:

$$g\big(E(y_{i,k}|\, t,p,q,X)\big) = \alpha_k + \beta_{k1}t + \beta_{k2}p + \beta_{k3}pt + \beta_{k4}q + \beta_{k5}qt + X_i\beta_{k6}$$

$$E(y_{i,k}|\, t,p,q,X) = \pi_{i,k}, \text{and } g(\pi_{i,k}) = ln(\frac{\pi_{i,k}}{\pi_{i,b}}) \tag{4}$$

where

$y_{i,k}$ indicator for individual i choosing outcome category k (systemic therapy, surgery, both)

t calendar time for first metastasis diagnosis

p ipilimumab's phase II disclosure

q ipilimumab's phase III disclosure

X_i characteristics of individual i, including age, CCI, health plan type, region, number of distant sites at diagnosis, and distance to the nearest ipilimumab trial center

In the first model, we included the interaction between time and phase II disclosure and the interaction between time and phase III disclosure; in the second model, we excluded such interactions. We tested the assumption of independence of irrelevant alternatives (IIA) using the Hausman test.(Hausman & McFadden, 1984) The test result did not indicate that the IIA assumption was violated. In one sensitivity analysis, we ran the multinomial probit model to relax the IIA assumption. In another sensitivity analysis, we excluded cohorts diagnosed within three months before phase II disclosure and within three months before phase III disclosure, as the news was released during the follow-up of these cohorts of patients. We also excluded the month after phase II disclosure and the month after phase III disclosure as lag periods. As a falsification test, we examined the

use of antihyperlipidemics among the same metastatic melanoma population, which was not likely to change due to the two disclosures. For all models, we used robust variance estimators and assessed model fit with the following goodness-of-fit tests: Pearson's correlation test and a modified Hosmer-Lemeshow test.

2.4 RESULTS

From January 2008 to January 2011, there were 1,846 metastatic melanoma patients (37 monthly cohorts) who met our inclusion criteria in the MarketScan database. Sociodemographic and clinical characteristics of the study population was summarized in **Table 1**. The average age at baseline was 57 years old (standard deviation [SD]: 14.0). Females accounted for 36.8% of the study population. About 47.4% of patients had metastasis only to lymph nodes at diagnosis, 38.9% had metastasis to one distant site, 9.8% had metastasis to two distant sites, and 3.9% had metastasis to three distant sites or more. Mean CCI at baseline was 1.5 (SD: 2.4). Approximately 14.1% of the study population were from the northeast, 27.5% were from the north central, 39.4% were from the south, and 17.6% were from the west. The average distance between an individual and the nearest ipilimumab clinical trial center was 89.8 miles (SD: 78.7). 11.3% of the study population had a partially or fully capitated health insurance plan.

Within three months following the first metastasis diagnosis, 17.2% of metastatic melanoma patients only initiated systemic therapy, 27.8% only underwent surgical resection of tumor, 11.3% received both, and 43.7% received no treatment (**Table 2**).

Percentage of patients receiving no treatment was higher before the announcement of ipilimumab's phase II result (48.6%) than between its phase II and phase III announcements (36.9%) and after its phase III announcement (38.8%). Percentages of patients receiving only systemic therapy were similar in all three periods (17.8% vs. 14.3% vs. 20.5%). Before the announcement of ipilimumab's phase II result, percentage of patients receiving only surgery (24.4%) was lower than between phase II and phase III announcements (35.1%) and after phase III announcement (27.1%). Similarly, percentage of patients receiving both systemic therapy and surgery before ipilimumab's phase II announcement (9.2%) was lower than between phase II and phase III announcements (13.7%) and after phase III announcement (13.6%).

Results from the multinomial logistic regressions are summarized in **Table 3** and demonstrated in **Figure 2**. In the model with calendar time and disclosure interactions, there did not appear to be any significant temporal trends for the probabilities of using systemic therapy, surgical resection of metastasis, or both, relative to no treatment, among our study population in the study period. After adjusting for clinical and sociodemographic variables, the disclosure of ipilimumab's phase II result was associated with a nearly 2-fold immediate increase (SD: 0.61; p=0.033) in the probability of undergoing surgical resection of metastasis relative to no treatment and a 2.5-fold immediate increase (SD: 1.14; p=0.049) in the probability of undergoing both surgical resection of metastasis and systemic therapy relative to no treatment. The disclosure of phase II result did not significantly affect the probability of receiving systemic therapy alone relative to no treatment. The disclosure of ipilimumab's phase III result did not

significantly affect the probability of using any treatment. The effects of phase II and phase III disclosures did not vary over time.

Similarly, in the model without calendar time and disclosure interactions, there appeared to be no significant temporal trend for the probabilities of using systemic therapy, surgical resection of metastasis, or both, relative to no treatment. After adjusting for clinical and sociodemographic covariates, the disclosure of ipilimumab's phase II result was associated with a 1.7-fold immediate increase (SD: 0.42; p=0.048) in the probability of undergoing surgical resection of metastasis relative to no treatment. The disclosure of phase II result did not significantly affect the probability of receiving systemic therapy alone or in combination with surgical resection of metastasis, relative to no treatment. The disclosure of ipilimumab's phase III result did not significantly affect the probability of using any treatment. The effects of phase II and phase III disclosures did not vary over time.

Marginal effects of phase II disclosure were summarized in **Table 4**. In the model with calendar time and disclosure interactions, at phase II disclosure, the percentage of patients receiving no treatment in the first three months following first metastasis diagnosis decreased by 16% (SD: 6%, p=0.005). The percentages of patients receiving systemic therapy, surgical resection, and both increased by 4%, 8%, and 4%, but these marginal effects were not statistically significant. In the model without calendar time and disclosure interactions, at phase II disclosure, the percentage of patients receiving no treatment decreased by 10% (SD: 5%, p=0.047). The percentages of patients receiving

systemic therapy, surgical resection, and both increased by 2%, 8%, and 0.3%, but these marginal effects were not statistically significant.

In sensitivity analysis that excluded cohorts diagnosed within three months before and one month after each disclosure, the p-value for phase II disclosure in Model 1 increased from 0.049 to 0.055 (**Table 2.S1**). In the falsification test, the use of antihyperlipidemics in the study population did not change following the two disclosures of ipilimumab's clinical testing (**Table 2.S2**).

2.5 DISCUSSION

For metastatic melanoma patients, we examined the utilization of antineoplastic systemic therapies and surgical resection of metastasis before and after the announcements of ipilimumab's phase II and phase III clinical trial results. We found that patients responded to the announcement of ipilimumab's phase II result by increasing their use of surgical resection of metastasis. We did not find a similar effect on the use of systemic therapies or for the announcement of ipilimumab's phase III results. To our knowledge, this is the first revealed-preference study that examined the real-world evidence on the anticipation of an investigational new drug affecting the utilization of existing treatments.

The phase II press release of ipilimumab represented the first strong signal for the arrival of a potential breakthrough in metastatic melanoma in decades. It likely raised the survival outlook for this group of patients thus the option value of existing treatments that can either prolong survival or work in synergy with ipilimumab. Surgical resection of

metastasis may prolong survival, reduce tumor size, and reverse immunosuppression, while being well tolerated. Available systemic therapies at that time, on the contrary, had questionable overall survival benefit and low response rate, while having significant toxicities. Therefore, the option value for surgical resection of metastasis likely increased following the phase II announcement, while the option value for systemic therapies did not. This difference in option value between surgery and systemic therapies could explain the difference in the changes of their utilization. In this analysis, we only observed a significant effect for the announcement of ipilimumab's phase II result. This is possibly because ipilimumab's phase II result had already significantly changed the priors of both patients and their physicians, and its phase III result thus had less of an effect to change the priors again.

Findings from this study underscore the need for health care providers and payers to be aware of "non-conventional" attributes of treatment that may be valuable to patients. The concept of option value is important especially when the main goal of treatment is life extension and the rate of innovation is rapid. It implies that in some cases patients may be willing to accept very poor quality of life in exchange for a chance to live long enough to see a breakthrough for their disease. It also implies that in some cases patients may be willing to pay more for life extension than for quality-of-life improvement.[26] Understanding patients' preferences for treatments is critical for achieving patient-centered care, while understanding patients' and the society's valuation of treatment benefits is critical for achieving efficient resource allocation.[27]

There are several limitations of our study that are worth noting. First of all, there are many factors that are unobserved in claims data that may affect a patient's treatment decision for cancer: patient factors including personal beliefs and values, ethnicity, previous health-related experience, perception of the decision-making process, physician factors including physician personal beliefs and values, perception of lowered life expectancy, communication style, as well as contextual factors including availability of caregiver support and poor financial status.[28] More clinical and socioeconomic information on the patients and their physicians would give us a better understanding of the underlying process of decision-making and more precise effect estimates. Because of possible unmeasured confounding, along with borderline-significant effects, the results from this analysis need to be interpreted with caution.

Second, due to the short window of time between ipilimumab's phase III announcement and its FDA approval, we only analyzed treatment decisions in the first three months following the index metastasis diagnosis. The median survival for melanoma patients with metastasis only to lymph nodes was 24.3 month at diagnosis, and depending on the sites, the median survival for melanoma patients with distant metastases ranged from 5.1 months to 22.3 months.[29] While the conventional wisdom of treating metastatic melanoma is that treatments, especially surgery, should be offered soon after diagnosis, a three-month time horizon can only capture the initial decisions of treatment. Further research is needed to understand the option value of treatments later in the course of disease.

Third, due to the rarity of the disease, the average number of patients in each monthly cohort is fewer than 50. The small sample size may have contributed to the fluctuations in utilization and the wide confidence intervals of the effect estimates of the announcements. Furthermore, the small sample size made it impossible to stratify the analysis based on distant sites of metastasis. The majority of the study population, who had metastasis to zero or only one distant site at diagnosis, were most likely to benefit from surgery, while the small percentage who had metastasis to two or more distant sites were most likely to benefit from systemic therapy. In fact, in the multinomial logistic regressions, having metastasis to two or more distant sites was significantly associated with higher probability of using systemic therapy and lower probability of using surgery. The two distinct groups of patients may have reacted to the announcements differently, but our study lacked the statistical power to test any differential behavioral change.

Fourth, in the conceptual framework outlined in this paper, we omitted the out-of-pocket price for the treatment under the assumption that health insurance can reduce the effect of out-of-pocket price of medical care on consumption to negligibility in this population, thus not affecting their treatment decisions. However, in the real world, this assumption may not hold all the time. In a survey by Markman et al., among breast, prostate, colon, or lung cancer patients, 9% of respondents stated that they decided not to have a recommended cancer treatment because it was too expensive.[30] In that study, the average out-of-pocket spending on treating cancer incurred by the study population in the past 12 months was approximately $3,700 in 2008.[30] In our study, from 2008 to 2011, the average out-of-pocket spending in the three-month follow-up period were $199 on

systemic therapies among those who received any systemic therapy, and $109 on surgical resection of tumor among those who underwent the procedure. Compared to the Markman study, the cost of cancer care in our study population was likely lower, thus less likely to affect treatment decision-making. Furthermore, the out-of-pocket spending on systemic therapies and surgical resection in our study population did not change significantly over time. Therefore, excluding costs did not likely bias the result.

Last but not least, there are mechanisms other than increased option value that can explain the behavioral change we observed in the study. In this particular case, some may argue that knowing there is a breakthrough drug in clinical testing for one's disease may increase one's optimism (or "hope", as preferred by some), the generalized positive expectations towards the future.[31] With greater optimism, one may be more likely to see their desired outcomes as attainable and to engage in behaviors that promote the achievement of those outcomes.[31]

In conclusion, we found empirical evidence that supports the notion that option value of a treatment is considered by patients in their treatment decision-making. Future research is needed on the methods for estimating option value and its implications for the cost-effectiveness of a treatment and optimal resource allocation.

2.6 TABLES AND FIGURES

TABLE 2.1: SOCIODEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE STUDY POPULATION (N=1846)

Variable	Mean
Age, mean (SD)	57.2 (14.0)
Female, n (%)	679 (36.8)
CCI at baseline, mean (SD)	1.5 (2.4)
# Distant sites (beyond lymph nodes) at diagnosis, n (%)	
0	875 (47.4)
1	718 (38.9)
2	181 (9.8)
>=3	72 (3.9)
Miles from the nearest ipilimumab trials site, mean (SD)	89.8 (78.7)
Region, n (%)	
Northeast	261 (14.1)
North Central	507 (27.5)
South	727 (39.4)
West	325 (17.6)
Partially/fully capitated health plan, n (%)	208 (11.3)

TABLE 2.2: ANY USE OF SYSTEMIC THERAPY, SURGICAL RESECTION OF METASTASIS, BOTH, OR NO TREATMENT IN THE FIRST THREE MONTHS FOLLOWING FIRST METASTASIS DURING THE STUDY PERIOD FROM JANUARY 2008 TO MARCH 2011

Treatment strategy	Entire period, N=1846	Before phase II, N=988	Phase II-III, N=490	After phase III, N=273
No treatment	806 (43.7)	480 (48.6)	181 (36.9)	106 (38.8)
Systemic therapy only	318 (17.2)	176 (17.8)	70 (14.3)	56 (20.5)
Surgery only	514 (27.8)	241 (24.4)	172 (35.1)	74 (27.1)
Both	208 (11.3)	91 (9.2)	67 (13.7)	37 (13.6)

TABLE 2.3: RELATIVE RISK RATIOS (RRRS) ESTIMATING THE EFFECTS OF DISCLOSING IPILIMUMAB'S PHASE II AND PHASE III RESULTS ON UTILIZATION OF SYSTEMIC THERAPY, SURGICAL RESECTION OF METASTASIS, OR BOTH, BY INCIDENT METASTATIC MELANOMA PATIENTS IN THE FIRST THREE MONTHS FOLLOWING THEIR FIRST METASTASIS, COMPARED TO NO TREATMENT

Covariates	**Model 1** **Mean (s.e.) [p value]**	**Model 2** **Mean (s.e.) [p value]**
No treatment	Base outcome	Base outcome
Systemic therapy only		
Time of first metastasis diagnosis[a]	.96 (.03) [.202]	.99 (.02) [.482]
Phase II disclosure	1.85 (.72) [.111]	1.43 (.45) [.249]
Phase III disclosure	.76 (.46) [.648]	1.31 (.40) [.368]
Phase II and time interaction	1.04 (.05) [.472]	
Phase III and time interaction	1.03 (.06) [.575]	
Age	**.99 (.01) [.035]**	**.99 (.01) [.030]**
Charlson Comorbidity Index	.98 (.03) [.474]	.99 (.03) [.718]
Partially/fully capitated health plan	.89 (.21) [.629]	.89 (.21) [.618]
Region		
Northeast	Ref	Ref
North Central	1.40 (.33) [.147]	1.39 (.32) [.154]
South	.85 (.20) [.488]	.85 (.20) [.496]
West	1.13 (.29) [.641]	1.12 (.29) [.658]
# Distant sites at diagnosis		
0	Ref	Ref
1	1.15 (.19) [.380]	1.16 (.19) [.352]
2	**2.46 (.55) [<.001]**	**2.46 (.55) [<.001]**
>=3	**3.58 (1.12) [<.001]**	**3.58 (1.11) [<.001]**
Distance to the nearest ipilimumab trial site (100 miles)	1.09 (.11) [.359]	1.09 (.11) [.349]
Surgical resection of metastasis only		
Time of first metastasis diagnosis[a]	.99 (.03) [.737]	1.01 (.02) [.548]
Phase II disclosure	**1.95 (.61) [.033]**	**1.66 (.42) [.048]**
Phase III disclosure	.86 (.42) [.751]	.76 (.20) [.288]
Phase II and time interaction	1.06 (.04) [.175]	
Phase III and time interaction	.96 (.05) [.388]	
Age	1.01 (.005) [.196]	1.01 (.005) [.228]
Charlson Comorbidity Index	**.88 (.03) [<.001]**	**.89 (.03) [<.001]**
Partially/fully capitated health plan	1.12 (.22) [.563]	1.12 (.22) [.567]
Region		
Northeast	Ref	Ref
North Central	1.38 (.28) [.114]	1.37 (.28) [.119]
South	1.15 (.23) [.469]	1.16 (.23) [.454]
West	.91 (.20) [.657]	.90 (.20) [.652]
# Distant sites at diagnosis		

0	Ref	Ref
1	**.50 (.07) [<.001]**	**.50 (.07) [<.001]**
2	**.50 (.12) [.004]**	**.50 (.12) [.004]**
>=3	**.22 (.10) [.001]**	**.22 (.10) [.001]**
Distance to the nearest ipilimumab trial site (100 miles)	1.12 (.09) [.152]	1.21 (.09) [.145]
Systemic therapy and surgical resection of metastasis		
Time of first metastasis diagnosis[a]	.94 (.03) [.114]	1.00 (.02) [.925]
Phase II disclosure	**2.48 (1.14) [.049]**	1.33 (.46) [.406]
Phase III disclosure	.49 (.33) [.283]	1.15 (.40) [.685]
Phase II and time interaction	1.10 (.06) [.087]	
Phase III and time interaction	1.04 (.07) [.559]	
Age	**.97 (.01) [<.001]**	**.97 (.01) [<.001]**
Charlson Comorbidity Index	**.75 (.04) [<.001]**	**.77 (.04) [<.001]**
Partially/fully capitated health plan	1.15 (.32) [.621]	1.13 (.31) [.661]
Region		
Northeast	Ref	Ref
North Central	**2.41 (.71) [.003]**	**2.39 (.70) [.003]**
South	1.44 (.43) [.222]	1.44 (.43) [.210]
West	1.10 (.38) [.783]	1.09 (.37) [.797]
# Distant sites at diagnosis		
0	Ref	Ref
1	**.43 (.08) [<.001]**	**.44 (.08) [<.001]**
2	**.40 (.15) [.015]**	**.40 (.15) [.014]**
>=3	.65 (.31) [.363]	.65 (.31) [.361]
Distance to the nearest ipilimumab trial site (100 miles)	.96 (.11) [.733]	.96 (.11) [.725]

Note. Results in bold are significant at $p<0.05$. Multinomial probit models gave similar results. Model 1 included the interaction between time and phase II disclosure and the interaction between time and phase III disclosure; model 2 did not include such interactions.

[a] Centered at phase II disclosure.

TABLE 2.4: MARGINAL EFFECTS OF PHASE II DISCLOSURE ON THE USE OF SYSTEMIC THERAPY, SURGICAL RESECTION OF METASTASIS, OR BOTH, RELATIVE TO NO TREATMENT

Marginal Effect	**Model 1**	**Model 2**
	Mean (s.e.) [p value]	**Mean (s.e.) [p value]**
Systemic therapy	.04 (.04) [.357]	.02 (.03) [.566]
Surgical resection	.08 (.05) [.126]	.08 (.04) [.082]
Both	.04 (.03) [.167]	.003 (.03) [.919]
No treatment	**-.16 (.06) [.005]**	**-.10 (.05) [.047]**

Note The marginal effect is the difference in the change in utilization between each of the three active treatments and no treatment at the time of the phase II press release. Model 1 included the interaction between time and phase II disclosure and the interaction between time and phase III disclosure; model 2 did not include such interactions.

TABLE 2.S1: RELATIVE RISK RATIOS (RRRS) ESTIMATING THE EFFECTS OF DISCLOSING IPILIMUMAB'S PHASE II AND PHASE III RESULTS ON UTILIZATION OF SYSTEMIC THERAPY, SURGICAL RESECTION OF METASTASIS, OR BOTH, BY INCIDENT METASTATIC MELANOMA PATIENTS IN THE FIRST THREE MONTHS FOLLOWING THEIR FIRST METASTASIS, COMPARED TO NO TREATMENT, EXCLUDING TWO MONTHS BEFORE AND ONE MONTH AFTER EACH DISCLOSURE

Covariates	**Model 1** **Mean (s.e.) [p value]**	**Model 2** **Mean (s.e.) [p value]**
No treatment	Base outcome	Base outcome
Systemic therapy only		
Time of first metastasis diagnosis[a]	.96 (.03) [.183]	.99 (.02) [.550]
Phase II disclosure	1.80 (.73) [.148]	1.40 (.49) [.333]
Phase III disclosure	.85 (.57) [.817]	1.37 (.46) [.343]
Phase II and time interaction	1.06 (.05) [.284]	
Phase III and time interaction	1.01 (.06) [.855]	
Age	.99 (.01) [.068]	.99 (.01) [.059]
Charlson Comorbidity Index	.97 (.03) [.436]	.99 (.03) [.721]
Partially/fully capitated health plan	1.04 (.25) [.859]	1.04 (.25) [.874]
Region		
Northeast	Ref	Ref
North Central	1.41 (.37) [.182]	1.40 (.36) [.197]
South	.94 (.25) [.806]	.94 (.25) [.806]
West	1.15 (.33) [.621]	1.14 (.32) [.656]
# Distant sites at diagnosis		
0	Ref	Ref
1	1.11 (.19) [.567]	1.12 (.19) [.527]
2	**2.16 (.54) [.002]**	**2.16 (.54) [.002]**
>=3	**3.08 (1.03) [.001]**	**3.10 (1.03) [.001]**
Distance to the nearest ipilimumab trial site (100 miles)	.98 (.10) [.882]	0.99 (.10) [.908]
Surgical resection of metastasis only		
Time of first metastasis diagnosis[a]	.99 (.03) [.571]	1.01 (.02) [.681]
Phase II disclosure	**2.24 (.73) [.014]**	**1.87 (.54) [.030]**
Phase III disclosure	.53 (.30) [.262]	.64 (.19) [.126]
Phase II and time interaction	1.05 (.04) [.223]	
Phase III and time interaction	.99 (.05) [.856]	
Age	1.00 (.01) [.634]	1.00 (.01) [.675]
Charlson Comorbidity Index	**.86 (.03) [<.001]**	**.87 (.03) [<.001]**
Partially/fully capitated health plan	1.16 (.25) [.489]	1.15 (.25) [.507]
Region		
Northeast	Ref	Ref
North Central	1.15 (.26) [.531]	1.14 (.26) [.558]
South	1.07 (.24) [.742]	1.08 (.24) [.738]
West	.76 (.19) [.284]	.76 (.19) [.269]

# Distant sites at diagnosis		
0	Ref	Ref
1	**.48 (.07) [<.001]**	**.49 (.07) [<.001]**
2	**.53 (.14) [.017]**	**.53 (.14) [.016]**
>=3	**.22 (.10) [.001]**	**.23 (.11) [.002]**
Distance to the nearest ipilimumab trial site (100 miles)	1.12 (.10) [.198]	1.13 (.10) [.187]
Systemic therapy and surgical resection of metastasis		
Time of first metastasis diagnosis[a]	.94 (.03) [.070]	1.00 (.03) [.910]
Phase II disclosure	2.54 (1.24) [.055]	1.28 (.50) [.535]
Phase III disclosure	.22 (.19) [.079]	1.08 (.42) [.840]
Phase II and time interaction	1.11 (.06) [.082]	
Phase III and time interaction	1.09 (.08) [.240]	
Age	**.97 (.01) [<.001]**	**.97 (.01) [<.001]**
Charlson Comorbidity Index	**.72 (.04) [<.001]**	**.75 (.04) [<.001]**
Partially/fully capitated health plan	1.06 (.33) [.849]	1.04 (.32) [.897]
Region		
Northeast	Ref	Ref
North Central	**1.94 (.63) [.041]**	**1.90 (.62) [.049]**
South	1.12 (.37) [.722]	1.13 (.37) [.719]
West	.87 (.33) [.728]	.87 (.33) [.704]
# Distant sites at diagnosis		
0	Ref	Ref
1	**.45 (.10) [<.001]**	**.46 (.10) [<.001]**
2	.53 (.20) [.102]	.53 (.20) [.099]
>=3	.40 (.23) [.113]	.39 (.23) [.109]
Distance to the nearest ipilimumab trial site (100 miles)	1.00 (.14) [.993]	1.00 (.14) [.974]

Note. Results in bold are significant at $p<0.05$. Multinomial probit models gave similar results. Model 1 included the interaction between time and phase II disclosure and the interaction between time and phase III disclosure; model 2 did not include such interactions.

[a] Centered at phase II disclosure.

TABLE 2.S2: ODDS RATIO ESTIMATING THE EFFECTS OF DISCLOSING IPILIMUMAB'S PHASE II AND PHASE III RESULTS ON THE UTILIZATION OF ANTIHYPERLIPIDEMICS BY THE STUDY POPULATION IN THE STUDY PERIOD, FALSIFICATION TEST

Covariates	**Model 1**	**Model 2**
	Mean (s.e.) [p value]	**Mean (s.e.) [p value]**
Time of first metastasis diagnosis[a]	.96 (.03) [.090]	.99 (.02) [.479]
Phase II disclosure	1.57 (.55) [.197]	1.08 (.29) [.783]
Phase III disclosure	.70 (.34) [.470]	1.57 (.42) [.092]
Phase II and time interaction	1.03 (.05) [.456]	
Phase III and time interaction	1.06 (.05) [.207]	
Age	**1.05 (.005) [<.001]**	**1.05 (.005) [<.001]**
Charlson Comorbidity Index	.97 (.03) [.283]	.98 (.03) [.551]
Partially/fully capitated health plan	.94 (.20) [.771]	.93 (.20) [.746]
Region		
Northeast	Ref	Ref
North Central	.99 (.20) [.972]	.99 (.20) [.966]
South	1.12 (.23) [.572]	1.13 (.23) [.560]
West	**.63 (.15) [.049]**	**.62 (.15) [.046]**
# Distant sites at diagnosis		
0	Ref	Ref
1	.84 (.12) [.219]	.85 (.12) [.245]
2	1.11 (.25) [.627]	1.11 (.25) [.644]
>=3	**.26 (.14) [.013]**	**.26 (.14) [.013]**
Distance to the nearest ipilimumab trial site (100 miles)	.92 (.08) [.312]	.92 (.08) [.319]

Note. Results in bold are significant at $p<0.05$. Model 1 included the interaction between time and phase II disclosure and the interaction between time and phase III disclosure; model 2 did not include such interactions.

[a] Centered at phase II disclosure.

TABLE 2.S3: ODDS RATIOS (ORS) FROM THE LOGISTIC REGRESSION ESTIMATING THE EFFECTS OF DISCLOSING IPILIMUMAB'S PHASE II AND PHASE III RESULTS ON USING ANY ACTIVE TREATMENT (SYSTEMIC THERAPY, SURGICAL RESECTION OF METASTASIS, OR BOTH) BY INCIDENT METASTATIC MELANOMA PATIENTS IN THE FIRST THREE MONTHS FOLLOWING THEIR FIRST METASTASIS

Covariates	**Model 1** **Mean (s.e.) [p value]**	**Model 2** **Mean (s.e.) [p value]**
Time of first metastasis diagnosis[a]	.97 (.02) [.175]	1.00 (.01) [.947]
Phase II disclosure	**2.04 (.53) [.006]**	**1.53 (.33) [.050]**
Phase III disclosure	.73 (.31) [.469]	.97 (.21) [.875]
Phase II and time interaction	1.06 (.03) [.082]	
Phase III and time interaction	1.00 (.04) [.912]	
Age	.99 (.004) [.101]	**.99 (.004) [.013]**
Charlson Comorbidity Index	**.90 (.02) [<.001]**	1.09 (.18) [.598]
Partially/fully capitated health plan	1.04 (.17) [.802]	1.02 (.19) [.927]
Region		
Northeast	Ref	Ref
North Central	**1.53 (.26) [.012]**	**1.52 (.26) [.013]**
South	1.08 (.18) [.621]	1.09 (.18) [.598]
West	1.02 (.19) [.906]	1.02 (.19) [.927]
# Distant sites at diagnosis		
0	Ref	Ref
1	**.62 (.07) [<.001]**	**.62 (.07) [<.001]**
2	.87 (.16) [.466]	.87 (.16) [.453]
>=3	.92 (.26) [.763]	.93 (.26) [.783]
Distance to the nearest ipilimumab trial site (100 miles)	1.08 (.07) [.280]	1.08 (.07) [.266]

Note. Results in bold are significant at $p<0.05$. Multinomial probit models gave similar results. Model 1 included the interaction between time and phase II disclosure and the interaction between time and phase III disclosure; model 2 did not include such interactions.

[a] Centered at phase II disclosure.

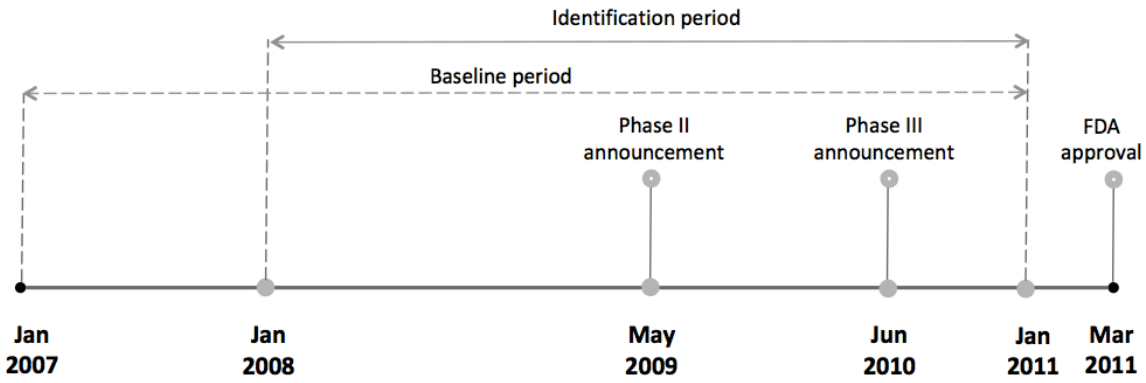

Figure 2.2: Study design

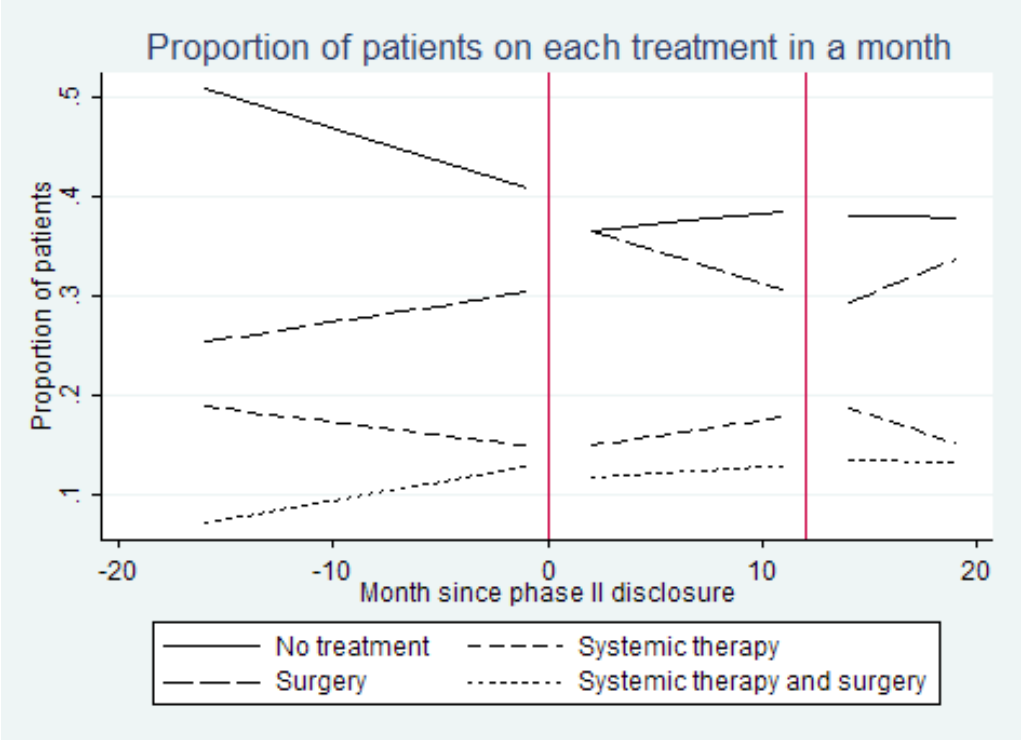

Figure 2.3: Probability of receiving systemic therapy, surgery, both, or neither in the first three months following first metastasis diagnosis by metastatic melanoma patients from 2008-2011. The two red lines represent the phase II and phase III announcements.

2.7 REFERENCE

[1] Neumann PJ, Cohen JT. Measuring the Value of Prescription Drugs. N ENGL J MED 2015:1–4.

[2] Becker B, Murphy K, Philipson T. The Value of Life Near Its End And Terminal Care. Cambridge, MA: 2007.

[3] Trigeorgis L. Real Options and Interactions With Financial Flexibility. Financ Manag 1993;22:202–24.

[4] Smith C. Option pricing. A review. J Financ Econ 1976;3:3–51.

[5] Philipson TJ, Becker G, Goldman D, Murphy KM. Terminal Care And The Value of Life Near Its End. vol. 1. Cambridge, MA: 2010.

[6] Thornton Snider J, Romley JA, Vogt WB, Philipson TJ. The Option Value of Innovation. Forum Health Econ Policy 2012;15.

[7] Sanchez Y, Penrod JR, Qiu XL, Romley J. The Option Value of Innovative Treatments in the Context of Chronic Myloid Leukemia. Am J Manag Care 2012;18:265–79.

[8] Thornton Snider J, Batt K, Wu Y, Tebeka MG, Seabury S. The option value of innovative treatments for non-small cell lung cance and renal cell carcinoma. Am J Manag Care 2017;23:e340–6.

[9] Driffield T, Smith PC. A Real Options Approach To Watchful Waiting: Theory And An Illustration. Med Decis Mak 2007;27:178–88.

[10] Smith R. Use, Option and Externality Values: Are Contingent Valuation Studies in Health Care Mis-specified? Health Econ 2007;16:861–9.

[11] American Cancer Society. Cancer Facts & Figures 2016. 2016.

[12] National Cancer Institute. Drugs Approved for Melanoma. Cancer Treat 2015. http://www.cancer.gov/about-cancer/treatment/drugs/melanoma (accessed July 8, 2016).

[13] U.S. Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. Drug Databases 2016. https://www.accessdata.fda.gov/scripts/cder/drugsatfda/ (accessed August 7, 2016).

[14] Crosby T, Fish R, Coles B, Mason M. Systemic treatments for metastatic cutaneous melanoma. Cochrane Database Syst Rev 2000:CD001215.

[15] Bhatia S, Tykodi S, Thompson J. Treatment of Metastatic Melanoma : An Overview. Oncol Park 2009;23:488–96.

[16] Sasse A, Sasse E, Clark L, Ulloa L, Clark O. Chemoimmunotherapy versus chemotherapy for metastatic malignant melanoma. Cochrane Database Syst Rev 2007:CD005413.

[17] Leung A, Hari D, Morton D. Surgery for distant melanoma metastasis. Cancer J 2012;12:176–84.

[18] Deutsch G, Flaherty D, Kirchoff D, Bailey M, Vitug S, Foshag L, et al. Association of Surgical Treatment, Systemic Therapy, and Survival in Patients With Abdominal Visceral Melanoma Metastases, 1965-2014. JAMA Surg 2017;111:980–4.

[19] Ollila D. Review Complete metastasectomy in patients with stage IV metastatic melanoma. Lancet Oncol 2006;7:919–24.

[20] Morton D, Ollila D, Hsueh E, Essner R, Gupta R. Cytoreductive surgery and adjuvant immunotherapy: a new management paradigm for metastatic melanoma. CA CANCER J CLIN 1999;49:101–16, 65.
[21] Bristol-Myers Squibb. Results from Three Phase 2 Studies Reported a Two-Year Survival Rate Ranging from 30 to 42 Percent in Metastatic Melanoma Patients Treated with Ipilimumab (10 mg/kg) | BMS Newsroom 2009. http://bms.newshq.businesswire.com/press-release/rd-news/results-three-phase-2-studies-reported-two-year-survival-rate-ranging-30-42-pe (accessed March 26, 2017).
[22] Hodi S, O'Day S, McDermott D, Weber R, Sosman J, Haanen J, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N ENGL J MED 2010;362:2251–9.
[23] Bristol-Myers Squibb. Investigational Compound Ipilimumab Demonstrates Improved Overall Survival in Phase 3 Trial of Previously-Treated Patients with Metastatic Melanoma | BMS Newsroom 2010. http://bms.newshq.businesswire.com/press-release/rd-news/investigational-compound-ipilimumab-demonstrates-improved-overall-survival-pha (accessed March 26, 2017).
[24] The National Bureau of Economic Research. ZIP Code Distance Database -- ZIP Code Tabulation Area (ZCTA) Distance Database 2017. http://www.nber.org/data/zip-code-distance-database.html (accessed October 1, 2017).
[25] Hausman J, McFadden D. Specification Tests for the Multinomial Logit Model. Econometrica 1984;52:1219–40.
[26] Ryen L, Svensson M. The Wilingness to Pay for a Quality Adjusted Life Year: A Review of the Empirical Literature. Health Econ 2015;24:1289–301.
[27] Garrison L, Neumann P, Willke R, Basu A, Danzon P, Doshi J, et al. A Health Economics Approach to US Value Assessment Frameworks;Summary and Recommendations of the ISPOR Special Task Force Report [7]. Value Heal 2018;21:161–5.
[28] Tariman J, Berry D, Cochrane B, Doorenbos A, Schepp K. Physician, Patient, and Contextual Factors Affecting Treatment Decisions in Older Adults With Cancer and Models of Decision Making: A Literature Review. Oncol Nurs Forum 2012;39:E70-83.
[29] Song X, Zhao Z, Barber B, Farr A, Ivanov B, Novich M. Overall survival in patients with metastatic melanoma. Curr Med Res Opin 2015;31:987–91.
[30] Markman M, Luce R. Impact of the Cost of Cancer Treatment: An Internet-Based Survey. J Oncol Pract 2010;6:69–73.
[31] Rius-Ottenheim N. The Role of Dispositional Optimism in Physical and Mental Well-Being. In: Efklides A, Moraitou D, editors. A Posit. Psychol. Perspect. Qual. Life. illustrate, Springer Netherlands; 2012, p. 300.

Chapter 3. HOW DOES OPTION VALUE AFFECT THE POTENTIAL COST-EFFECTIVENESS OF A TREATMENT? THE CASE OF IPILIMUMAB FOR METASTATIC MELANOMA

3.1 ABSTRACT

Background. Innovations that extend life can generate option value and cost of experiencing future technologies.

Objectives. To understand how consideration of option value may affect the potential cost-effectiveness of a treatment, through a case study of ipilimumab for previously untreated metastatic melanoma.

Methods. We estimated the cost-effectiveness of ipilimumab in two scenarios: a conventional scenario, with a model constructed using the standard methods that rely on efficacy data directly from the phase III trial of ipilimumab, and an option value scenario, that incorporates future hypothetical improvements in mortality for metastatic melanoma due to innovations. We developed two approaches to incorporating option value. The first approach projected mortality improvements based on historical trends from the Surveillance, Epidemiology, and End Results Program registry. The second, alternative approach identified drugs being studied in clinical trials at the time of ipilimumab's approval on clinicaltrials.gov and estimated their likelihood and timing of approval as well as their potential efficacy and cost. We accounted for increases in overall cancer treatment cost and unrelated medical cost in the option value scenario.

Results. In the option value scenario, using the SEER approach, the incremental QALY gained and the incremental cost increased by 6.3% and 3.8%, respectively, while the ICER decreased by 2.3%, compared to the conventional scenario. Using the

clinicaltrials.gov approach, the incremental QALY gained and the incremental cost increased by 7.5% and 7.1%, respectively, while the ICER decreased by 0.4%. *Conclusions.* We developed generalizable approaches to estimating option value in cost-effectiveness analysis.

3.2 BACKGROUND

The past two decades have witnessed a sharp increase in the use of cost-effectiveness analysis (CEA) to assess the value of medical technologies. Many of these analyses were conducted on newly approved medicines based on efficacy and safety data from their pivotal trials, with the goal of influencing decision-making on their pricing, reimbursement, and utilization. Many of these models adopted a time horizon that was longer than the length of the pivotal trial, and one challenge brought by a long time horizon is whether and how to account for future technology advancement, both related and unrelated to the disease and treatments under study. Most CEAs to date have simply ignored this issue, and as a result, they may have omitted the potential "option value" of some life-extending treatments, which is the opportunity to benefit from future innovations during the extended life.[1,2]

In the healthcare value assessment literature, a few studies have estimated the option value of existing medical technologies. Philipson et al. examined the case for mono-therapy zidovudine (AZT) for HIV/AIDS patients, which can improve life expectancy by a few months to 1.6 years, before the advent of the highly active antiretroviral therapy (HAART), which can improve life expectancy by about 10 years.[3] They estimated the

"*ex post*" option value of AZT to be as much as 400% of the conventional value in cohorts of HIV/AIDS patients diagnosed right before the arrival of HAART.[3] Sanchez et al. examined the case of tyrosine kinase inhibitors for chronic myelogenous leukemia, and estimated the option value from future medical innovation to be equivalent to 9% of the average survival gains from existing treatments.[4] In a similar study, Thornton Snider et al. estimated the option value of nivolumab to be 18%, 5%, and 10% of the conventional value for renal cell carcinoma, squamous non-small cell lung cancer (NSCLC), and nonsquamous NSCLC.[5]

This small literature on quantifying option value for medical technologies has demonstrated that in cases where the main goal of treatment is life extension and the speed of innovation is rapid, option value may not be negligible. However, none of the existing studies addressed the issue of how option value of a new medical technology can be estimated in a CEA conducted *at the time of its regulatory approval*, when the only data on the new technology are from its pivotal trials and when cost-effectiveness information is needed to aid pricing and reimbursement decisions. In this study, we used ipilimumab for the treatment of previously untreated metastatic melanoma to demonstrate how to account for option value from technology advancement in a CEA and how it may affect the potential cost-effectiveness of a treatment.

Ipilimumab was the first metastatic melanoma drug that has demonstrated significant survival benefit over placebo in randomized controlled trials.[6,7] Since its approval in 2011, seven additional new molecules have been approved to treat metastatic melanoma

either as a monotherapy or as a part of a combination therapy, and nearly all demonstrated significantly superior overall survival benefit over either chemotherapies or ipilimumab in their phase III trials.[8–16] For metastatic melanoma patients, ipilimumab in itself can prolong survival and improve quality of life (before progression), and these constitute the value of ipilimumab captured by a conventional CEA. However, longer survival can also give patients the opportunity to benefit from later innovations, and this is the potential option value of ipilimumab.

In this study, we estimated the cost-effectiveness of ipilimumab in two scenarios: the *conventional scenario* and the *option value scenario*. In the conventional scenario, we constructed the cost-effectiveness model using the standard methods that rely on efficacy data directly from the phase III trial of ipilimumab. In the option value scenario, we projected future improvement in mortality for metastatic melanoma patients and incorporated it in the CEA. We used data available by 2011, when ipilimumab was granted approval by the FDA, and estimated the *ex ante* option value of ipilimumab. The goal for this study was to illustrate how option value can be estimated for a new drug when initial decision on pricing and reimbursement is made.

3.3 METHODS

Model Structure

A Markov model consisting of three health states – progression-free survival (PFS), progressive disease, and death (**Figure 3.1**) – was constructed in Microsoft Excel™ to estimate the cost and quality-adjusted life-years (QALYs) on ipilimumab plus dacarbazine vs, dacarbazine alone under the two scenarios. The model's population started in PFS, and can transition to progressive disease, directly to death, or stay progression-free in each cycle. Those in the progressive disease state can either transition to death or stay in progressive disease in each cycle. Complete or partial response was modeled as a sub-state of the PFS in which patients have a different utility but the same cost. The model had a cycle length of one month and a lifetime horizon for a typical patient of 57 years old. The analysis was conducted from the health system's perspective.

Study Population

The patient population for this study was previously untreated patients with unresectable stage III or stage IV melanoma who initiated ipilimumab plus dacarbazine or placebo plus dacarbazine.

Dosing

Dosing and frequency of administration for each arm in the Markov model reflected those in the phase III trial: patients received either ipilimumab (10 mg/kg) plus dacarbazine (850 mg/m^2) or dacarbazine (850 mg/m^2) plus placebo at weeks 1, 4, 7, and 10, followed by dacarbazine alone every 3 weeks through week 22 (induction phase), and

ipilimumab or placebo every 12 weeks starting from week 24.[6] Treatments were discontinued if any of the following occurred: progression of the disease, development of drug-related adverse events, or the end of the study.[6] In the trial, approximately 34% of patients in the ipilimumab group and 4% in the dacarbazine group discontinued the study drug due to a drug-related adverse event in the induction phase; 9.3% in the ipilimumab group and none in the dacarbazine group discontinued their therapy after receiving treatment in the maintenance phase.[6]

Transition Probabilities: Conventional Scenario

The monthly transition probabilities for the conventional scenario were derived directly from the phase III trial. As indicated by the Kaplan-Meier (KM) overall survival (OS) curves in the publication, a large amount of censoring happened in the fourth (last) year of the trial and approximately 20% of study participants did not have the event of interest (death) by the end of the trial.[6] As a result, extrapolation of mortality beyond the trial follow-up was required. Standard parametric methods were first attempted, but they provided poor fit to the actual survival data for both arms. Given the clear plateau of the KM OS curves at the tails, we assumed that the patients who survived through the end of the trial were "cured" and died at the same rate as the general population of the same birth cohort after the trial ended. Extrapolations of PFS curves were not needed, as no study participant remained progression-free by the end of the trial. The monthly transition probabilities during the trial period were calculated nonparametrically using the published PFS and OS curves for each arm. Furthermore, we used mortality of the

general population from the Social Security Actuarial Life Table to approximate death rates while on PFS.[17]

Transition Probabilities: Option Value Scenario

We assumed the rates of progression on each treatment in the option value scenario were the same as in the conventional scenario. We approximated death rates while on PFS in the same way as in the conventional scenario by using the Social Security Actuarial Life Table.[17] The key difference in the option value scenario relative to the conventional scenario is that mortality on progressive disease was lower to account for the effect of technology advancement on mortality. We developed two approaches – one based on historical trends (SEER approach) and the other on likely future drug approvals (clinicaltrials.gov approach). In the SEER approach, we assumed mortality on progressive disease decreased continuously over time. We estimated the mortality trends for metastatic melanoma using the Surveillance, Epidemiology, and End Results Program (SEER) registry.[18] We selected patients using the following criteria: (1) diagnosed between 1988 and 2010; (2) had a primary site of melanoma of the skin; (3) were at regional or distant stage at diagnosis; (4) were at least 18 years old at diagnosis; and (5) were not recommended surgery. We fit a Cox proportional hazard model to all-cause mortality in the first four years following diagnosis, with the year of diagnosis as the main predictor of interest. We adjusted for age, sex, marital status, race, ethnicity, and number of tumors in each regression. In the regression, the hazard ratio (HR) of being diagnosed one year later on all-cause mortality was 0.964 (95% CI: 0.955-0.973; $p<0.001$;

Table 3.S3). This indicated that the hazard of all-cause death of metastatic melanoma patients decreased by 3.6% annually from 1988 to 2010. We applied the HR to the OS of the dacarbazine arm and calculated the decrease in mortality on progressive disease. We then applied this decrease to the mortality on progressive disease in the ipilimumab arm. We also fit a Cox proportional hazard model to other-cause mortality in the same population and found no significant trend in hazard over time. This indicated that the improvement in mortality in this population came primarily from the improvement in cancer-specific mortality. Finally, beyond four years, we made the same assumption as in the conventional scenario that survivors in both treatment and control arms died at the same rate as the general population of the same birth cohort.

In the clinicaltrials.gov approach, we assumed that mortality on progressive disease in the option value scenario is the same as in the phase III trial until a new treatment for metastatic melanoma becomes available. We further assumed that once a new treatment that improves OS (compared to best supportive care) becomes available, the mortality on progressive disease will decrease to the level of the new treatment. To project new arrivals in metastatic melanoma, we systematically reviewed phase III clinical trials registered on clinicaltrials.gov. The inclusion criteria included: (1) unresectable stage III or stage IV melanoma; (2) interventional studies; (3) adult (>=18 years old) population; (4) phase III; (5) study start date between January 01, 2001 and March 28, 2011; (6) compared a new molecule entity or gene therapy to a placebo or an active pharmacological treatment; and (7) included at least one site in the US. Exclusion criteria included: (1) stage I/II; (2) resectable stage III; (3) adjuvant setting; (4) did not report a

start date; (5) start date was before 2001; (6) completed or terminated before January 2010; (7) status was missing; (8) extended use study; and (9) experimental drug was ipilimumab.

Six phase III studies registered on clinicaltrials.gov met our inclusion and exclusion criteria (**Table 3.S6**). We identified their phase II studies and extracted the response rates of the treatments under investigation (**Table 3.S6**). Allovectin-7 and CP-675,206 had a response rate of 11% and 7% in their phase II testing, respectively, and were therefore excluded as DiMasi et al. found that investigational cancer drugs from 1990 to 2005 that had a response rate of $\leq$ 13.8% in their phase II studies had a 2.5% probability of being approved by the FDA. For the remaining four investigational drugs in phase III testing when ipilimumab was approved, we assumed the likelihood of approval is equal at 77% and estimated their potential FDA approval dates (**Table 3.S7**).[19,20] From thEse estimated approval dates, the rate of new drug arrival in metastatic melanoma from 2011 to 2014 is roughly one in every seven months, with a probability of approval at 77%. We also compared our projection with actual approvals (**Table 3.S8**). We further extracted median OS from the phase II studies of the four investigational drugs, and instead of using the average OS from the four phase II studies (14.5 months), we used the smallest OS (13 months) to get a conservative estimate and to account for the possibility that effect estimates from non-randomized phase II studies may be larger than those from their randomized phase III studies (**Table 3.S7**).

We assumed hazard ratio is the inverse of the ratio of median survivals.[21] In the base

case, we assumed that 60% of patients on progressive disease will initiate another line of therapy once a new treatment arrives.[6] Similar to the first approach, we assumed those who survived beyond four years in both treatment and control arms died at the same rate as the general population of the same birth cohort. The OS curves in the conventional and the option value scenarios were presented in **Figures 3.4-3.7**.

Other Clinical Inputs

In addition to the OS and PFS data, the following clinical parameters from the trial were used in the model: the proportion of patients who had grade III or IV adverse events for each arm, the proportion of patients who had complete or partial response, and the proportion of patients who had stable disease. We included adverse events that affected at least 5% of patients in either arm. A list of clinical, cost, and utility inputs was summarized in **Table 3.S1**.

Cost Inputs: Conventional Scenario

Four categories of costs were included in the conventional scenario: ipilimumab or dacarbazine drug and administration costs, disease management costs while progression-free, costs of treating drug-related adverse events, and post-progression treatment cost. Drug unit costs were taken from AnalySource and the literature.[22,23] The costs of administration were taken from the CMS Physician Fee Schedule.[24] Disease management costs in the PFS state incorporated the costs of monitoring patients and

managing their symptoms and were treatment-specific.[23] Costs per adverse event episode and post-progression treatment cost were derived from the literature.[23,25]

Cost Inputs: Option Value Scenario

Costs in the option value scenario differed from those in the conventional scenario in a number of ways. First, we assumed the medical care inflation-adjusted cost of overall cancer care increased 0.33% annually.[26] This estimated was derived from a published retrospective analysis of Medicare and Commercially Insured Population Claim Data.[26] Second, we assumed annual unrelated medical cost for this patient population was $2,395 and did not increase above the inflation of medical care.[27] Third, in the clinicaltrials.gov approach to projecting mortality on progressive disease, we projected the costs of new arrivals using a model developed by Howard et al. on pricing for anticancer drugs.[28] All costs were adjusted to 2011 US dollars using the Consumer Price Index medical component.[29]

Utility Inputs

Utility for each health state and disutility associated with each grade III/IV adverse event were taken from a societal preference elicitation study for advanced melanoma.[30] We assumed each severe adverse event lowered the patient's quality of life for one month.

Base Case Analysis

We calculated the incremental costs, QALYs, and cost-effectiveness ratios (ICERs) of ipilimumab plus dacarbazine vs. dacarbazine alone under both the conventional and the option value scenarios. We also calculated the changes in incremental costs, QALYs, and ICERs from the conventional scenario to the option value scenario. Discount rates were set at 3% for both costs and outcomes.

Scenario Analysis

In scenario analysis, we varied ipilimumab's efficacy (HR of OS relative to dacarbazine) by +/- 20% and examined its impact on the change in incremental QALY gained from the conventional scenario to the option value scenario.

Sensitivity Analysis

We conducted one-way and probabilistic (PSA) sensitivity analyses on the change in ICER from the conventional scenario to the option value scenario. We conducted 10,000 simulations in the PSA.

3.4 RESULTS

Base Case

The base case results were summarized in **Tables 3.1-3.3**. In the conventional scenario, the incremental QALY gained of ipilimumab plus dacarbazine vs. dacarbazine alone was 0.76. In the option value scenario, it increased by 6.3% to 0.81 using the SEER approach and by 7.5% to 0.82 using the clinicaltrials.gov approach.

In the conventional scenario, the incremental cost of ipilimumab was $175,087 and $171,823, with and without unrelated medical cost. In the option value scenario, the incremental costs increased by 3.8% and 3.7% to $181,742 and $178,256 using the SEER approach, and by 7.1% and 7.0% to $187,432 and $183,907 using the clinicaltrials.gov approach.

In the conventional scenario, the ICERs of ipilimumab, with and without unrelated medical costs, were $229,249/QALY and $224,975/QALY, respectively. In the option value scenario, the ICERs decreased by 2.43% and 2.38% to $223,791/QALY and $219,498/QALY using the SEER approach, and by 0.43% and 0.41% to $228,313/QALY and $224,019/QALY using the clinicaltrials.gov approach.

Scenario Analysis

The smaller the HR of ipilimumab, the greater the percent increase in incremental QALY gained in the option value scenario (**Figure 3.2**).

Sensitivity Analysis

In one-way sensitivity analysis, annual increase in cancer treatment cost, ipilimumab cost per administration, HR associated with being diagnosed one year later, and OS on new second-line treatment had the biggest impacts on the change in ICER from the conventional scenario to the option value scenario (**Figures 3.8-3.11**). In PSA, the 5-95 percentiles of the absolute change in ICER, with and without unrelated medical cost, were negative $11,259/QALY to $4,538/QALY and negative $11,274/QALY to $4,524/QALY using the SEER approach, and negative $6,855/QALY to $14,826/QALY and negative $6,890/QALY to $14,810/QALY using the clinicaltrials.gov approach (**Table 3.3**).

3.5 DISCUSSION

In this study, we developed a framework for incorporating the option value of life-extending treatment into a CEA, and applied this framework to the case of metastatic melanoma. We found that for the case of ipilimumab, the incremental QALYs gained increased by 6-8% and the ICER decreased by 0%-2%, after accounting for option value from technology advancement. Assuming a $150,000/QALY threshold, the results of this study suggest that a "value-based" price of ipilimumab could increase by $7,500 - $9,000 above $114,000 per course of treatment.[31] While economic theory suggests the presence of option value in the context of medical treatment, this source of value has been ignored in the practice of CEA thus far. This is to our knowledge the first study that incorporated option value in an *ex ante* CEA and estimated its potential impact on the cost-effectiveness of a treatment.

The main challenge with estimating option value is projecting future improvement in survival and the costs of future treatments. In our case study, we developed two alternative approaches to this projection and obtained similar results qualitatively and quantitatively. Our estimates of percent change in incremental QALY were similar to previous *ex ante* estimates on incremental survival gain due to technology advancement in other metastatic cancers.[4,5]

However, unlike previous studies, we conducted our analysis in a CEA in the context of estimating potential cost-effectiveness for new medical technologies prior to launch. Our approach has several advantages. First of all, it allowed us to quantify the cost implications of accounting for technology advancement. In our case, costs related to melanoma increased significantly in the option value scenario, due to rising cancer treatment cost and the high cost of new second-line treatment. In the base case, the higher incremental costs nearly offset the greater incremental QALYs in the option value scenario. Secondly, it allowed us to quantify the overall uncertainty on the estimate of the change of ICER. Last but not least, CEA is frequently used for assessing the value of new medical technologies with the goal of guiding pricing and reimbursement decisions. By estimating option value in a CEA, our analysis provides a useful and familiar tool for decision-makers.

Recent developments in healthcare value assessments have expanded the definition of value for medical technologies.[2,32] Comprehensive estimation of value is critical for

setting the price that can achieve efficient resource allocation within the current budget as well as for sending the correct signal to manufacturers about potential rewards for future innovations. The concept of option value is particularly important in disease areas where the main goal of treatment is life extension and the rate of innovation is rapid. While our analysis is tailored to the specific context of metastatic melanoma, our methodologies can be easily applied to other metastatic cancers as well as other disease areas. In this study, we presented an "augmented" CEA, and calculated the ICERs with and without considering the potential option value of ipilimumab.[2,33] In addition to this approach, option value can also be converted to net monetary benefit with a willingness-to-pay threshold, or included as a separate element of value alongside the conventional cost-per-QALY estimate in an Impact Inventory or in a multi-criteria decision-analysis.[34–37] Including option value when making pricing or coverage decisions may change the ranking of technologies.

There are several limitations of this study that are worth noting. First, we did not include potential quality-of-life improvement from technology advancement and assumed that the increase in incremental QALYs came solely from reduced mortality. This gave us a conservative estimate of the change in incremental QALYs, and a conservative estimate of the change in ICER. Second, in the SEER approach to projecting future reductions in mortality for metastatic melanoma, we used historical data before 2011 and assumed historical trend will continue into the future. However, the rate of new drug approval for metastatic melanoma has accelerated since the approval of ipilimumab in 2011. Our approach that used historical data likely gave us a conservative estimate of the real

improvement in mortality after 2011. Third, in the clinicaltrials.gov approach, we limited our search of clinical trials to phase III studies for projecting new arrivals. By doing this, we ignored the possibility of new arrivals being approved without a Phase III study. For future practice, the review can be potentially expanded to include phase I and phase II trials and can be combined with expert opinions and an analysis of the FDA's Fast Track, Breakthrough Therapy, and Accelerated Approval programs. However, analysts will likely need to balance the accuracy of estimation with practical limits. Fourth, in the review of clinicaltrials.gov, we only included trials that compared a new molecule entity or novel gene therapy to a placebo (usually chemotherapy). Since off-label use is common in oncology, the benefits of off-label use of drugs approved for other cancers were likely captured in the ipilimumab trial data. However, it's possible that getting FDA approval will lead to greater uptake of a drug, which may confer greater benefit than being used off-label at the population level. Fifth, in the clinicaltrials.gov approach, we assumed that after the new second-line treatment arrives, a certain percentage of patients will be able to benefit from it, regardless of when they developed progressive disease. In the real world, newly progressed patients may benefit more from a subsequent therapy than those who had disease progression a few months ago. To account for the potential difference, a separate health state for second-line treatment may be needed. Our simplified approach likely gave a conservative estimate for the change in incremental QALY gained, as progression on the control arm dacarbazine is faster, and by the time the new second-line treatment arrives, dacarbazine patients on average have spent more time in the progressive disease state. Last but not least, this research does not address the issue of how to apportion option value. Option value is created by the combination of life

extension from the current treatment and further reductions in mortality and/or morbidity from future innovations, and it is difficult to determine their relative contributions. Though not able to provide an answer to this question, our study can be viewed as the critical first step to address it.

In conclusion, in this study, we developed methods for incorporating option value into standard CEAs, and provided one example of their application. The study results underscored the need for private and public payers to be aware of attributes of treatment that are not reflected in traditional value metrics. Further research is needed on how to reward option value among the emerging new treatments, which are economic complements to prior treatments.

3.6 TABLES AND FIGURES

TABLE 3.1: BASE CASE RESULTS – COSTS, QALYS, AND ICERS IN CONVENTIONAL AND OPTION VALUE SCENARIOS

	QALY Gained	Total Cancer Cost, $	Total Healthcare Cost[a], $
Conventional Scenario			
Ipilimumab+dacarbazine	2.29	275,156	284,780
Dacarbazine	1.53	103,333	109,694
Incremental	0.76	171,823	175,087
ICER, $/QALY		224,975	229,249
Option Value Scenario – SEER Approach			
Ipilimumab+dacarbazine	2.61	308,056	319,153
Dacarbazine	1.80	129,801	137,411
Incremental	0.81	178,256	181,742
ICER, $/QALY		219,498	223,791
Option Value Scenario – Clinicaltrials.gov Approach			
Ipilimumab+dacarbazine	2.71	356,867	368,408
Dacarbazine	1.89	172,960	180,977
Incremental	0.82	183,907	187,432
ICER, $/QALY		224,019	228,313

[a] Total healthcare cost included unrelated medical cost.

TABLE 3.2: BASE CASE RESULTS – ABSOLUTE AND PERCENT DIFFERENCES IN COSTS, QALYS, AND ICERS BETWEEN OPTION VALUE AND CONVENTIONAL SCENARIOS

	QALY (%)	Total Cancer Cost, $ (%)	Total Healthcare Cost[a], $ (%)
SEER Approach			
Ipilimumab+dacarbazine	0.32 (13.9)	32,900 (12.0)	34,373 (12.1)
Dacarbazine	0.27 (17.7)	26,467 (25.6)	27,717 (25.3)
Incremental	0.05 (6.3)	6,433 (3.7)	6,655 (3.8)
ICER, $/QALY (%)		-5,478 (-2.43)	-5,458 (-2.38)
Clinicaltrials.gov Approach			
Ipilimumab+dacarbazine	0.42 (18.1)	81,710 (29.7)	83,628 (29.4)
Dacarbazine	0.36 (23.5)	69,627 (67.4)	71,283 (65.0)
Incremental	0.06 (7.5)	12,084 (7.0)	12,345 (7.1)
ICER, $/QALY (%)		-956 (-0.43)	-936 (-0.41)

[a] Total healthcare cost included unrelated medical cost.

TABLE 3.3: SIMULATED VALUES FOR DIFFERENCE IN ICERS BETWEEN OPTION VALUE AND CONVENTIONAL SCENARIOS

	Change in ICER, $/QALY		
	Base Case Value[b]	**Mean Value**[c]	**5-95 Percentile**
SEER Approach			
Total cancer cost	-5,478	-5,288	-11,274 – 4,524
Total healthcare cost[a]	-5,458	-5,268	-11,259 – 4,538
Clinicaltrials.gov Approach			
Total cancer cost	-956	2,051	-6,890 – 14,810
Total healthcare cost[a]	-936	2,068	-6,855 – 14,826

[a] Total healthcare cost included unrelated medical cost.
[b] Base case value is the same as in Table 3.2.
[c] Mean value is the mean of the 10,000 simulations.

TABLE 3.S1: CLINICAL, COST, AND UTILITY INPUTS

Parameter	Base case	95% CI	Distribution	Source
General				
Age at diagnosis	57 years			[6]
Percent female	40%			[6]
Average body surface area	1.78 m^2			[38]
Year of analysis	2011			
Months until the next arrival	7	6.7 – 9.7	Normal	Analysis
Probability of approval	77%	74% – 100%	Beta	[19]
Overall survival on new 2L drug	13	7.9-18.1	Normal	[39–43]
Percent of patients on progressive disease initiating new 2L drug	60%	40% - 80%	Beta	[6]
Discount rate	3%			
Dosing				
Ipilimumab	3 mg/kg			[6]
Dacarbazine	850 mg/m^2			[6]
Efficacy				
Ipilimumab complete response	1.6%			[6]
Dacarbazine complete response	0.8%			[6]
Ipilimumab partial response	13.6%			[6]
Dacarbazine partial response	9.5%			[6]
Ipilimumab stable disease	18.0%			[6]
Dacarbazine stable disease	19.8%			[6]
Trend in melanoma hazard				
Hazard ratio of being diagnosed one year later	0.968	0.954 – 0.974	Normal	Analysis
Treatment discontinuation due to adverse events				
Ipilimumab, induction	34%			[6]
Dacarbazine, induction	4%			[6]
Ipilimumab, induction	9%			[6]
Dacarbazine, induction	0%			[6]
Grade 3/4 adverse events				
Fatigue, ipilimumab	10.9%			[6]
Fatigue, dacarbazine	4.8%			[6]
Increase in liver enzymes, ipilimumab	21.9%			[6]
Increase in liver enzymes, dacarbazine	1.2%			[6]
Costs				
Ipilimumab cost per administration	30,000	18,240 – 41,760	Gamma	[23]
Dacarbazine cost per administration	91	55 – 126		[22]

Cost per treatment course, new 2L treatment	140,617	85,495 – 195,738	Gamma	[28]
Chemotherapy administration, first hour	117			[24]
Chemotherapy administration, additional hour	24			[24]
Chemotherapy administration, additional drug	55			[24]
Monthly disease management cost, ipilimumab	822			[23]
Monthly disease management cost, dacarbazine	1,518			[23]
Monthly cancer cost on progressive disease	3,578	2,175 – 4,981	Gamma	[27,44,45]
Annual unrelated medical cost	2,395	1,456 – 3,334	Gamma	[27]
Cost of treating severe fatigue	2,069			[23]
Cost treating increase in liver enzymes	3,540			[25]
Annual increase in cancer treatment cost, inflation-adjusted	0.33%	0% - 1.21%	Beta	[26]
Utilities				
Complete/partial response	0.88			[30]
Stable disease	0.80			[30]
Progressive disease	0.52			[30]
Elevated liver enzymes	-0.17			[30]
Severe fatigue	-0.17			[30]

TABLE 3.S2: CHARACTERISTICS OF UNRESECTABLE STAGE III/IV MELANOMA PATIENTS, SEER 1988-2010

Variable	Value (N=1,529)
Age at diagnosis, mean (SD)	64.6 (15.3)
Sex, n (%)	
Male	1,040 (68.0)
Female	489 (32.0)
Marital status, N (%)	
Unmarried	591 (38.7)
Married	938 (61.3)
Race, N (%)	
White	67 (4.4)
Non-white	1,462 (95.6)
Ethnicity, N (%)	
Non-Hispanic	1,489 (97.4)
Hispanic	40 (2.6)
Number of tumors at diagnosis, N (%)	
0	1,148 (75.1)
1	49 (3.2)
2	269 (17.6)
>=3	63 (4.1)

TABLE 3.S3: COEFFICIENTS FROM COX PROPORTIONAL HAZARD REGRESSION ON ALL-CAUSE MORTALITY (IN THE FIRST FOUR YEARS AFTER DIAGNOSIS) OF UNRESECTABLE STAGE III/IV MELANOMA PATIENTS, SEER 1988-2010

Variable	Hazard ratio	95% Confidence interval	P-value
Diagnosis year	0.964	0.955-0.973	<0.001
Age at diagnosis	1.010	1.005-1.014	<0.001
Female	0.863	0.760-0.981	0.024
Married	0.927	0.820-1.046	0.219
White	1.181	0.881-1.584	0.265
Hispanic	1.240	0.857-1.794	0.254
Number of tumors	0.941	0.881-1.004	0.065

TABLE 3.S4: COEFFICIENTS FROM COX PROPORTIONAL HAZARD REGRESSION ON MELANOMA-SPECIFIC MORTALITY (IN THE FIRST FOUR YEARS AFTER DIAGNOSIS) OF UNRESECTABLE STAGE III/IV MELANOMA PATIENTS, SEER 1988-2010

Variable	Hazard ratio	95% Confidence interval	P-value
Diagnosis year	0.962	0.952-0.973	<0.001
Age at diagnosis	1.007	1.002-1.011	0.004
Female	0.857	0.739-0.992	0.039
Married	0.930	0.809-1.070	0.311
White	1.129	0.811-1.573	0.472
Hispanic	1.051	0.666-1.658	0.830
Number of tumors	0.165	0.118-0.231	<0.001

TABLE 3.S5: COEFFICIENTS FROM COX PROPORTIONAL HAZARD REGRESSION ON OTHER-CAUSE MORTALITY (IN THE FIRST FOUR YEARS AFTER DIAGNOSIS) OF UNRESECTABLE STAGE III/IV MELANOMA PATIENTS, SEER 1988-2010

Variable	Hazard ratio	95% Confidence interval	P-value
Diagnosis year	0.970	0.925-1.018	0.219
Age at diagnosis	1.059	1.035-1.083	<0.001
Female	0.604	0.313-1.165	0.132
Married	1.061	0.574-1.961	0.849
White	0.450	0.176-1.146	0.094
Hispanic	5.365	1.898-15.16	0.002
Number of tumors	0.357	0.193-0.660	0.001

TABLE 3.S6: ELIGIBLE PHASE III TRIALS REGISTERED ON CLINICALTRIALS.GOV BETWEEN JANUARY 2001 AND MARCH 2011

Investigational drug	Phase III start date	Patient population	Comparator	Response rate in phase II
GSK1120212	Nov 2010	BRAF V600E/K mutation-positive advanced or metastatic melanoma	Chemotherapy	25%
Talimogene Laherparepvec	Apr 2009	Unresectable stage III or stage IV melanoma	GM-CSF	28%
Vemurafenib	Jan 2010	Previously untreated unresectable stage III or stage IV melanoma with BRAF V600E mutation	Dacarbazine	53%
GSK2118436	Dec 2010	Previously untreated advanced or metastatic melanoma with BRAF mutation positive	Dacarbazine	59%
Allovectin-7	Oct 2006	Recurrent stage III or IV melanoma	Dacarbazine or temozolomide	11%
CP-675,206	Mar 2006	Previously untreated metastatic melanoma	Dacarbazine or temozolomide	7%

GM-CSF: Granulocyte macrophage colony stimulating factor

TABLE 3.S7: PROJECTED DEVELOPMENT TIMELINE OF INCLUDED INVESTIGATIONAL TREATMENTS

Investigational drug	Phase III start date	Phase III primary completion date, if before March 2011	Estimated FDA approval date	Probability of FDA approval	OS in phase II, months
GSK1120212	Nov 2010		Jan 2014	77%	14.2
Talimogene Laherparepvec	Apr 2009		May 2012	77%	14.7
Vemurafenib	Jan 2010	Dec 2010	Jul 2011	77%	15.9
GSK2118436	Dec 2010		Feb 2014	77%	13

Note We assumed that the average time from the start of a phase III study to the start of NDA/BLA submission is 31 months, and the average time of FDA regulatory review is 7 months.

TABLE 3.S8: ESTIMATED VS. ACTUAL FDA APPROVAL DATE FOR INCLUDED INVESTIGATIONAL TREATMENTS

Investigational drug	Estimated FDA approval date	Actual FDA approval date
Vemurafenib	Jul 2011	Aug 2011
Talimogene Laherparepvec	May 2012	Not approved
GSK1120212 (Trametinib)	Jan 2014	May 2013
GSK2118436 (Dafrafenib)	Feb 2014	May 2013

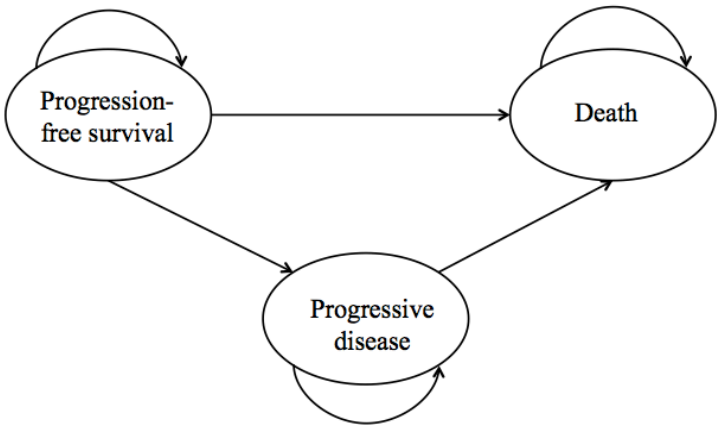

Figure 3.1: Markov model structure

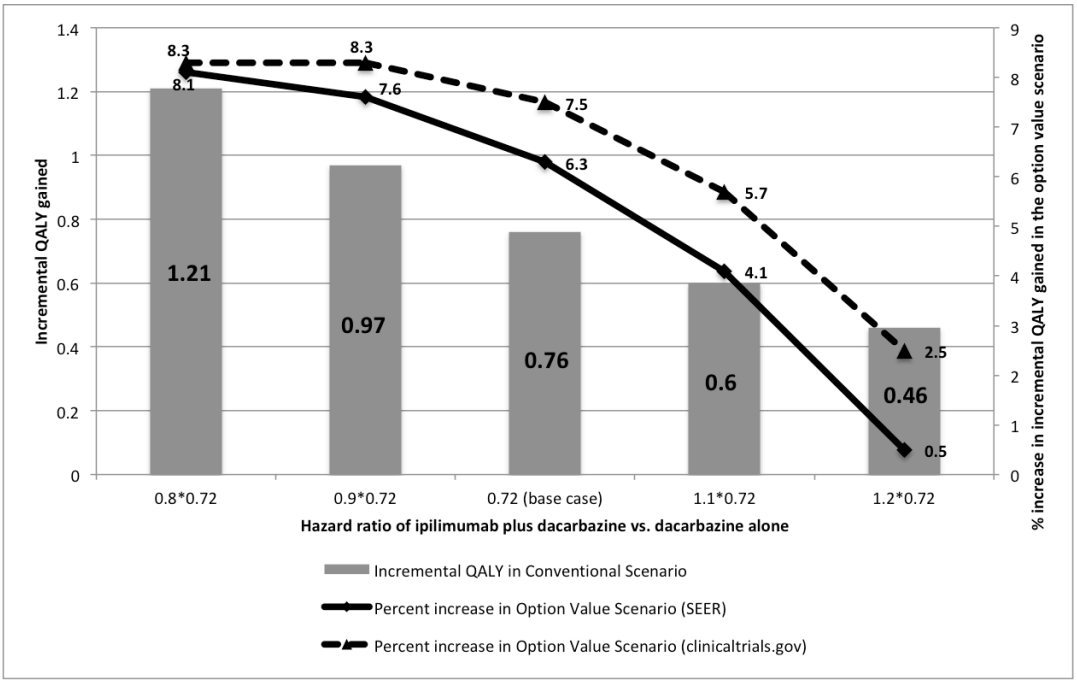

Figure 3.2 Scenario analysis of ipilimumab's efficacy (hazard ratio of all-cause mortality relative to dacarbazine) and the change in incremental QALY gained from the conventional scenario to the option value scenario. In the clinical trial (base case), the hazard ratio of ipilimumab was 0.72

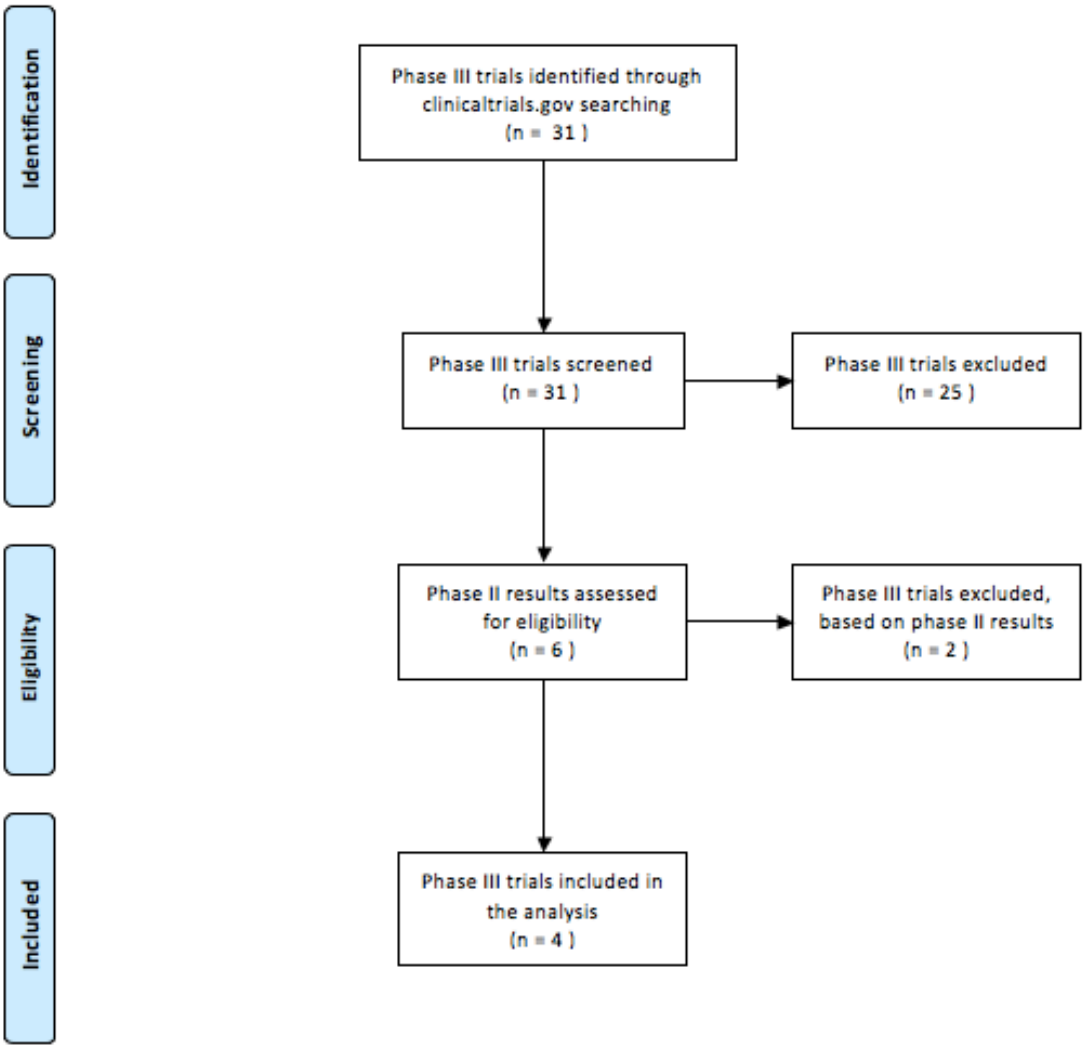

Figure 3.3: Flow chart for systematic review of clinicaltrials.gov

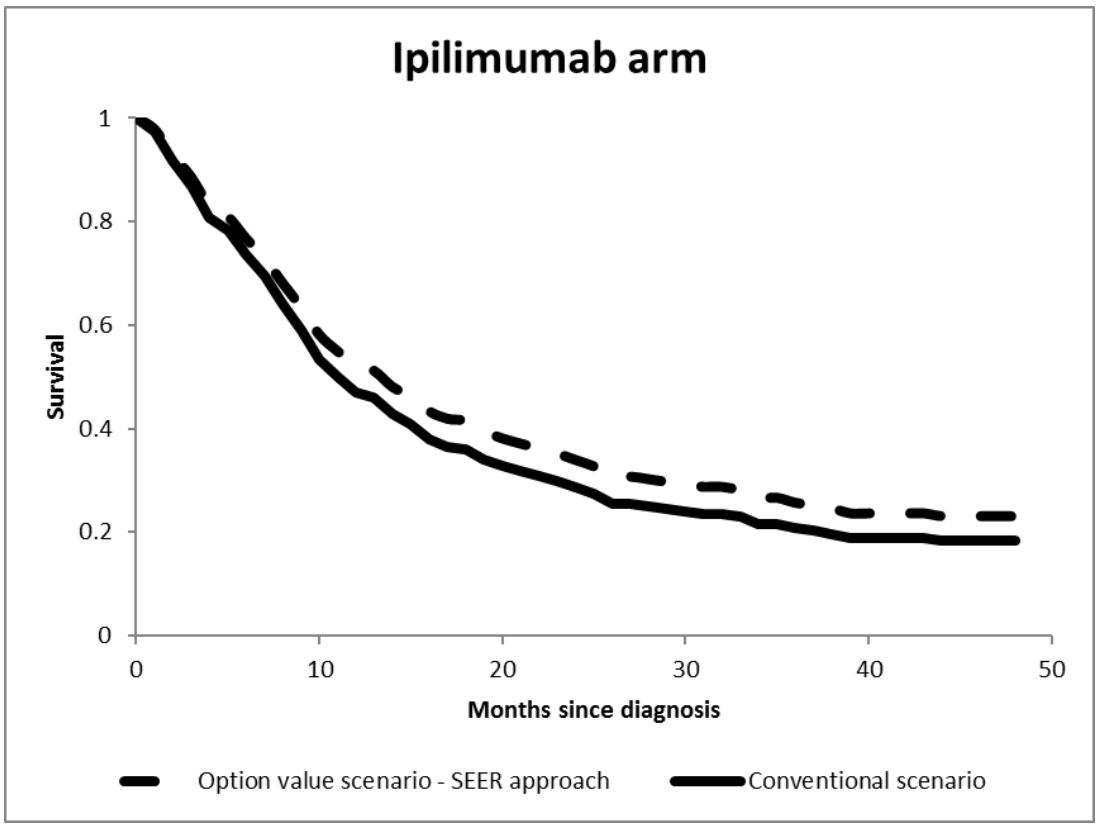

Figure 3.4: Overall survival curves in the ipilimumab arm: solid line is the conventional scenario and dashed line is the option value scenario using the SEER approach

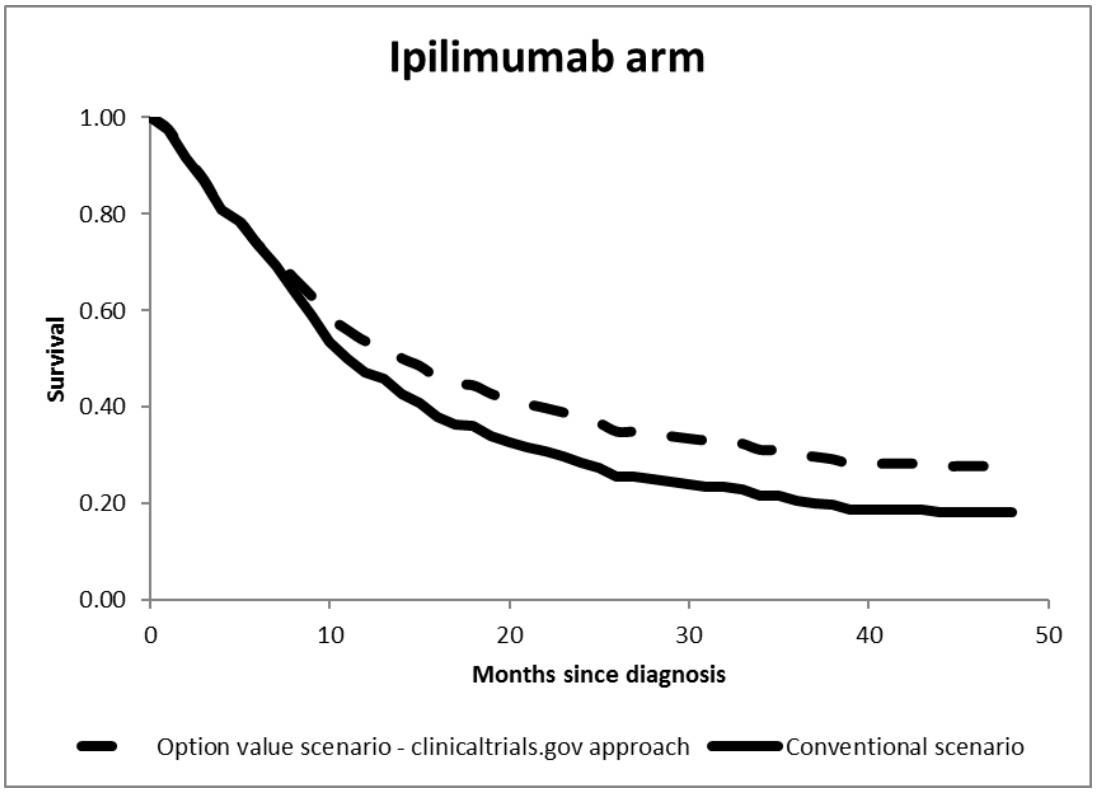

Figure 3.5: Overall survival curves in the ipilimumab arm: solid line is the conventional scenario and dashed line is the option value scenario using the clinicaltrials.gov approach

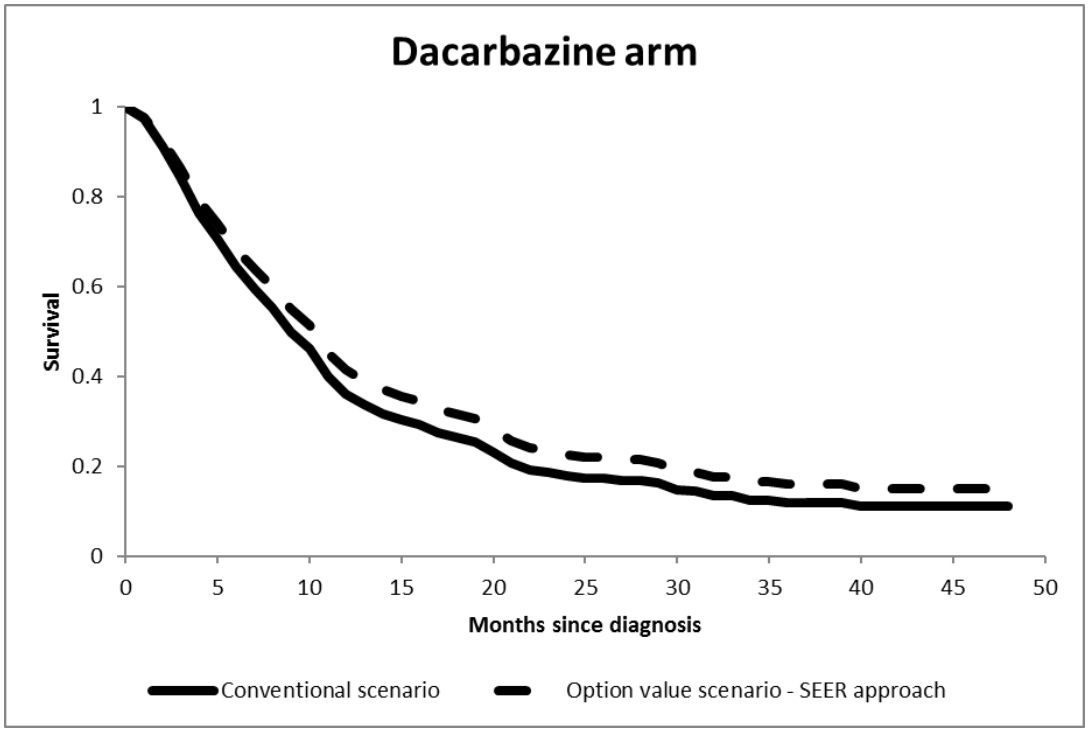

Figure 3.6: Overall survival curves in the dacarbazine arm: solid line is the conventional scenario and dashed line is the option value scenario using the SEER approach

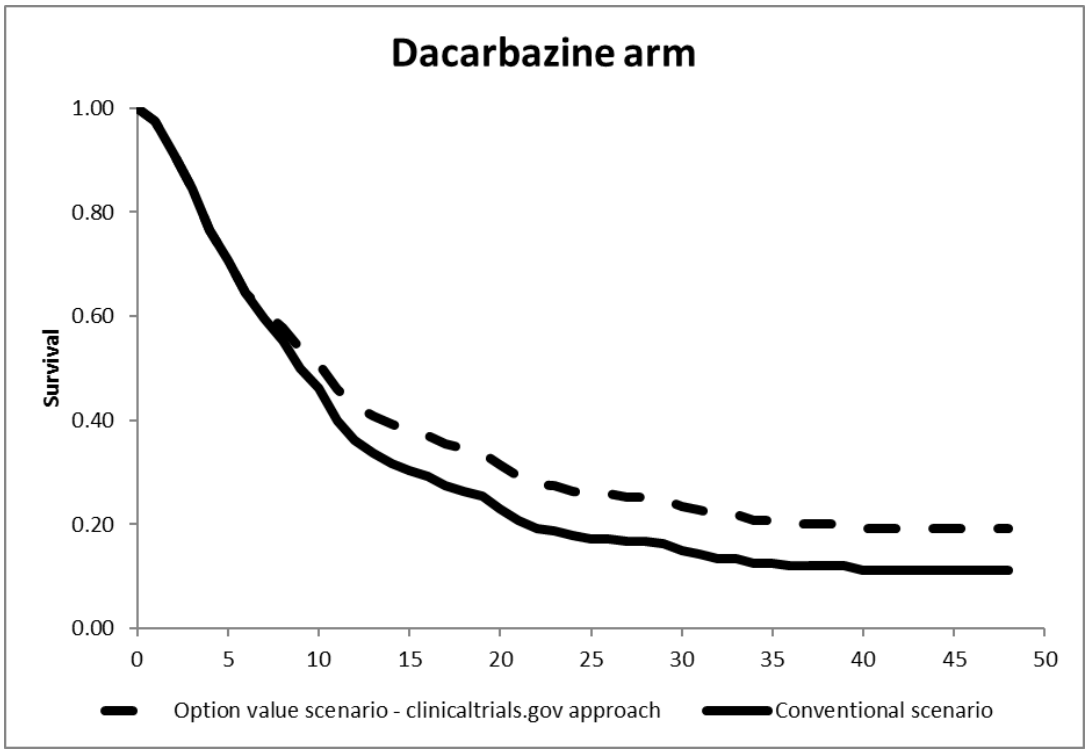

Figure 3.7: Overall survival curves in the dacarbazine arm: solid line is the conventional scenario and dashed line is the option value scenario using the clinicaltrials.gov approach

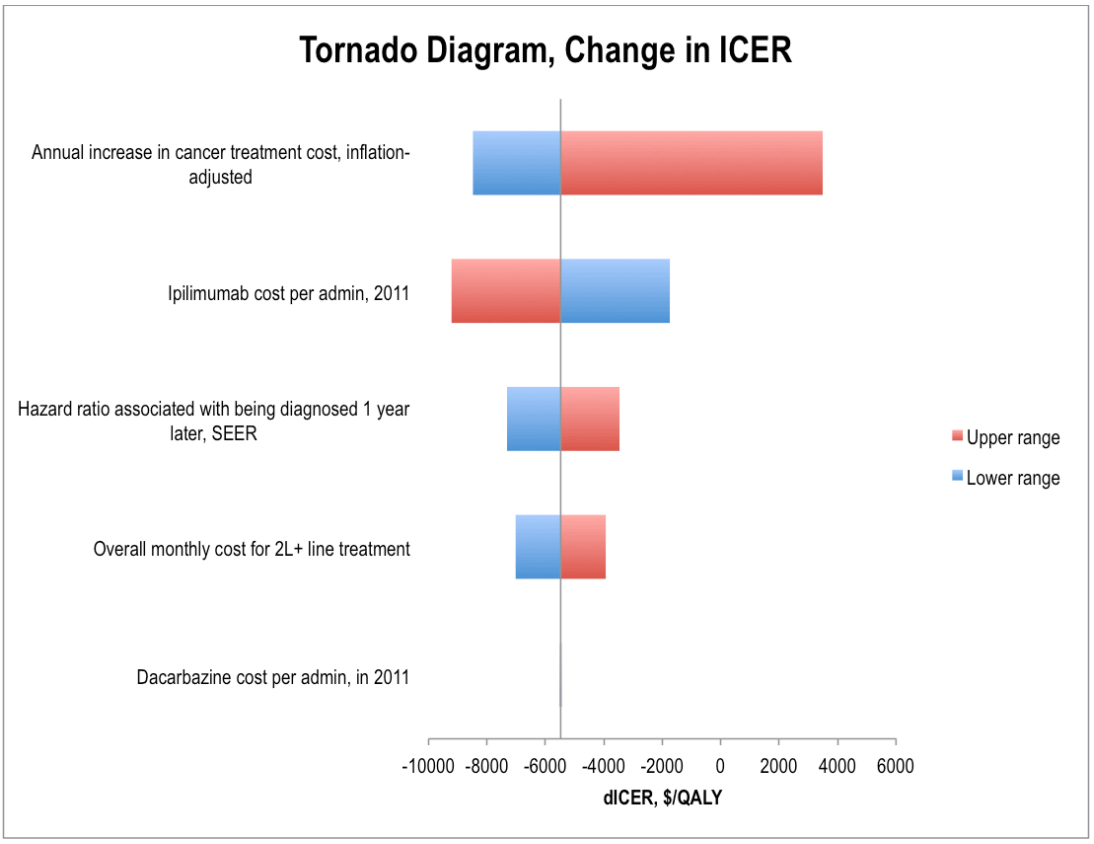

Figure 3.8: One-way sensitivity analysis of the difference in ICER (total cancer cost per QALY) between the option value and the conventional scenarios, SEER approach

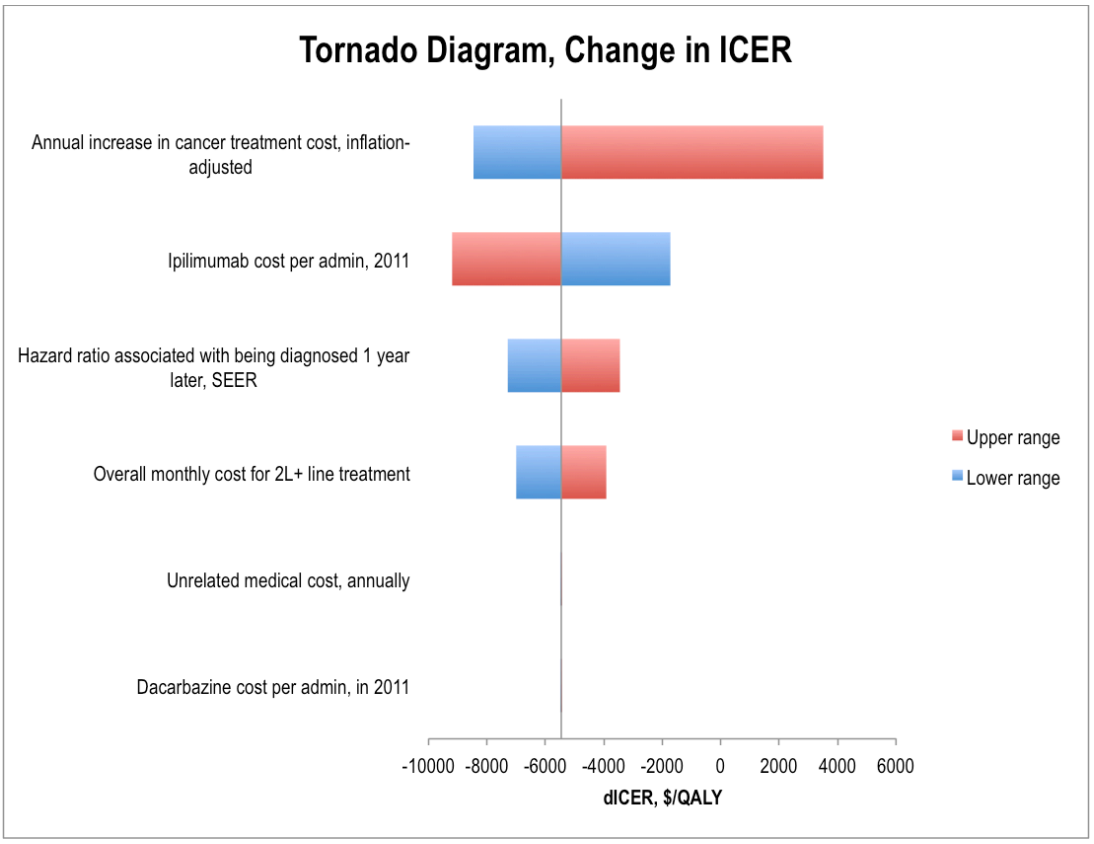

Figure 3.9: One-way sensitivity analysis of the difference in ICER (total healthcare cost per QALY) between the option value and the conventional scenarios, SEER approach

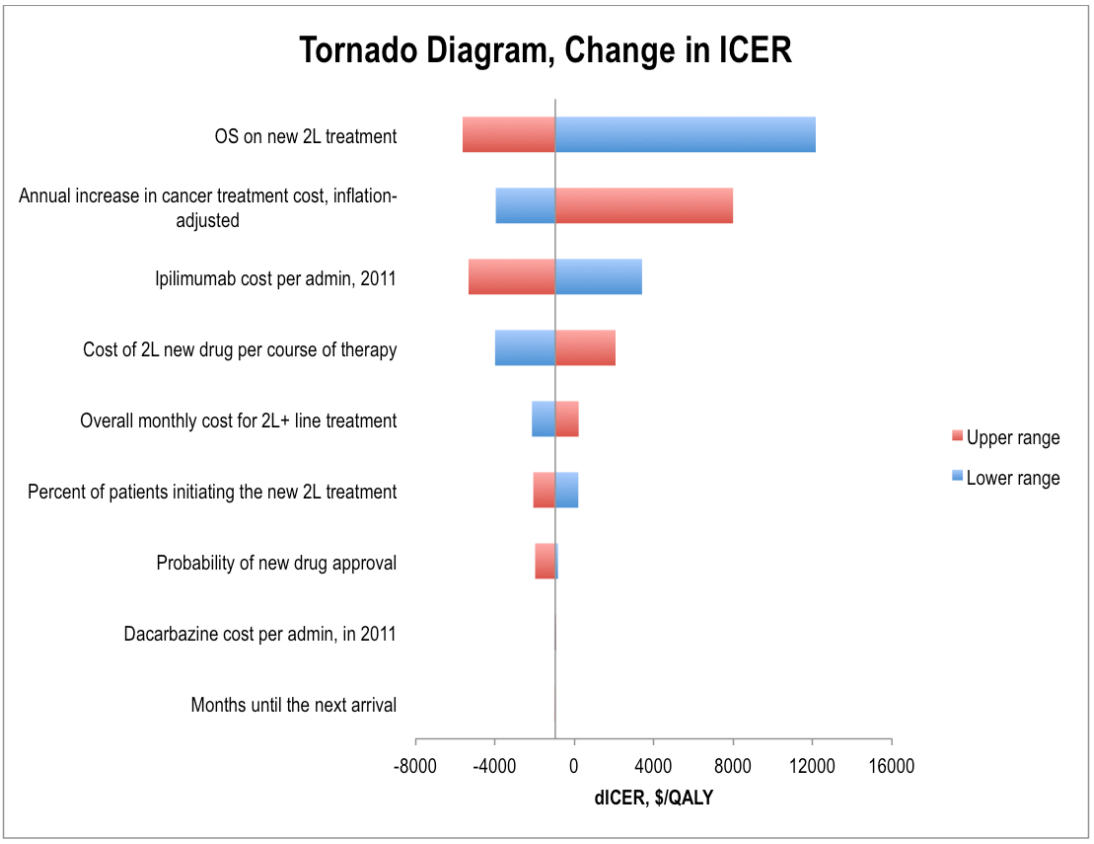

Figure 3.10: One-way sensitivity analysis of the difference in ICER (total cancer cost per QALY) between the option value and the conventional scenarios, clinicaltrials.gov approach

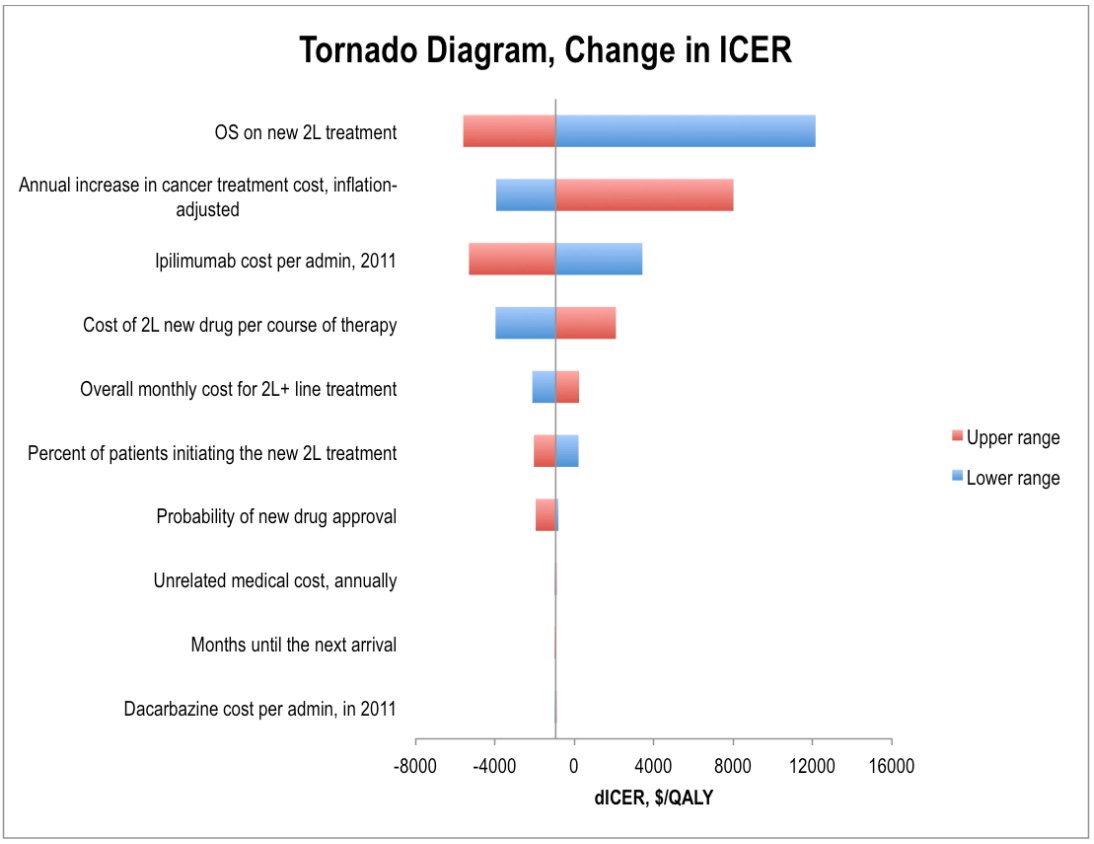

Figure 3.11: One-way sensitivity analysis of the difference in ICER (total healthcare cost per QALY) between the option value and the conventional scenarios, clinicaltrials.gov approach

3.7 REFERENCES

[1] Becker B, Murphy K, Philipson T. The Value of Life Near Its End And Terminal Care. Cambridge, MA: 2007.

[2] Lakdawalla DN, Doshi JA, Garrison LP, Phelps CE, Basu A, Danzon PM. Defining Elements of Value in Health Care—A Health Economics Approach: An ISPOR Special Task Force Report [3]. Value Heal 2018;21:131–9. doi:10.1016/j.jval.2017.12.007.

[3] Philipson TJ, Becker G, Goldman D, Murphy KM. Terminal Care and the Value of Life Near its End. Cambridge, MA: 2010. doi:10.1017/CBO9781107415324.004.

[4] Sanchez Y, Penrod JR, Qiu XL, Romley J. The Option Value of Innovative Treatments in the Context of Chronic Myloid Leukemia. Am J Manag Care 2012;18:265–79.

[5] Thornton Snider J, Batt K, Wu Y, Tebeka MG, Seabury S. The option value of innovative treatments for non-small cell lung cancer and renal cell carcinoma. Am J Manag Care 2017;23:e340–6.

[6] Robert C, Thomas L, Bondarenko I, O'Day S, M D JW, Garbe C, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011;364:2517–26. doi:10.1056/NEJMoa1104621.

[7] Hodi S, O'Day S, McDermott D, Weber R, Sosman J, Haanen J, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N ENGL J MED 2010;362:2251–9. doi:10.1056/NEJMoa1304048.

[8] U.S. Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. Drug Databases 2016. https://www.accessdata.fda.gov/scripts/cder/drugsatfda/ (accessed August 7, 2016).

[9] Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011;364:2507–16. doi:10.1056/NEJMoa1103782.

[10] Andtbacka RHI, Kaufman HL, Collichio F, Amatruda T, Senzer N, Chesney J, et al. Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. J Clin Oncol 2015;33:2780–8. doi:10.1200/JCO.2014.58.3377.

[11] Flaherty KT, Robert C, Hersey P, Nathan P, Garbe C, Milhem M, et al. Improved Survival with MEK Inhibition in BRAF-Mutated Melanoma. N Engl J Med 2012;367:107–14. doi:10.1056/NEJMoa1203421.

[12] Hauschild A, Grob JJ, Demidov L V., Jouary T, Gutzmer R, Millward M, et al. Dabrafenib in BRAF-mutated metastatic melanoma: A multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012;380:358–65. doi:10.1016/S0140-6736(12)60868-X.

[13] Larkin J, Ascierto PA, Dréno B, Atkinson V, Liszkay G, Maio M, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med 2014;371:1867–76. doi:10.1056/NEJMoa1408868.

[14] Robert C, Schachter J, Long G V, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med 2015;372:2521–32. doi:10.1056/NEJMoa1503093.

[15] Robert C, Long G, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015;372:320–30. doi:10.1056/NEJMoa1412082.

[16] Weber JS, D'Angelo SP, Minor D, Hodi FS, Gutzmer R, Neyns B, et al. Nivolumab

versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): A randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2015;16:375–84. doi:10.1016/S1470-2045(15)70076-8.
[17] Bell FC, Miller ML. Life tables for the United States social security area 1900-2100. 2005.
[18] Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) Research Data (1973-2014), released April 2017, based on the November 2016 submission n.d.
[19] DiMasi J, Hermann J, Twyman K, Kondru R, Stergiopoulos S, Getz K, et al. A tool for predicting regulatory approval after phase II testing of new oncology compounds. Clin Pharmacol Ther 2015;98:506–13.
[20] DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: New estimates of R&D costs. J Health Econ 2016;47:20–33. doi:10.1016/j.jhealeco.2016.01.012.
[21] Cortés J, González JA, Campbell MJ, Cobo E. A hazard ratio was estimated by a ratio of median survival times, but with considerable uncertainty. J Clin Epidemiol 2014;67:1172–7. doi:10.1016/j.jclinepi.2014.05.017.
[22] AnalySource: Premier access to the First Databank drug pricing database n.d. https://www.analysource.com (accessed March 24, 2018).
[23] Barzey V, Atkins MB, Garrison LP, Asukai Y, Kotapati S, Penrod JR. Ipilimumab in 2nd line treatment of patients with advanced melanoma: a cost-effectiveness analysis. J Med Econ 2013;16:202–12. doi:10.3111/13696998.2012.739226.
[24] Centers for Medicare & Medicaid Services. Physician Fee Schedule 2018. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PhysicianFeeSched/ (accessed March 24, 2018).
[25] Rashid N, Koh HA, Baca HC, Lin KJ, Malecha SE, Masaquel A. Economic burden related to chemotherapy-related adverse events in patients with metastatic breast cancer in an integrated health care system. Breast Cancer (Dove Med Press 2016;8:173–81. doi:10.2147/BCTT.S105618.
[26] Fitch K, Pelizzari PM, Pyenson B. Cost driver of cancer care: a retrospective analysis of Medicare and commercially insured population claim data 2004-2014. 2016.
[27] Guy GP, Yabroff R, Ekwueme DU, Rim SH, Li R, Richardson LC. Economic burden of chronic conditions among survivors of cancer in the United States. J Clin Oncol 2017;35:2053–61.
[28] Howard DH, Bach PB, Berndt ER, Conti RM. Pricing in the Market for Anticancer Drugs. J Econ Perspect 2015;29:139–62.
[29] Bureau of Labor Statistics. Consumer Price Index 2018. https://www.bls.gov/cpi/# (accessed March 23, 2018).
[30] Beusterien KM, Szabo SM, Kotapati S, Mukherjee J, Hoos a, Hersey P, et al. Societal preference values for advanced melanoma health states in the United Kingdom and Australia. Br J Cancer 2009;101:387–9. doi:10.1038/sj.bjc.6605187.
[31] Institute for Clinical and Economic Review. Final value assessment framework for 2017-2019 2017. https://icer-review.org/final-vaf-2017-2019/#cost (accessed April 4, 2018).
[32] Garrison LPJ, Kamal-Bahl S, Towse A. Toward a Broader Concept of Value: Identifying and Defining Elements for an Expanded Cost-Effectiveness Analysis. Value Heal J Int Soc Pharmacoeconomics Outcomes Res 2017;20:213–6. doi:10.1016/j.jval.2016.12.005.

[33] Garrison L, Neumann P, Willke R, Basu A, Danzon P, Doshi J, et al. A Health Economics Approach to US Value Assessment Frameworks—Summary and Recommendations of the ISPOR Special Task Force Report [7]. Value Heal 2018;21:161–5. doi:10.1016/j.jval.2017.12.009.
[34] Neumann PJ, Sanders GD, Russell LB, Siegel JE, Ganiats TG. Cost-Effectiveness in Health and Medicine. Second Edi. New York: Oxford University Press; 2017.
[35] Thokala P, Devlin N, Marsh K, Baltussen R, Boysen M, Kalo Z, et al. Multiple Criteria Decision Analysis for Health Care Decision Making--An Introduction: Report 1 of the ISPOR MCDA Emerging Good Practices Task Force. Value Heal J Int Soc Pharmacoeconomics Outcomes Res 2016;19:1–13. doi:10.1016/j.jval.2015.12.003.
[36] Marsh K, IJzerman M, Thokala P, Baltussen R, Boysen M, Kalo Z, et al. Multiple Criteria Decision Analysis for Health Care Decision Making--Emerging Good Practices: Report 2 of the ISPOR MCDA Emerging Good Practices Task Force. Value Heal J Int Soc Pharmacoeconomics Outcomes Res 2016;19:125–37. doi:10.1016/j.jval.2015.12.016.
[37] Phelps CE, Lakdawalla DN, Basu A, Drummond MF, Towse A, Danzon PM. Approaches to Aggregation and Decision Making—A Health Economics Approach: An ISPOR Special Task Force Report [5]. Value Heal 2018;21:146–54. doi:10.1016/j.jval.2017.12.010.
[38] Sacco JJ, Botten J, Macbeth F, Bagust A, Clark P. The average body surface area of adult cancer patients in the UK: a multicentre retrospective study. PLoS One 2010;5:e8933. doi:10.1371/journal.pone.0008933.
[39] Senzer NN, Kaufman HL, Amatruda T, Nemunaitis M, Reid T, Daniels G, et al. Phase II clinical trial of a granulocyte-macrophage colony-stimulating factor-encoding, second-generation oncolytic herpesvirus in patients with unresectable metastatic melanoma. J Clin Oncol 2009;27:5763–71. doi:10.1200/JCO.2009.24.3675.
[40] Sosman JA, Kim KB, Schuchter L, Gonzalez R, Pavlick AC, Wever JS, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. N ENGL J MED 2012;366:707–14.
[41] Kim KB, Kefford R, Pavlick AC, Infante JR, Ribas A, Sosman JA, et al. Phase II study of the MEK1/MEK2 inhibitor Trametinib in patients with metastatic BRAF-mutant cutaneous melanoma previously treated with or without a BRAF inhibitor. J Clin Oncol 2013;31:482–9. doi:10.1200/JCO.2012.43.5966.
[42] Report S. Infectious complications of propionic acidemia in Saudia Arabia 1998:90–4.
[43] Ascierto P, Minor D, Ribas A, Lebbe C, O'Hagan A, Arya N, et al. Phase II trial (BREAK-2) of the BRAF inhibitor dabrafenib (GSK2118436) in patients with metastatic melanoma. J Clin Oncol 2013;31:3205–11. doi:10.1200/JCO.2013.49.8691.
[44] Tsao H, Rogers GS, Sober AJ. An estimate of the annual direct cost of treating cutaneous melanoma. J Am Acad Dermatol 1998;38:669–80.
[45] Seidler AM, Pennie ML, Veledar E, Culler SD, Chen SC. Economic burden of melanoma in the elderly population: population-based analysis of the Surveillance, Epidemiology, and End Results (SEER)--Medicare data. Arch Dermatol 2010;146:249–56. doi:10.1001/archdermatol.2009.389.

Chapter 4. IMPLICATIONS AND CONCLUSIONS

4.1 SUMMARY OF FINDINGS

In this dissertation, I first examined the utilization of antineoplastic systemic therapies and surgical resection of metastatic among metastatic melanoma patients, before and after the announcements of ipilimumab's phase II and phase III clinical trial results. I found that patients responded to the announcement of ipilimumab's phase II result by nearly doubling their likelihood of using surgical resection of metastasis. I then developed modeling approaches for incorporating option value of life-extending treatment into an augmented CEA, and applied them to the case of ipilimumab for the treatment of metastatic melanoma. I found that for ipilimumab, the incremental QALYs gained increased by 5 to 8% and the ICER decreased by 0 to 2%, after accounting for option value from technology advancement. To my knowledge, this dissertation research is the first to provide revealed-preference evidence on option value being considered in treatment decision-making and to incorporate option value of a treatment into a CEA. Findings of this dissertation have important implications on the practice of CEA, regulatory benefit-risk assessment for new drugs, and value-based pricing.

4.2 IMPLICATIONS ON PRACTICE OF CEA

The Second Panel on Cost-Effectiveness of Health and Medicine has emphasized that all costs and benefits incurred as a result of life extension from a treatment should be included in the CEA.[1] With technology advancement, life extension brings option value, which has largely

been omitted in the practice of CEA thus far. From an implementation point of view, including option value will require estimating the rate of innovation and/or the rate of future reduction in mortality, and possibly more complex decision models. It will place an additional burden on pricing and reimbursement agencies. Therefore, it is critical to first assess whether the option value is likely to be small enough that it would not significantly bias the results if omitted. This assessment can be done qualitatively rather than through a quantitative decision model. In cases where survival benefit of a treatment is very small compared to its quality-of-life benefit and/or the likelihood of arrival of new breakthrough therapies during the extended life is low, the option value can be omitted without losing much accuracy or usefulness of the results.

In cases where option value is likely to be large, several steps can be taken to ensure that it is properly accounted for in a decision model. First, identify the most appropriate data sources and methods for estimating future mortality reduction in the study population. This could be an analysis of historical trend using disease registry data or other large, population-level observational data. It could also be an analysis of drug pipeline for potential new approvals in the future. When neither type of data is available, expert opinion may be used. Second, based on the data source chosen in the first step, identify the appropriate CEA model structure to include option value. In some cases, it may only involve adjusting transition probabilities from one health state to another. In other cases, adding one or more health states for the new treatments may be needed. Third, based on the approach to estimating future improvement in mortality, identify the appropriate method to account for potential increase in cost. This could involve analyzing historical trend in the cost of treating the disease of interest. It could also involve projecting the costs of new drugs that may be approved in the future. Lastly, quantify the

uncertainty of the estimate of option value. Estimating option value requires projecting what will happen in the future in terms of available treatments and potential health outcomes. It brings additional uncertainty to the cost-per-QALY estimate in an augmented CEA. Therefore, it is important to identify plausible ranges for inputs that are determinants of option value, either through literature review or through elicitation of expert opinions. Estimates of option value should be presented with credible intervals.

4.3 Implications on Regulatory Benefit-Risk Assessment for New Drugs

Benefit-risk assessment is the basis of the FDA's regulatory decisions in the pre-market and post-market review processes. In 2009, the FDA initiated an effort to explore systematic approaches to benefit-risk assessment for human drug review.[2] In a draft plan published in 2013, the FDA stated their position on adopting a structured qualitative approach that is designed to support the identification and communication of the key considerations in FDA's benefit-risk assessment and how that information led to the regulatory decision.[2] The basic structure of the qualitative approach includes five key decision factors: analysis of condition, current treatment options, benefit, risk, and risk management. During a regulatory review, the FDA's technical and scientific advisory committees are presented with a body of evidence in each of these five domains and are asked to provide a vote for or against a product's approval after hearing and discussing presentations from the sponsor, the FDA, and others. The vote is therefore based on the committee members' own implicit weighing of different outcomes and judgment of whether the new product benefits outweigh its risks.

As an alternative to the FDA's qualitative approach, Garrison et al. proposed a quantitative health outcomes modeling approach, using QALY as the metric for evaluation.[3] In their proposal, outcomes from a new treatment are separated into expected health improvements with positive QALYs (benefits, B) and adverse health impacts with negative QALYs (risks, R) and the incremental net health benefit (INHB) of new treatment 2 versus the current treatment 1 can be expressed as:

$$INHB = (B_2 - B_1) - (R_2 - R_1)$$

A "favorable" benefit-risk balance is therefore $(B_2 - B_1) \geq (R_2 - R_1)$. That is, the expected QALY gains from improved efficacy exceed the expected QALY losses to safety problems. In the case of a placebo comparator, the benefit of the new treatment should at least outweigh the risk: $B_2 \geq R_2$. The calculations of B and R in their proposal involve explicit weighing and integration of different health outcomes based on societal preference.

Findings from this dissertation have implications on new product's benefit-risk assessment under either the FDA's qualitative approach or the quantitative health outcomes modeling approach. Under either approach, option value should be considered in situations where it will likely affect the regulatory decisions. Such situations include but are not limited to life extension being the main purpose of treatment in a disease area with rapid innovations. Omitting option value in these cases will likely affect life-extending treatments differently than those that are developed primarily for improving quality of life at the regulatory approval phase. A treatment that primarily prolongs survival may be deemed less favorable in a regulatory review than another treatment that primarily improves quality of life, simply because the option value from prolonged survival is not accounted for in the benefit-risk assessment. Consideration of option value will

require the FDA to reassess their evidentiary standards, and include option value as an additional element of benefit when appropriate. In this dissertation, I developed approaches to estimate option value in terms of additional gains in incremental QALYs, which can be readily incorporated in the quantitative health outcomes modeling approach to benefit-risk assessment. I also developed approaches to estimating rate of new drug approvals and rate of future reduction in mortality, which are determinants of option value, and can be included as factors for consideration in the FDA's qualitative approach to benefit-risk assessment.

4.4 Implications on Value-Based Pricing

The goal of pharmaceutical reimbursement and pricing policies is to balance the static efficiency (maximizing current health benefits within the current budget) with the dynamic efficiency (producing the optimal amount of innovation in the long run). Value-based pricing (VBP) proposes to link payments for pharmaceutical or healthcare services to their values, with a goal of providing incentives to innovators to invest in the R&D of technologies that are more likely to be cost-effective. Recent developments in healthcare value assessments have expanded the definition of value for medical technologies, and have included option value, productivity, scientific spillovers, insurance value, value of hope, reduction in uncertainty, etc., along with traditional value elements such as life years gained and improvement in quality of life.[4,5] VBP should in theory account for all elements of value, and considering the option value of a medical technology may require adding an "option premium" to its price. Many health systems have set, formally or informally, thresholds for their willingness to pay (WTP) for a QALY gained. The monetary value of the additional health gain due to technology advancement is therefore the WTP threshold multiplied by the additional QALY gained. However, the additional health gain

is created by the combination of life extension from the current treatment and further reduction in mortality and/or morbidity from future innovations, and the reward should in theory be shared by the current treatment and future innovations, which can be viewed as economic complements. Without formally establishing and solving a model for each unique complementary good, the simplest thing might be to put more money in the general reimbursement fund, as was done to allow for cost-increasing technologies under the Medicare diagnosis-related group Prospective Payment System.[6]

4.5 Conclusion

In this dissertation, we answered two closely related research questions: (1) is option value considered in real-world treatment decision-making, and (2) how does accounting for option value affect the projected cost-effectiveness of a new treatment. This research contributes to existing research on the value of medical technology in two important ways. First, it presents the first study that provides revealed-preference evidence on option value being considered in treatment decision-making. Second, it presents the first study to estimate the option value of a treatment in a CEA. Findings from this dissertation underscore the importance for health care providers and payers to consider attributes of treatment that are not reflected in traditional value metrics.

4.6 REFERENCES

[1] Neumann PJ, Sanders GD, Russell LB, Siegel JE, Ganiats TG. Cost-Effectiveness in Health and Medicine. Second Edi. New York: Oxford University Press; 2017.

[2] Frey P. PDUFA V : Benefit-Risk Assessment and Patient-Focused Drug Development A Benefit-Risk Framework What problem are we trying to address ? FDA REdI Conf., 2013, p. 1–11.

[3] Garrison LP, Towse A, Bresnahan BW. Assessing a structured, quantitative health outcomes approach to drug risk-benefit analysis. Health Aff 2007;26:684–95.

[4] Lakdawalla DN, Doshi JA, Garrison LP, Phelps CE, Basu A, Danzon PM. Defining Elements of Value in Health Care—A Health Economics Approach: An ISPOR Special Task Force Report [3]. Value Heal 2018;21:131–9.

[5] Garrison LPJ, Kamal-Bahl S, Towse A. Toward a Broader Concept of Value: Identifying and Defining Elements for an Expanded Cost-Effectiveness Analysis. Value Heal 2017;20:213–6. doi:10.1016/j.jval.2016.12.005.

[6] Neumann PJ, Wojcik SW, Garrison LP. Estimating the Impact of Scientific and Technological Advances on Increases in Medicare Costs Per Case for FY 1989: Implications for the Discretionary Adjustment Factor for FY 1989. Project HOPE report prepared for the Prospective Payment Assessment Commission under Contract No. T-47540329. May 1988.

VITA

Prior to pursuing her PhD in Pharmaceutical Outcomes Research & Policy at University of Washington, Meng Li received her Masters in Epidemiology from Johns Hopkins University Bloomberg School of Public Health. Meng's research focuses on expansions of value in cost-effectiveness analysis, economic evaluations of medical technologies, instrument development and validation, cost-of-illness analysis, etc.