"The long run is a misleading guide to current affairs. In the long run we are all dead."

- John Maynard Keynes

University of Alberta

The pharmaceutical industry's willingness-to-sell targeted chemotherapy for incurable solid cancers

by

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I dedicate this work to my Father and Mother, David Conter and Felicia Goldstein, for their unwavering love and support. And to my grandparents, Monroe Alan Goldstein and Blanche Mainster Goldstein, whose positive influence on my life is everlasting.

Abstract

How the costs of research and its associated risks contribute to a minimum price that would support continued private pharmaceutical investment is unclear.

We employed a linear cost-volume-revenue breakeven analysis to equate initial capital investment and risk, and its associated post-drug-approval revenue. A decision-tree analytic model was utilized to define the relationships between investment events, outcomes, and risk. A systematic review was employed to determine the model inputs.

In oncology, the minimum revenue required to support R&D is $4.34 billion USD to $5.21 billion USD. The strategy undertaken to develop a new drug can reduce the associated revenue to $2.77 - $3.49 billion USD. Utilizing multi-tumour phase I clinical trials may allow for $853 million USD to $983 million USD in additional reductions.

The minimum required return on investment varies with estimates for cost of capital and the approach a firm uses when developing novel therapeutics.

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Chapter 1 – Introduction

Cancer continues to be a leading cause of death in the developed world (1). An estimated 1 in 4 Americans (2) and 1 in 3 Canadians (3) will die of cancer. Of all cancer types, solid tumours account for 93% of all cancer deaths. Cancer related mortality has been declining and survival has been improving (4, 5) as a result of significant investment in detection and treatment, but overall five-year survival rates have improved by less than 5% from 1992-2004. Some survival rates, including those for common tumours such as lung cancer and pancreatic cancer, have improved only marginally (6). Much of this lack of progress probably relates to the universally poor prognosis for advanced and metastatic disease. Despite the large variation in the metastatic potential and differing behaviours of tumours and the large variation in their chemotherapeutic sensitivity, the general cellular and genetic mechanisms for the development of metastatic disease are largely similar (7). There are now over 24 identified genes that may be involved in the metastatic transformation of a solid tumour, and each may be a potential target for therapy (8).

The economic effects of cancer are also significant. Cancer care in the United States of America cost $124.57 billion USD in 2010, and will cost approximately $157.77 billion USD in 2020 (9). This projection assumes a constant incidence and survival rate from cancer with the absence of healthcare cost inflation. However, others estimate increases in incidence and prevalence rate of cancer types (10) and healthcare inflation (11, 11-13). Moreover, as new and more expensive therapies to treat cancer

emerge, they may expedite increases in oncology expenditure[1]. Targeted therapy, cancer treatments that inhibit cancer growth by interfering with specific oncogenic pathway, represent a prominent area of pharmaceutical growth. In contrast to public and industrial enthusiasm for targeted therapies, overall impact of these drugs on median survival of metastatic solid cancer has not been established. There are examples of gain, but whether such gains warrant aggressive investigation through trials is questionable.

Advances in oncology offer hope, but at significant monetary cost (14-17). The value for money in these scenarios can be questionable: with median incremental cost-effectiveness ratios of between $22,000 and $48,000 and higher (18). Monoclonal antibodies and tyrosine-kinase inhibitors, which include many of the major recent advances in cancer treatment, can be especially expensive, with some approved drugs having cost-effectiveness ratios of £71,000 in the United Kingdom, and $144,000 in Canada (19-22). In addition to the cost-benefit ratio concerns, the expense of providing these drugs and their budgetary impact may also impede their addition to public formularies and private insurance plans (23). And the restriction of therapeutic access may conflict with public opinion on the societal value of these targeted treatments (24-27) despite seemingly strong support for health care expense containment by the public

[1] On May 28, 2001, when the Food and Drug Administration approved imatinib, *Time* magazine publicized the drug as a breakthrough in cancer treatment. As the first targeted therapy approved for the treatment of cancer, it has proven efficacy in the treatment of chronic myelogenous leukemia (CML) (125, 126) and is now considered to be the primary first-line treatment for CML by the National Comprehensive Cancer Network (127). Other successes have followed: e.g. trastuzumab as treatment for Her2/neu positive breast cancer (128, 129). Targeted chemotherapies can be categorized into two major groups: small-molecule tyrosine kinase inhibitors and monoclonal antibodies - imatinib in the former category, trastuzumab in the latter. Despite their different mechanisms of action, the classes can be understood more simply as providing different methods of inhibiting a given target (130). There is considerable overlap between the genetic targets of the drugs within and between each category. Since 2001, over 15 targeted therapies have been developed for use in the treatment of metastatic solid tumours; with additional targeted therapies in use for non-malignant conditions. And over 800 more are currently in development (131).

(28-30). Commonly cited reasons for the increasing cost of targeted chemotherapy agents include: rising development costs, the low success rate of developing a novel drug to market, the high value-added for patients, and the need to promote continued research and development (31, 32). That being said, it is not clear whether the current price of drugs reflects these issues (33).

Both public and private organizations have responded to concerns over cost by incorporating economic evaluation of drugs as part of their approvals process (34, 35). Cost-utility analyses, exemplified by determining a drug´s cost per quality-adjusted life-year gained (QALY), have become a staple of the economic evaluation of new drugs. Theoretically, healthcare budgets are fixed and cost/QALY measurements represent health forgone by the removal of other services that are replaced by the integration of the new technology (36). For example, based on current estimates of the productivity of the National Health Service (NHS) in the United Kingdom, a threshold of £20,000-£30,000 (37) should represent the least productive aspects of their delivered service. If the calculated cost/QALY of a new intervention is below that threshold, then it is considered cost-effective (38). In practice, the establishment of the National Institute of Clinical Excellence (NICE), an official government body that utilizes health technology assessment in making recommendations to the NHS on drug approvals, has coincided with large increases in the real budget of the NHS, demonstrating the variable nature of health budgets. Additionally, the threshold values for willingness to accept the removal of treatments that are already being provided seem higher than the willingness to pay thresholds for new medical therapies (39). These two confounders in the idealized use of cost-effectiveness analysis may help explain why, despite NICE's guidance supports their

current use of a cost-effectiveness guidance close to £20,000-£30,000, the upper threshold may be £50,000 or higher (40) -- although uncertainty and disease burden also play a role when considering specific cases. As for the NHS itself, despite counsel from NICE, decision-making on coverage seems to focus more on clinical benefit and budget implications, rather than economic evaluation. It is important to note that the public appears to value improvements in health-related quality of life and length of life, but improvement of health-related quality of life alone is very important (41). In the case of oncologic medications, the belief that treatment tends to improve health related quality alone may influence the public's opinion in favour of support for drugs that are not considered cost-effective (42). For example, when the NHS initially rejected all targeted chemotherapeutic interventions for renal cell carcinoma from their formulary, it prompted negative publicity and strong public sentiment relating to how decisions on funding cancer drugs should me made (43, 44). The NHS has since reversed its decision on sunitinib, a targeted therapeutic agent employed in the treatment of metastatic renal cell carcinoma, despite evidence that it is not a cost-effective treatment. NHS committee members have since expressed concern over the basis of NICE's cost-effectiveness threshold and its use in decision-making (45).

The less than predictable nature of how cost-effectiveness measurement is incorporated into the drug approvals process may create confusion amongst external stakeholders, such as the public and industry. With regard to cancer treatment, the public has much to gain from a productive pharmaceutical industry. Life expectancy improvements achieved overall (46) are in part a reflection of new chemotherapeutic

agents in different cancers[2]. From the industry perspective, ensuring a consistent and predictable approvals process allows for better risk management and a more efficient allocation of resources (47). The public can benefit most fully from pharmaceutical development when purchasers utilize methods to maximize health gains by incorporating acceptably cost-efficient cancer treatments into the formulary (36).

The United Kingdom's pharmaceutical price regulation scheme (PPRS) combines profit and price controls to control NHS expenditure on drugs. Secondary aims of the scheme are to secure value for money for the NHS while simultaneously encouraging continued research and development (R&D) by the pharmaceutical industry (48). Profit controls limit pharmaceutical return on investment to 17%-21% (34), requiring excess profits be returned, but also allowing for price increases if profits fall below a predetermined threshold. Price controls allow suppliers the opportunity to set the initial price of a new therapeutic compound, but limit price increases and allow the NHS to re-negotiate future prices. However, profit and price controls do not reflect the value of a drug based on clear criteria and so does not directly address the objective of securing value for money for the NHS on behalf of patients (48). To address this shortcoming, the Office of Fair Trading proposes value-based pricing, which sets prices based on the expected cost-utility achieved in a specific group or subgroup. The health service organization achieves surplus for patients by pricing at the margin: negotiating a price that equals the marginal benefit obtained for a targeted subset of patients, while other subgroups obtain a greater marginal benefit (49). Some form of value-based pricing will

[2] E.g. taxanes and anthracyclines in breast cancer (49, 132), oxaliplatin and irinotecan in colorectal cancer (133, 134), taxanes and carboplatin in ovarian cancer (135, 136), imatinib mesylate in chronic myelogenous leukemia (137), rituximab in B-cell non-Hodgin's lymphoma(138), gemcitabine in pancreatic cancer (139), among others.

likely be implemented by the UK in the near future (50). This may address the issue of value for money for organizations such as NICE, but does not address cost containment for governments or private insurers, nor should it (51). Even if value-based pricing is appealing in the UK or similar countries, the societal values underlying value-based pricing may not be global. Notably, these values may not be shared in the United States of America (52). Although maximizing the benefit obtained from every dollar spent on healthcare may be a laudable goal, it explicitly places a value on human life. Such an act may void all other arguments supporting healthcare reform in like-minded regions, even if implicit acts are tolerated (53). This may seem to be an inevitable bi-product in the attempt to systematically constrain healthcare expenditure growth, but alternative methods that focus on the pharmaceutical industry may be employed to avoid the issue of directly affixing a measured value to human life.

The issue becomes how to harmonize the patient's desire for immediate access to cancer medication, their desire for improved future treatments, the public's desire to maximize the overall health status, both now and in the future, and the public payer's need to balance health care expenditure – all of these over against other expenses such as education or infrastructure, and the private insurers desire to minimize costs while competing with other insurers on services covered.

Cost-effectiveness analysis sets an upper limit on what a healthcare purchaser should pay for a new intervention, but does not clarify at what price a company would be willing to sell their wares. For pharmaceutical firms and their shareholders, value-based pricing thresholds provide information on the consumer's willingness-to-pay for newly proven effective therapies (54). In the pharmaceutical marketplace, this public

information allows for pre-emptive determination of maximum costs compared to minimum benefits that may be incurred by future products if such products are to be successful. A pharmaceutical firm can thus improve its efficiency, and its return on investment to shareholders, by focusing on potentially successful drugs that are more likely able to achieve acceptable cost-benefit ratios. This improvement in efficiency may limit the production of clinically useful compounds, but would not reduce societal benefit given that therapies that are not cost-effective should not be funded anyway, unless society is willing to sacrifice greater marginal gains achieved elsewhere. Furthermore, the knowledge of willingness-to-pay for the marketplace can act as a guidepost in reimbursement negotiations between the payers and pharmaceutical companies (55), and should therefore reduce investor uncertainty in the post phase III market approvals process.

At the point of sale, or reimbursement negotiations proceedings, all pharmaceutical development costs may be considered sunk (49). Although this is true for a given pharmaceutical at the end of development, a sustainable pharmaceutical company needs to reflect on what the expected risk-adjusted future returns on investment will be based on current reimbursement for similar pharmaceuticals. For example, if value-based pricing indicates that the maximum reimbursement that should be paid to the company is less than the minimum risk-adjusted revenue, then although the company will sell the drug in question, it should adjust its R&D to reflect the future losses that would accrue if similar endpoints were met. Conversely, if value-based pricing indicates that the maximum reimbursement that should be paid to the company is more than the minimum risk-adjusted return on investment revenue, the company should increase investment in

that area. This assumes that the company is sufficiently developed to make such adjustments. A small-capitalization or micro-capitalization company may be insufficiently liquid to make such adjustments, but the industry as an aggregate may be assumed to adjust accordingly. From a the payer's perspective, the difference between their maximum willingness to pay and a company's minimum required return on investment represents a prime target for successful negotiation to improve the payer's share of benefit. In a public system, this may be successfully translated into a lower effective cost per QALY, or in a private system, this may assist in cost containment.

To this end, we set out to estimate the pharmaceutical industry's minimum acceptable revenue for the research and development of new targeted chemotherapy in incurable solid cancers. Although there can be debate, we assumed that there are benefits to a long-running, vibrant pharmaceutical industry focusing on the creation and development of new pharmaceutical agent. Although some companies may be focused primarily on the creation on intellectual property, which could subsequently be sold to larger pharmaceutical firms or other investors, we chose to maintain the perspective of a large pharmaceutical firm that completes the entire R&D process in-house. There are also multiple factors that contribute to the minimum revenue required for the long-run sustainability of a firm. In addition to the costs associated with research and development of an agent, a company, or the industry as an aggregate, must also generate enough revenue to cover the costs of manufacturing the new drug, storage and shipping costs, marketing costs, administration costs, and others. These costs are drug specific and firm-specific. Instead, we set out to specifically estimate the component of future

revenue for a drug that is dictated by the costs associated with research and development only.

To accomplish this primary aim, the following objectives were set:

1. Develop conceptual framework for determining the pharmaceutical industry's minimum acceptable revenue for sustainable drug research and development.

2. Create a functional decision-analytic model based on this framework.

3. Conduct a systematic literature search to provide general cost and probability estimates over the research and development process, from inception to market approval, as inputs into the model.

4. Conduct a systematic literature search to provide data on phase III success rates of targeted therapies for incurable solid cancers and the magnitude of clinical success they have achieved.

Chapter 2 – Conceptual methods and model development

To remain solvent over the long-run any company, including the members of the pharmaceutical industry, must consistently generate adequate returns to recover its costs of production, over an acceptable time horizon. However, defining "adequate" returns can prove elusive. In addition to generating sufficient revenue to cover the out-of-pocket costs of the company, the company also has to generate profit for its investors. The opportunity cost of investment, or cost of capital, reflects the forgone earnings from alternative uses of capital in investments of similar risk. Both the Capital Asset Pricing Model (56) and the Fama-French Three Factor Model (57) can be used to estimate the cost of capital, but neither provides fully authoritative values for the costs of capital (58). Conversely, the costs of production can be measured as a matter of corporate accounting and direct measurement.

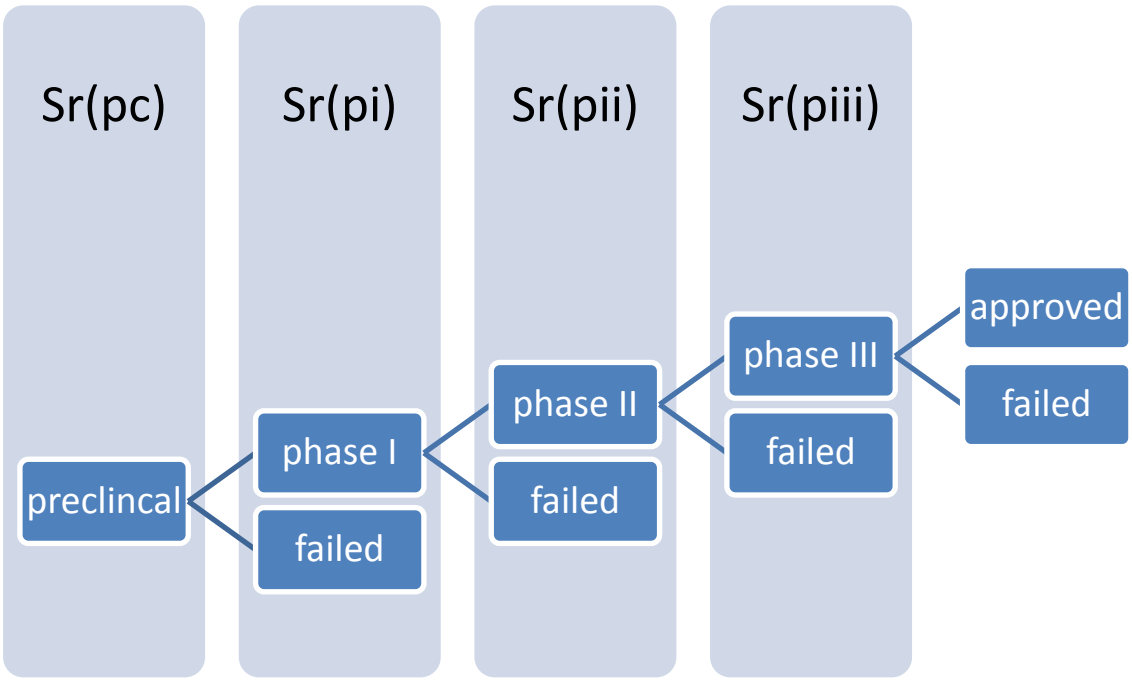
3.1 Description of the Model

In the simplest scenario, a company develops a therapeutic entity from initial concept to market sales in a linear fashion. Although likely true for most pharmaceuticals, individual therapeutics in oncology progress in a stepwise fashion from pre-clinical development to phase I investigation, then to phase II exploration, then through phase III randomized clinical trials to market approval if the clinical trial proves successful (59). Development in oncologic chemotherapeutics differ from development of other pharmaceuticals in that phase I trials are generally performed in robust patients with end-stage cancer who have exhausted standard therapies or for cancers where no effective standard therapy exists. In contrast, non-oncology phase I therapeutic trials are

often conducted using healthy volunteers as subjects. These trials are often used to assess drug toxicity and the in-human pharmacokinetics. Traditionally, for cytotoxic chemotherapy the appropriate dose is defined by a 33% toxicity rate or less, but in practice this approach may not suit targeted cancer therapy (60). Molecularly targeted therapy may not produce a dose-limiting toxicity at the maximum biologically effective dose. Unfortunately, a validated, uniform method for determining the maximum biologically effective dose does not currently exist, and so most targeted therapy phase I clinical trials still use traditional designs (61). Based largely on the recommended phase II dose determined by the phase I trial, a decision must be made by the pharmaceutical company of whether the results justify the additional investment of further development. Similarly, phase II trials are used to inform decisions on further progression to a phase III randomized control trial. Additionally, the results of phase II trials must be interpreted in order to determine if they should advance to the final phase of development. Phase II trials take on a variety of forms, including comparative dose-finding studies, single arm response-rate analyses, and small randomized trials. Phase III randomized control trials in oncology, unlike phase I and phase II studies, are generally powered to conclusively detect a clinical benefit, such as improvement in progression free survival (62, 63), improvement overall survival, or improvement in health-related quality of life, compared a given standard of care. So, phase III trials are interpreted on more transparent statistical measurement, and successful trials are relatively easy to identify. For the purpose of this model, we assume that a successful phase III clinical trial can be used as a surrogate for market approval. As a drug progresses through the phases on development, it must

therefore pass through each step, and at the completion of each step, has a probability (p) of proceeding to the next phase and a probability (1-p) for failing (figure 2.1)(64, 65).

Figure 2.1. Primary conceptual model of drug development



Legend:

- Sr(pc) = preclinical success rate
- Sr(pi) = phase I success rate
- Sr(pii) = phase II success rate
- Sr(piii) = phase III success rate

We developed a second conceptual model with the understanding that once a drug successfully completed the pre-clinical phase, a company may attempt to demonstrated efficacy for a multitude of cancer indications. Through discussions with oncologists

familiar with drug development, two potential scenarios where identified: studying the drug for multiple stages of the same cancer or for separate malignancies entirely (figure 2.2). In the former model, the outcomes of testing a drug in different states of the same illness cannot be assumed to be independent, as drug development for earlier stage malignancy can actually be based on a reverse-migration strategy (66); that is, therapeutics that are effective in late-stage cancer can be considered excellent candidates as therapies in earlier stages of the same malignancy. In the latter model, it may be reasonable to assume that the success of testing drugs in different cancers represent statistically independent events. For companies choosing to study a compound in multiple cancers, additional costs for phase I, phase II, and phase III would be incurred for each new indication, but preclinical costs would only be incurred once. A similar approach can be used in the phase I setting, that is, a single phase I trial can be used to study a single drug in multiple cancer types, thereby potentially limiting the number of phase I trials required to move a drug through the development pathway (Figure 2.3) (67-70). Simultaneously studying novel drugs for multiple indications may therefore be attractive from an industrial perspective to decrease the overall mean cost of drug development per indication while increasing the overall probability of that the drug will receive at least one market-approved indication.

Figure 2.2. Conceptual model of drug development for multiple indications.

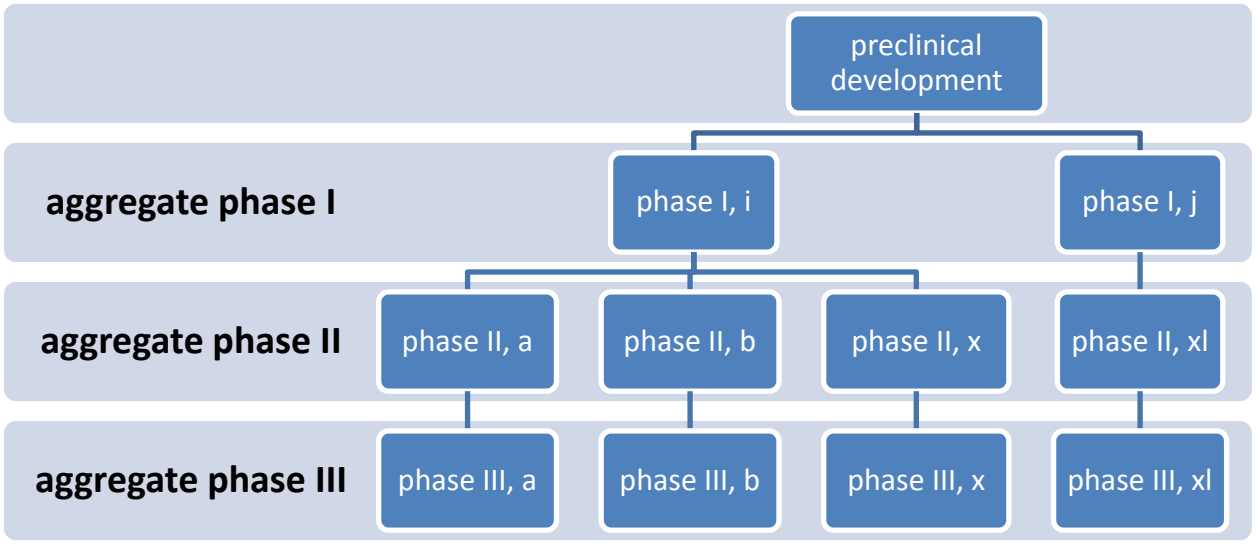
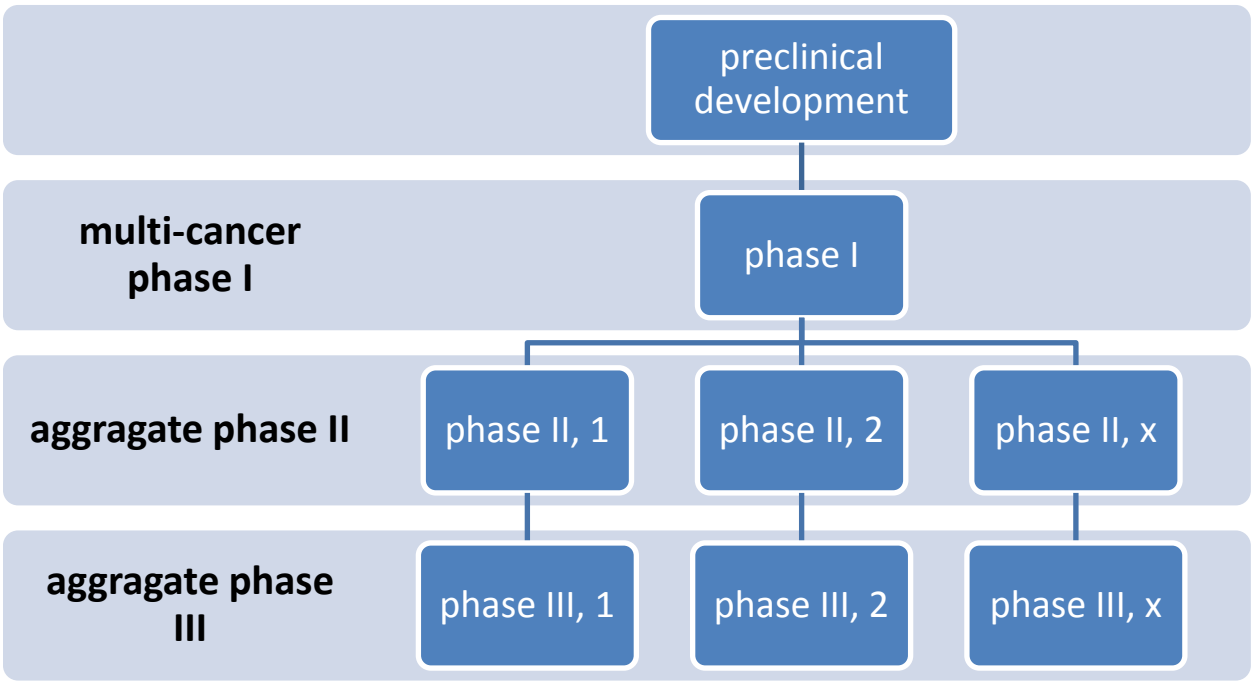


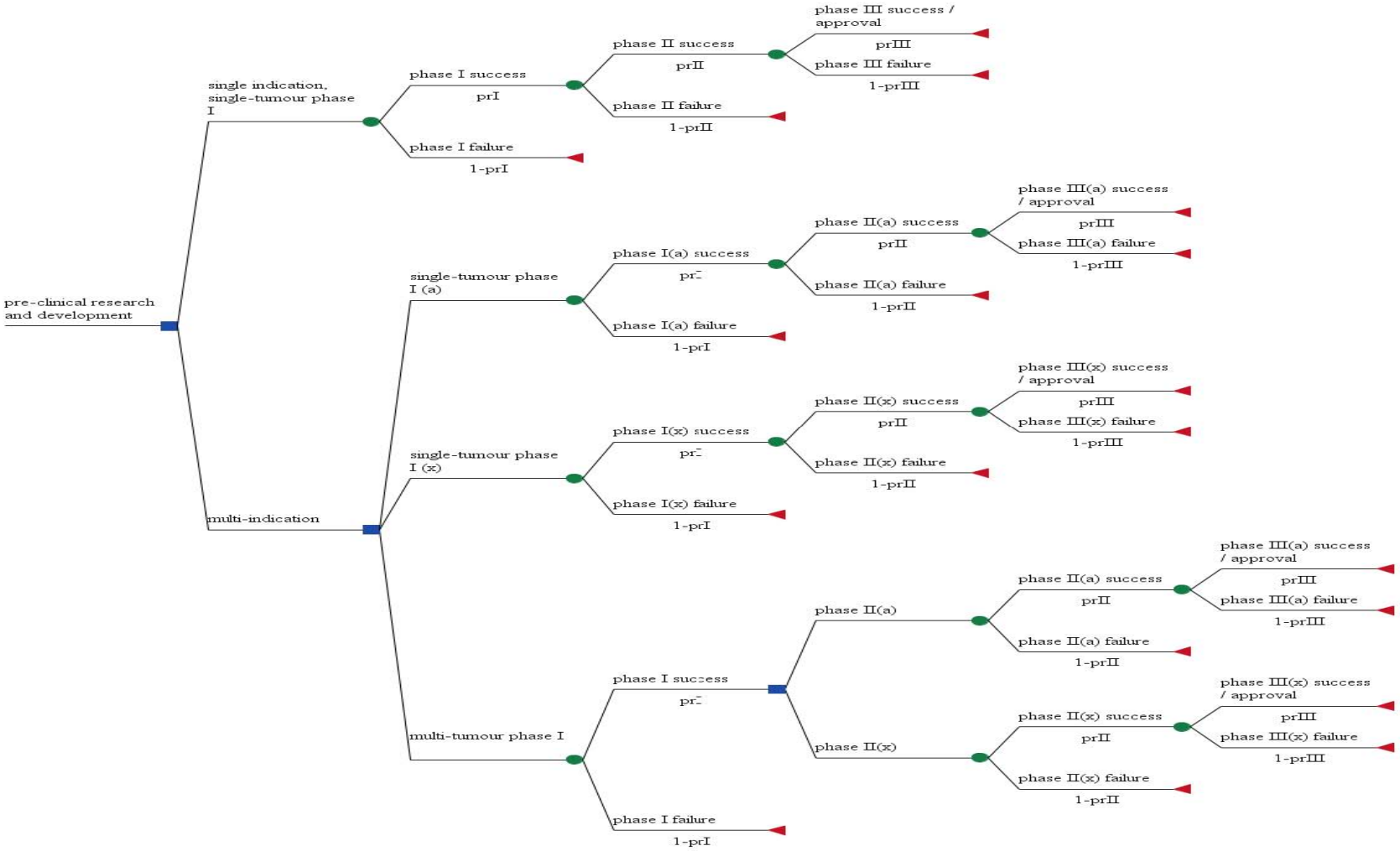
Figure 2.3. Conceptual model of the utilizing a common phase I strategy for drug development.



Assuming that sustainable industry in the long-run should only invest in ventures where their net income will be positive, the sum of costs and return on investment are less than the total revenue related to that product. In the life cycle of a drug, a pharmaceutical company may be envisioned to have two phases of incurred costs: pre-market approval and post-market approval. If the company is sufficiently able, such as in a large-capitalization pharmaceutical firm, it can take a drug through pre-clinical and clinical phases of research and development all the way through to market approval. In this scenario, the company's future revenue must be sufficient to cover these costs plus the cost of capital. Successful agents must also generate enough revenue to cover the costs of unsuccessful agents for a company to remain solvent, in the long run. Once the drug has attained market approval, revenue must also be sufficient to pay all of the additional costs fixed and variable costs of the pharmaceutical firm, including manufacturing costs, marketing costs, legal costs, and more. To estimate the component of the total revenue required for a sustainable pharmaceutical industry dictated by the costs associated with research and development, we chose to employ a linear cost-profit breakeven analysis to equate initial capital investment and risk, and post-drug-approval revenue; where drug development represents the bulk of investment (appendix A). To simplify use of the model, we assumed that all costs were incurred at the beginning of each clinical trial. A decision tree analysis was also utilized to define the relationships between investment-decision events (pre-clinical and clinical trials), their risk, and to identify areas of choice (Figure 2.4). In addition to a trial result, as mentioned above, a separate decision must be made at the completion of each phase of development, with the exception of phase III, of whether to proceed with further development or to abandon the

therapeutic agent for the specific studied indication (the investment-decision event). The methods by which the pharmaceutical companies make such decisions are unknown and likely to be company and disease specific. Instead, phase transition probabilities may be calculated by dividing the number of molecules that completed a specific phase and entered the subsequent phase by the difference between agents that entered the phase and those still in the phase at the time of study (71). By this method, the overall approvals success rate can be calculated as a product of the phase success rate probabilities and the phase success rates implicitly incorporate the go-no-go decisions of the pharmaceutical companies.

Figure 2.4. Decision tree for pharmaceutical research and development.



3.2 Data Sources

The required inputs to the decision-tree model include:

- Overall cost of therapeutic development.
- Overall probability of developing a novel compound from a pre-clinical state to market approval.
- Incremental costs of each phase of drug development.
- The probabilities of progressing through each phase of drug development.

To apply the model to targeted chemotherapy for incurable solid cancers, additional inputs include:

- Oncology specific overall costs of research and development.
- Oncology specific overall and incremental probabilities of developing a drug from a pre-clinical state to market approval.
- Accurate phase III targeted chemotherapy success rates for incurable solid tumours.
- Range of progression-free survival, or length of drug use, for approved targeted therapies for incurable solid cancers.

To collect these inputs, two separate literature reviews were undertaken.

1. Systematic review of costs of novel drug research and development.
2. Systematic review and meta-analysis of randomized controlled trials on targeted therapies for incurable solid cancers.

3.3 Analysis

We took the perspective of a large-capitalization pharmaceutical firm with the intent and ability to develop a compound from preclinical through to phase III clinical research and market approval. From the systematic review of new drug development we estimated capitalized cost of pre-clinical development, phase I, phase II, and phase III clinical trial costs and the associated phase transition probabilities. We assumed that the probability of developing a successful compound for one cancer type was independent of the probability that the same compound would be successful in a different cancer. We assumed that any compound would be considered for market-approval if it was able to demonstrate a incremental improvement in progression-free survival, the lowest threshold accepted by the Food and Drug Administration. We did not adjust for the possibility of rejection based on an unacceptable incremental cost effectiveness ratio; we assumed for the purpose of this analysis we focused exclusively on the effect of R&D costs (our research objective), ignoring manufacturing and sales costs (which are outside the scope of this analysis), on final minimum revenues, which are sunk at the time of price negotiation.

For the reference case for minimum required revenue dictated by R&D, we employed a cost of capital estimate of 11%(72-74) (75, 76), the most commonly used estimate. In the base case, we also used the cancer-specific estimates for R&D cost when directly tied to phase transition probabilities (72-74), to decrease the internal variability of the data. However, we performed a series of analyses to estimate the minimum required revenue over the entire range of R&D costs and phase transition probabilities. We used the year of dollars denominated in the original studies to avoid the issues relating to estimates of R&D specific cost inflation above standard inflation.

To estimate the minimum required revenue required per month per patient, the base case employed the above to estimate the total revenue and the average median progression free survival of all drugs that demonstrated an incremental benefit over the standard of care for the specific cancer type. Revenue realized beyond one year was discounted at the cost of capital instead of the inflation rate because the opportunity cost of deferred revenue to the firm is the inability to re-invest the proceeds in further R&D. Maximum and minimum required revenues were computed across the range of reported progression-free survival estimates, phase transition probabilities, and chosen strategy for drug development.

Chapter 3 – Methods of systematic literature reviews for model inputs

3.1 Systematic review of new drug development

Criteria for inclusion/exclusion of manuscripts

Studies of the cost per novel drug developed were considered for inclusion. The studies could be disease non-specific, but if a single disease was specified then only manuscripts that dealt with oncology chemotherapy were included. Both risk adjusted and non-risk adjusted analyses were included provided that they reported on out-of-pocked costs and the time for a phase of trial and the time between phases. The analyses did not necessarily have to report on the cost of capital to be included. Papers that examined only the probabilities of progression through drug phases were not specifically searched since cost of drug development was considered the primary goal, and such probabilities would be a natural component of such analyses. However, papers reporting only research phase transition probabilities were included in the analysis.

Papers were excluded from this analysis if they reported only on non-cancer treatments. Inclusion was also limited to English language papers.

All inclusion and exclusion criteria were decided *a priori*.

Identification of manuscripts

We searched PubMed and EMBase on April 8th, 2011 using the search term headings “cost and cost analysis” and “drug evaluation.” These two subject headings were deemed the most appropriate method for searching these databases for drug development data by a certified research librarian. In addition, manual “grey” literature

searches of NHS Economic Evaluation Database, the Center for Health Economics, the Center for Health Economics and Policy Analysis, and the International Society for Pharmacoeconomics and Outcomes, recommended by the Institute of Health Economics as high-quality health economic resources.

Methods for application of inclusion/exclusion criteria

Serial title and abstract searches were performed by two reviewers, independently. All articles identified by either reviewer as being of possible relevance, defined as not obviously an inappropriate disease, were subsequently scrutinized by abstract. Abstracts were analysed independently and in duplicate. All articles that did not demonstrate reason for exclusion were included in the final analysis.

Relevance and data abstraction

A standardized form was created by the primary author to assist in data abstraction. This form was employed by two authors independently and in duplicate. Consensus for disagreement was achieved after careful review and discussion. Identifying information, including primary author, date of publication, and phase of trial were abstracted. The assumed cost of capital with the method used to estimate this cost was abstracted. Mean and ranges of total and incremental out-of-pocket costs, capitalized costs were collected as well. Finally, the overall success rate of drug approval and the phase-specific probabilities for successful advancement were abstracted.

3.2 Systematic review and meta-analysis of targeted therapy for incurable solid cancers

Criteria for inclusion/exclusion of trials

Only randomized controlled trials of patients greater than 18 years of age with incurable solid cancer were considered for inclusion. Incurable cancers included all metastatic solid tumour, stage IIIB non small-cell lung cancer, advanced melanoma, or recurrent disease. The primary intervention of study should be the addition or substitution of a targeted chemotherapy into a treatment regimen. This includes trials that add a second targeted agent to a treatment protocol that already contains any number of other targeted drugs. RCTs that compared a targeted therapy to placebo alone were also eligible for inclusion.

Papers were excluded from this meta-analysis if they were reporting only on a subgroup of a RCT that would otherwise be included, to avoid double counting of patients. Trials that compared two doses of the same chemotherapy regimens and nuclear-based treatments were to be excluded. Phase I trials, combination phase I-II trials, and trials that included more than 15% curable cancer patients, and review articles of any type were also deemed ineligible. Inclusion was also limited to English language papers.

All inclusion and exclusion criteria were decided *a priori*.

Identification of manuscripts

We searched Medline, EMBase, and the Cochrane Central Register of Controlled Trials from 1975 – March 9 2009, the original date of database access. The search was subsequently updated, by searching the same databases from 2009 to April 21 2010, the second date of database access (appendix B). Since humanized monoclonal antibodies

had not been developed until 1988 (77), we are confident that our search did not miss articles as a result of time-limited search. The search strategy was developed by a certified research librarian, a Royal College of Physicians and Surgeons of Canada certified medical oncologist, and included a validated search strategy for identifying RCTs in Medline (78). The EMBase search incorporated a similar search strategy specific to EMBase that was created by the same group, but had not been validated before use. Drug names added to the search were decided on in consultation with a medical oncologist specializing in experimental clinical trials. Unpublished data and conference proceedings were not explored because of the assumed small benefit of targeted therapy on the overall course of metastatic cancer.

Methods for application of inclusion/exclusion criteria

Serial title and abstract searches were performed by two reviewers, independently. All articles identified by either reviewer as being of possible relevance, defined as not obviously an inappropriate disease or an irrelevant treatment, were subsequently scrutinized by abstract. Abstracts were analysed independently and duplicated. Excluded articles were classified as either being the wrong type of study or an inappropriate disease. All articles that did not demonstrate reason for exclusion were included in the final analysis.

Relevance and data abstraction

A standardized form was created by the primary author to examine each article for relevance and for data abstraction, which was employed by two authors independently and in duplicate. Consensus for disagreement was achieved after careful review and

discussion. Identifying information, including primary author, date of publication, and phase of trial were abstracted. The study intervention, the comparison, the type of cancer being treated, the participants, and the pre-specified outcomes were also abstracted. All included manuscripts were assessed using the Cochrane Risk of Bias tool (79).

Survival data was collected as a continuous variable, using inverse variance statistical modeling. Heterogeneity was expected and so random-effects analysis was to be used. In consultation with a meta-analysis statistician, even though survival is measured as a median value, for the purpose of analysis, the true value was assumed to be normally distributed; consequently, its properties in a large meta-analysis would be similar to a mean. Pooled standardized mean differences would also be calculated to help determine if the differences in PFS and OS that will be observed across studies are the result of the intervention or a function of the cancer type: a reduction in heterogeneity by effect size would suggest that changes in survival outcomes across studies are accompanied by corresponding changes in variance of those outcomes and related to the natural history of the tumor instead of the therapy, *per se*.

Grade 3 and Grade 4 toxicity was abstracted as a dichotomous variable and Mantel-Haentszel modeling was used. Individual event rates and total included subjects were collected and converted into odds ratios (OR) for the purpose of comparable analysis between treatment regimens that include other chemotherapeutic agents with placebo controls.

Pre-specified subgroup analyses were planed based on effect and class of treatment.

Chapter 4 – Results

4.1 Systematic review of new drug development

Description of studies

The searches of PubMed and EMBase yielded 291 citations. Given the small number, title and abstract searches were performed simultaneously. Only three contained target input data and met inclusion criteria (72-74). To improve the robustness of the data, explicit critique of the included papers on the cost of research and development for pharmaceutical companies were sought. Two critical analyses of the cost estimates were included (75, 76). However, they do not provide original cost estimates. Instead, they reanalyse the original data and apply different assumptions by incorporating tax deduction to cost, the potential for inflated average sizes of phase III clinical trials in the original analysis, and how a smaller number of very expensive trials increased the mean cost per new molecule discovered. The validity of each analysis has been publically debated by the authors (80, 81). Unfortunately, these alternative analyses do not provide specific information on how their new analyses would modify the costs of specific portions of research and development, and so, we were forced to assume that the reduced costs would be exercised in the similar proportions as the original studies. Bias favouring inflated industry costs appears probable in the papers concluding higher costs of drug development, but without descriptions on the revised mean phase costs, we are unable to incorporate these lower estimates into the complete analysis. This may lead to an overestimation of the required return on capital investment.

Much of the data is based on the *DiMassi et al. (2003)* estimates on the cost of drug development. Ten multinational pharmaceutical companies were surveyed on their research and development costs of self-originated compounds. However, 24 firms were invited to participate in the study and 2 firms provided insufficient data for inclusion. Compounds developed with research originating from academic institutions were excluded, but this was deemed reasonable as 93.3% of novel therapeutics have been reported to originate from industrial sources (82, 83). The 68 studied drugs were reported to be chosen at random from the Tufts Center for the Study of Drug Development database of investigational compounds. Weighted mean, median, and the standard deviation of costs were estimated through the survey data. The capital asset pricing model was employed as an estimate of the discount rate based on the industry's market value of debt and equity (84, 85). Probability estimates on phase transition estimates were obtained from analysis of the Tufts Center for the Study of Drug Development database using drugs similar in type to the compounds included in the study.

The methods employed by *Adams, et al.* were identical to those utilized by *DiMassi et al. (2003),* but instead of using estimates from the Tufts Center for the Study of Drug Development database, the used the *Pharmaprojects* database. *Pharmaprojects* differs from the Tufts database in that it is publically available and compiles information from press releases, presentations, and other publically available information on drug development. Taking advantage of the larger database, they incorporated 3,181 novel therapeutic compounds into their analysis of overall and phase-specific success rates. The larger sample size allowed for cost analysis across drug indications and specialties. However, the costing data per phase of development and cost-of-capital estimates were

taken directly from *DiMassi et al. (2003).* Cost across specialties was assumed to be related to phase success rates rather then cost per phase. However, time-cost of oncology drug development likely plays a significant role as clinical drug development in oncology seems to require an additional 1.5 years to complete when compared to other specialties (71).

Instead of developing independent data, *Vernon et al.* argued for the utilization of the Fama-French Three Factor Model for estimating cost of capital rather than the Capital Asset Pricing Model. The cost of capital estimated using the Three Factor model was greater than the Capital Asset pricing model estimate as a result of added company size-risk, the blockbuster payoffs of successful new therapeutic entities, and added dependence on external funding for research and development when compared to the entire equity market. They relied entirely on the original data collected by *DiMassi et al. (2003)* for all other inputs. Despite the benefits of incorporating additional measures into the cost-of-capital measurement, 74% of chief financial officers actually use the capital asset pricing model to compute the cost of capital (86). Moreover, for the purpose of our analysis, industry is assumed to be sufficiently large to invest in a wide variety of pharmaceutical molecules, decreasing the corresponding size-related risk component of the Three Factor model. Subsequently, the Capital Asset Pricing Model may be more appropriate for this analysis.

Description of costs and success rates

All desired inputs of general and oncology specific costs, as well as general and oncology specific phase success rates were collected (table 4.1). For the purpose of this

analysis, phase success rates and phase transition probabilities, the probability of progressing through a given phase and proceeding with the subsequent phase, were assumed to be equivalent. Cost of capital estimates range from 9% to over 14% depending on the method used. This translates into mean capitalized costs ranging from $707 million USD (in year 2000 dollars) to $992 million USD. Excluding exceptionally expensive new therapeutic entities by using the median cost per molecular entity, reduces the estimated capitalized cost of drug development to $300 million USD. Incorporating potential tax benefits and subsidies may further reduce the effective cost, but no study provides detailed information on how to calculate the potential reduction.

Phase success rates were comparable amongst studies irrespective of whether the new drugs were analysed in a generic or oncology specific setting. All studies assumed a 100% rate of progression from pre-clinical to clinical trials. Phase I trials uniformly had the highest success rate, ranging from 68% to 78% of investigated drugs progressing through this developmental stage. The estimates for phase II and phase III success rates were more variable. Phase II and phase III success rates ranged from 44% to 59% and 43% to 68%, respectively. However, since such estimates vary by the disease and method used to calculate them, we felt that analyzing the breakeven revenue required per new therapeutic across the studies represents a more methodologically sound approach to the interpretation of these results, rather than testing across the full potential ranges of phase success rates. Since each rate probably cannot be considered independent of the study that measure it and different companies at different times may change their criteria for identifying drugs that should proceed to the subsequent phase of development, we could not adjust for these unreported potential confounders. Despite the fact that these

studies are not specific to the cost of developing a targeted therapeutic agent, there is no available data on how that would change the expenditures of each phase. Unless the development of biomarker is required as a part of the drug development process, there is little reason to suspect a large difference in costs between the development of cytotoxic chemotherapy and targeted therapy. Additionally, the average cost of R&D for broadly diversified company would be buffered by non-oncologic departments.

Table 4.1. Costs, time, and success rates of drug trials

	DiMasi, 2003	Adams, 2006	Vernon, 2009	Light, 2007	DiMasi, 2007
cost of capital / year	11.02% (9%-12%)	11%	14.36%	11%	N/A
out-of-pocket cost / novel drug	$403 million USD $282 million clinic	$443 million USD $310 million clinic	N/A		N/A
cost/novel drug	$802 million USD	$868 ($1042*) million USD	$992 million USD	$300 million USD $50-$600 million USD	N/A
capitalized cost, pre-clinical	$335 million USD	$381 million USD	N/A	N/A	N/A
mean cost, phase I	$31 million USD	$32 million USD	N/A	N/A	N/A
mean cost, phase II	$42 million USD	$40 million USD	N/A	N/A	N/A
mean cost, phase III	$119 million USD	$113 million USD	N/A	N/A	N/A
success rate, overall	0.21	0.2*	N/A	N/A	0.25 (0.26*)
success rate, pre-clinical	1	1	N/A	N/A	1
success rate, phase I	0.71	0.78*	N/A	N/A	0.68 (0.77*)
success rate, phase II	0.44	0.59*	N/A	N/A	0.53 (0.59*)
success rate, phase III	0.67	0.43*	N/A	N/A	0.68 (0.57*)

*cancer specific data

4.2 Systematic review and meta-analysis of targeted therapy for incurable solid cancers

Description of studies

The original search of Medline, EMBase, and the Cochrane Central Register of Controlled Trials for randomized phase II or phase III on tyrosine-kinase inhibitors and monoclonal antibodies studied for the potential treatment of incurable solid cancers identified 5,846 citations. 1,072 of those citations were duplicates. Applying the exclusion criteria in a title search eliminated over 4000 citations because they were either studies of an inappropriate disease or non-targeted treatment. And the abstract search excluded a further 1,116 articles. The full text of the remaining 122 articles were collected and critically reviewed. A further 56 articles were excluded, leaving 65 articles to be included in the final review (figure 4.1). The data from all 65 manuscripts were extracted and synthesized. The updated search of the same databases yielded an additional 1,888 citations. Over 1800 papers were excluded as duplicates, non-solid cancer studies, inappropriate phase of trial, or non-English studies. 4 studies from the second search were already included from the first database search and were not included a second time (figure 4.2).

Figure 4.1. Flowchart illustrating the process and the reasons for original trial selection in this meta-analysis

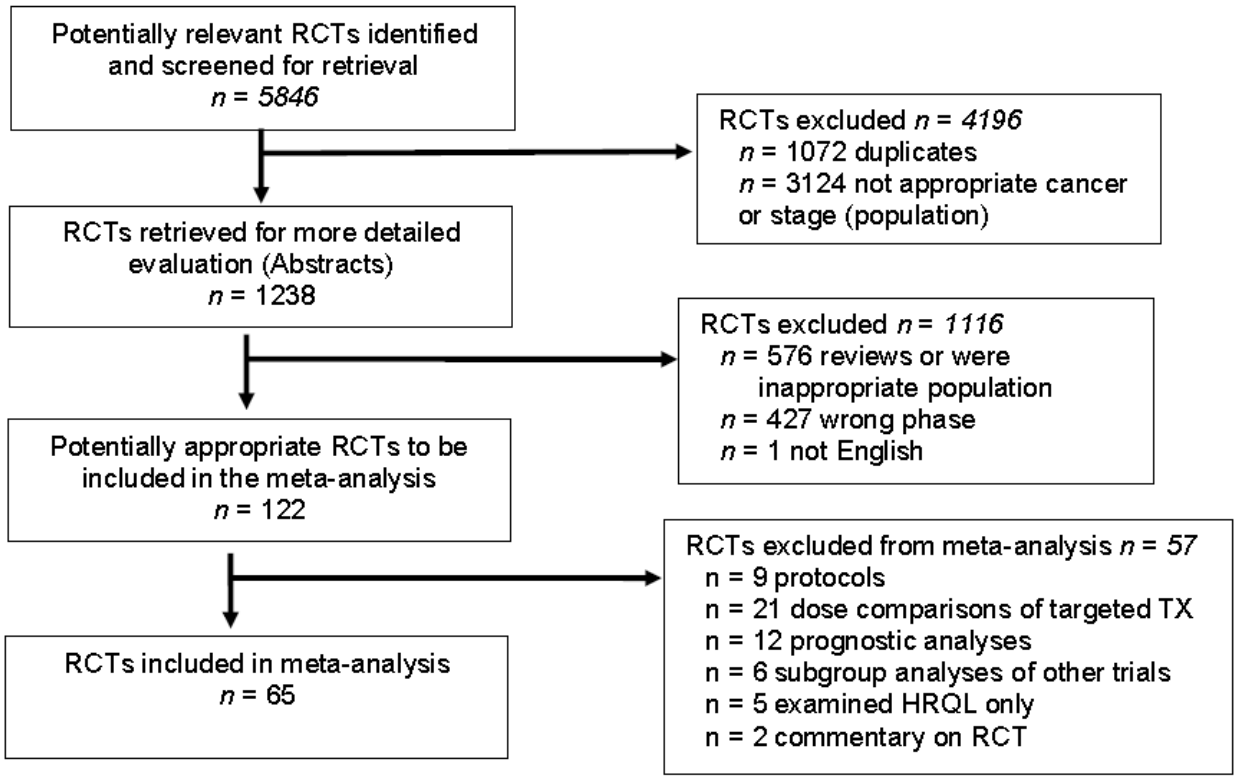
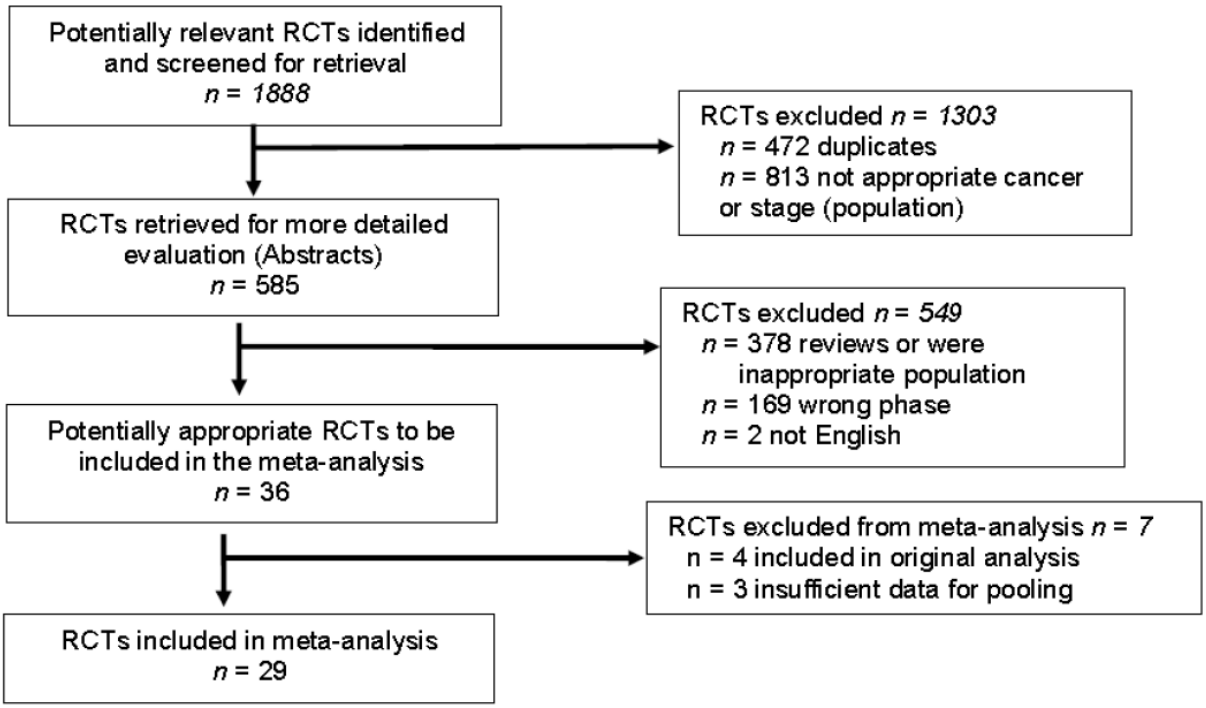


Figure 4.2. Flowchart illustrating the process and the reasons for trial selection the second portion meta-analysis.



All of the articles provided progression free survival and toxicity data. But only 64 trials included sufficient median survival data to allow for pooling (appendix C: MA included references). Median survival data could not be included if the median survival of patients in the trial had not been reached or statistical analysis of survival data had not been completed. 42 trials studied the use of a monoclonal antibody, and the remainder studied small molecule inhibitors. In total, 19 different treatments were tested. 60% of the trials were phase III. Examining the effect of the addition of a treatment to an already proven chemotherapy regimen was by far the most common type of investigation; only 18 papers examined whether an entire regimen could be replaced by a targeted therapy. The types of cancer were varied; cancers

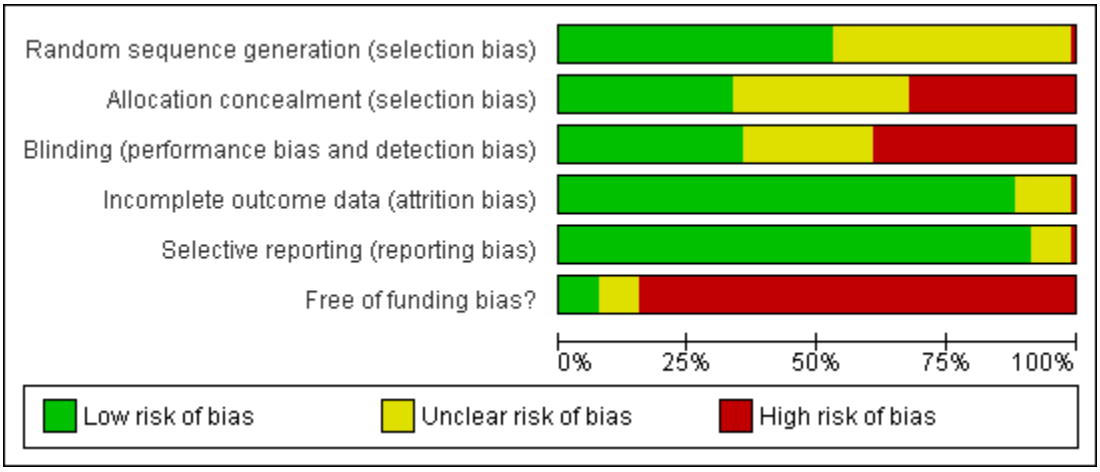
missing from analysis include thyroid cancer, oesophageal cancer, cancers that arise from the central nervous system (appendix D).

However, the studies inclusion criteria for the health status of patients at the beginning of the study was largely homogenous; 87 trials only included patients that had a WHO performance status of 2 (spending less that 50% of one's day in bed) or better.

Risk of bias assessment

The risk of bias for each study was assessed using the Cochrane Risk of Bias assessment tool (figure 4.3). Allocation and concealment were infrequently discussed, but was obviously absent in many studies as a consequence of open-label study designs. The absence of blinding was present in over 30% of all articles. 87% of manuscripts accounted for all patients in their final analyses and avoided selective reporting of patients. Attrition bias was only clearly present for 1 study. Funding bias was a major issue; over 80% were sponsored directly by the pharmaceutical company that produced the drug in question or the primary investigator was in some way associated with the company, compared to 29% present in the general oncology literature (87). Consequently, the risk of bias in this analysis is high and the overall treatment effect may be overestimated (88).

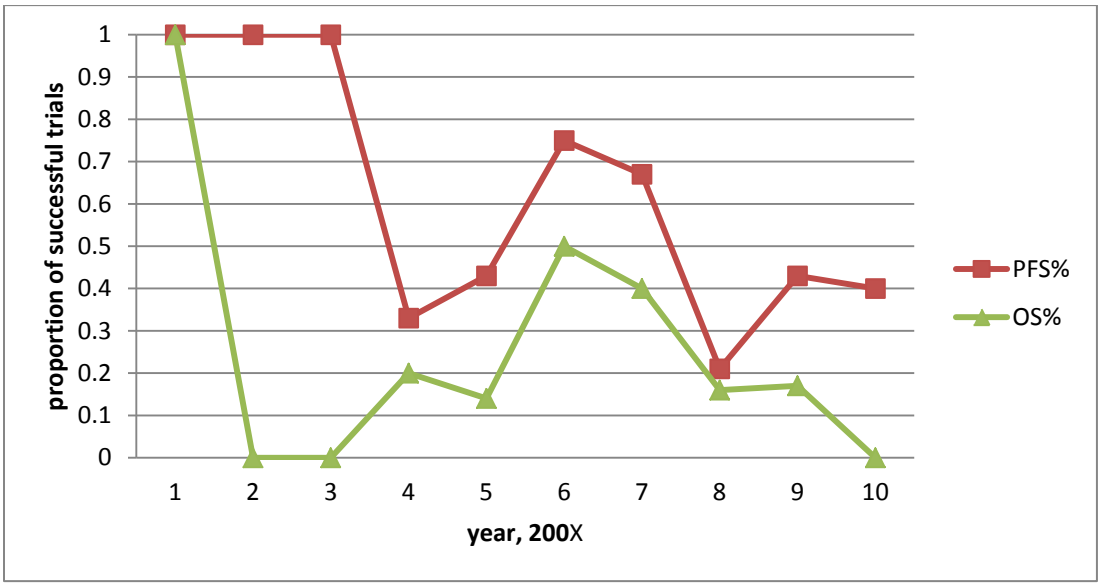
Figure 4.3. Methodological quality: as percentages across all included studies



Effects of interventions

There has been some success with the study of targeted chemotherapy for incurable solid cancer with regards to survival end-points (figure 4.4). For patients choosing to enrol in clinical trials, the advent of targeted chemotherapy has led to an increase in median progression free survival of 0.60 months (95% CI, 0.46-0.74, i^2=81%) (figure 4.5) and median overall survival of 0.79 months (95% CI, 0.29-1.14, i^2=50%) (figure 4.6). Standardizing for cancer type using the standardized mean difference did not appreciably reduce heterogeneity.

Figure 4.4. Trial successes rates achieved over the years.



From a public investment perspective, examining the medical oncology treatment population as a whole, where positive phase III trials translate into drug use, the increase in progression free survival becomes 1.69 months (95% CI, 1.41-1.97, i^2=86%) and a median survival increase of 2.52 months (95%CI, 1.88-3.15, i^2=17%). Grouping positive and equivocal trials while simultaneously standardizing for cancer through measuring effect size virtually eliminated heterogeneity in both groups. Although progression free survival and overall survival were measured in months for all studies, each cancer type's scale of benefit could be considered a function of its natural history survival. The progression free survival standardized mean difference has improved 0.29 (95% CI, 0.25-0.33, i^2=34%) (figure 4.6) and the overall survival standardized mean difference has improved 0.2 (95% CI, 0.16-0.24, i^2=0%) (figure 4.7) in the populations that targeted chemotherapy have been shown to be of benefit. The reduction in heterogeneity by effect size suggests that changes in survival outcomes across studies are accompanied by corresponding changes in variance of those outcomes. Targeted chemotherapy

may provide more predictable benefit in patients with very poor survival expectancies and greater variation for cancers that are relatively more indolent. Ranges of median progression free survival months obtained with targeted therapy- containing regimens are summarized by cancer type in table 4.2.

Table 4.2. Range of total progression free survival months with treatment regimens that include targeted therapy for incurable solid cancer

Cancer Type	PFS maximum (months)	PFS Average (months)	PFS Minimum (months)
Breast cancer	11.8	7.2	3
CRC	19.6	7.5	2
Head & neck SCC	6	5.6	5
Liver & bile duct cancer	3.58	2.8	2.6
Pancreatic cancer	4.6	4.2	3.75
NSCLC	9.2	5.9	3
RCC	11	7.5	3.8

Legend:

- CRC: colorectal cancer
- NSCLC: non small-cell lung cancer
- RCC: renal cell carcinoma
- SCC: squamous cell carcinoma
- PFS: progression free survival

Pooling of toxicity data was attempted, but significant heterogeneity (i^2=99%) precluded its value. Subgroup analysis was attempted based on class of drug, how it was incorporated into the study (i.e. versus placebo, versus standard chemotherapy, or as an addition to chemotherapy), and cancer type. Unfortunately, no improvement in heterogeneity was achieved. Therefore, no conclusion can be made as to a class effect on toxicity profiles of these classes of drugs. However, such data is not required for willingness-to-sell calculations, but would effect estimates on the breakeven revenue per month per patient.

Figure 4.5. Incremental average median progression free survival (months)

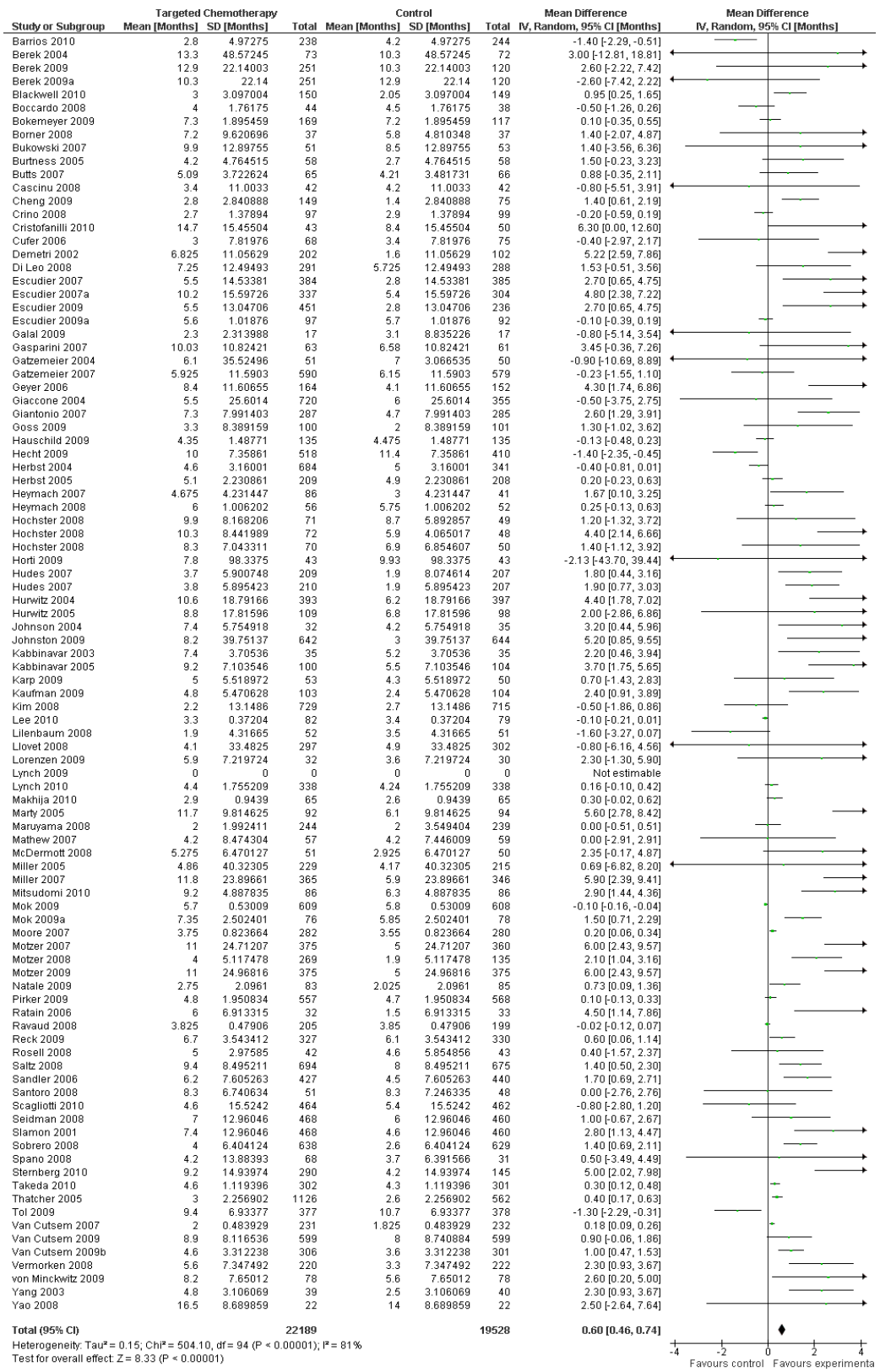


Figure 4.6. Incremental average median survival (months)

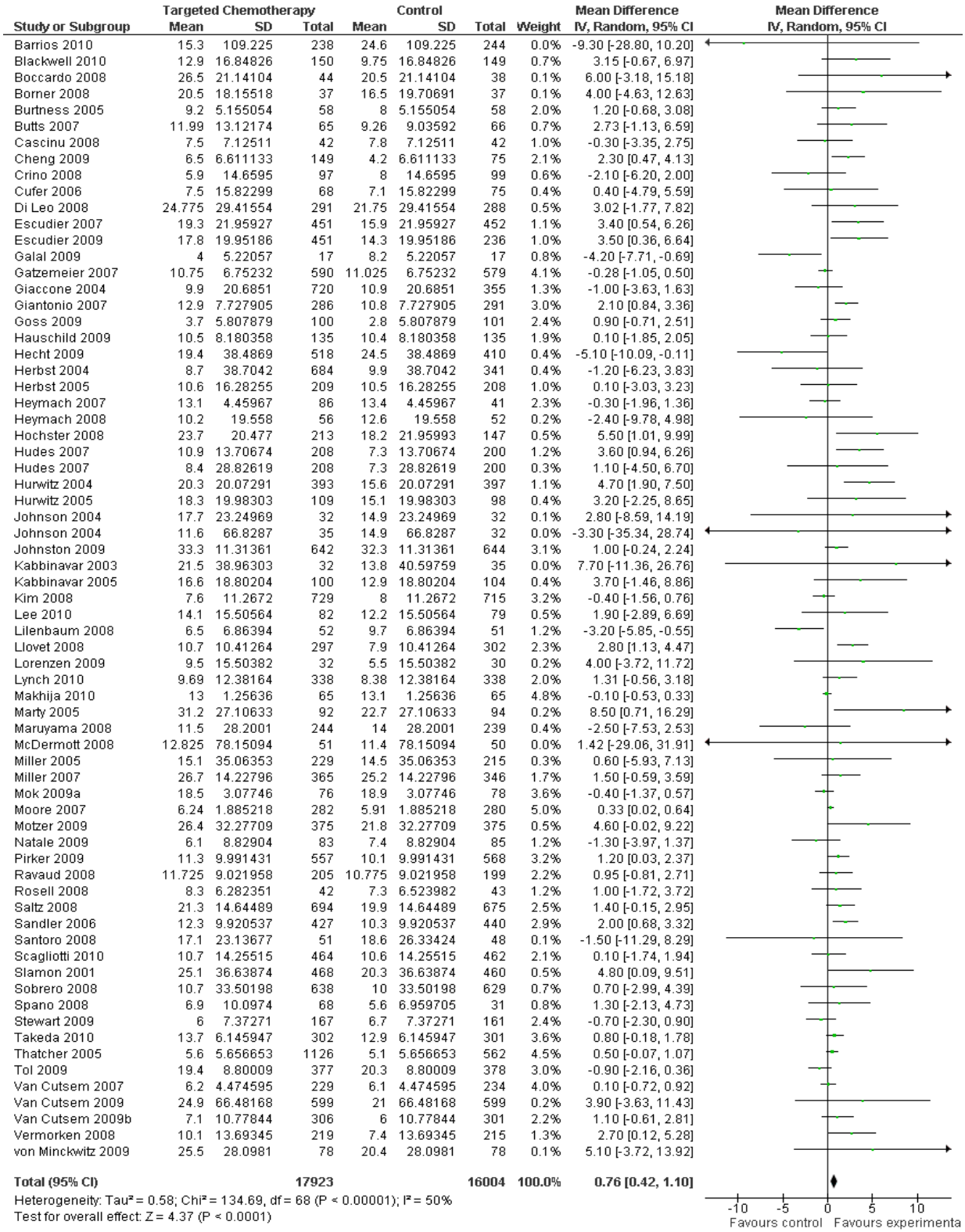


Figure 4.7. Standardized progression free survival for positive trials (unitless)

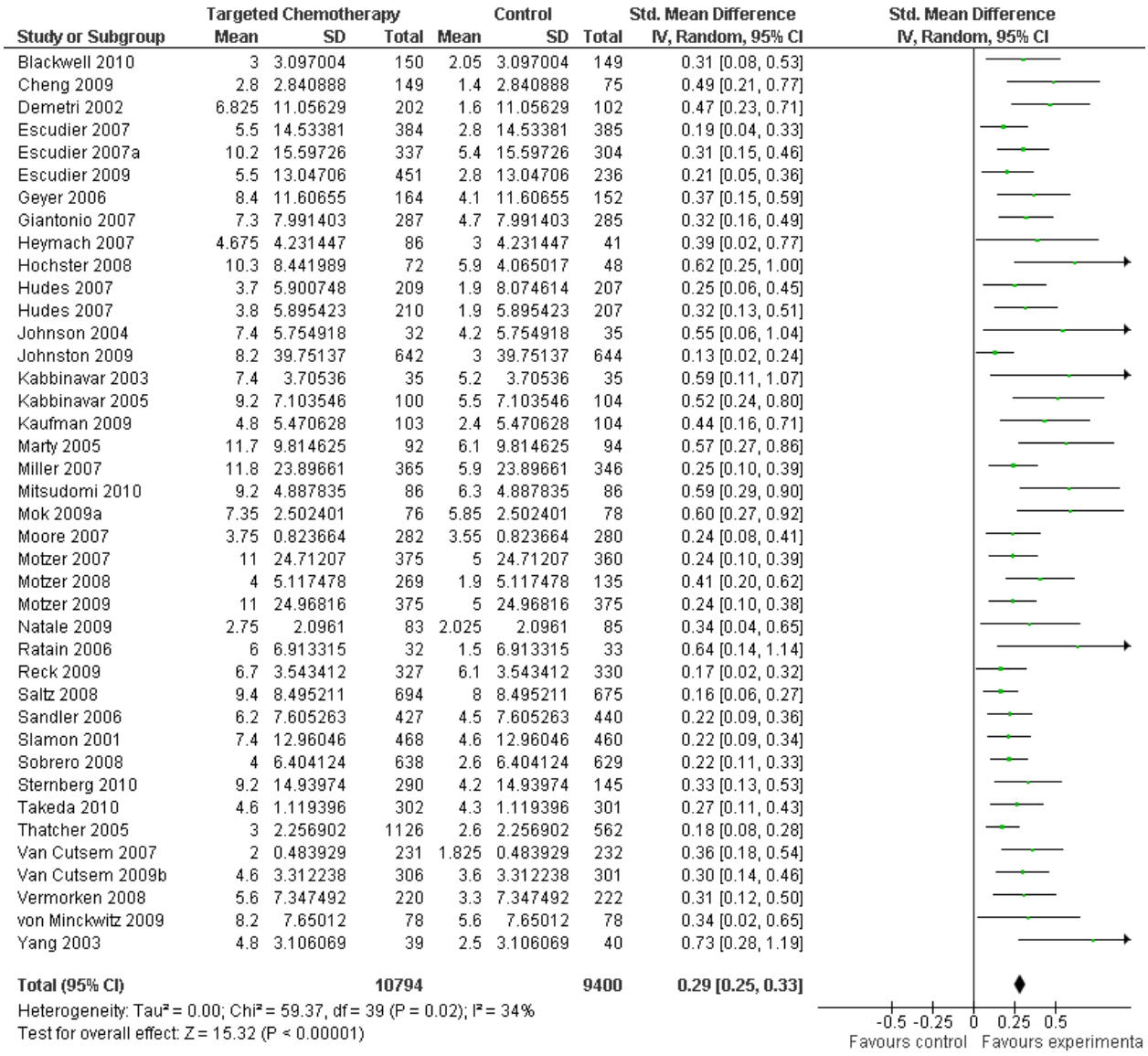
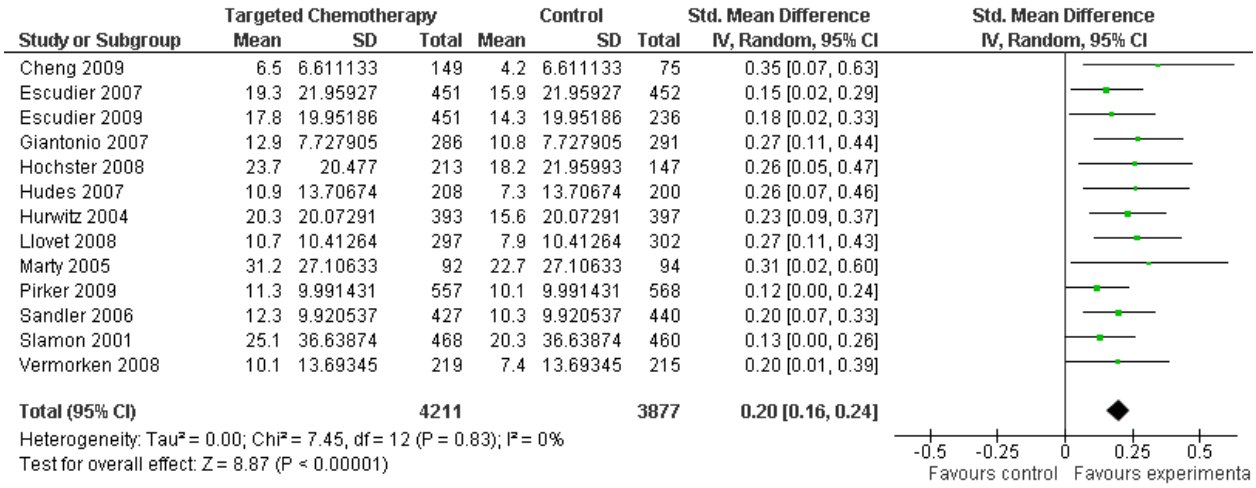


Figure 4.8. Standardized overall survival for positive trials (unitless)



4.3 Computing industry willingness to sell targeted therapy for incurable solid cancer

Drugs for single indications

When considering drug development a dynamic process, where at the completion of each phase previously accumulated expenses are considered sunk, the minimum required revenue associated with specifically with research and development (revenue) for continued drug development decreases substantially, even when only considering development of a drug for a single indication (figure 4.9). In the base-case scenario, where the total expense per novel drug developed approaches $802 million USD for an annualized cost-of-capital of 11%, the minimum revenue required to sustain the company's research and development (R&D) and encourage perpetual R&D of original therapeutics could be as high as $4.3 billion USD. However, the minimum revenue required per drug decreases exponentially in relation to increases in the market-approvals rate, the probability that a chemical compound will be successfully developed from pre-clinical phase to the completion of a phase III clinical trial that demonstrates a positive

important outcome, and the required revenue is linearly related to capitalized cost (figure 10). Company diversification across multiple disease classes can also significantly decrease the minimum required overall revenue by decreasing the average cost of drug development; increasing the scope of development from oncology-specific to broad diversification improves efficiency by $870 million USD per drug.

Figure 4.9. Minimum revenue required for continued research and development as development progresses.

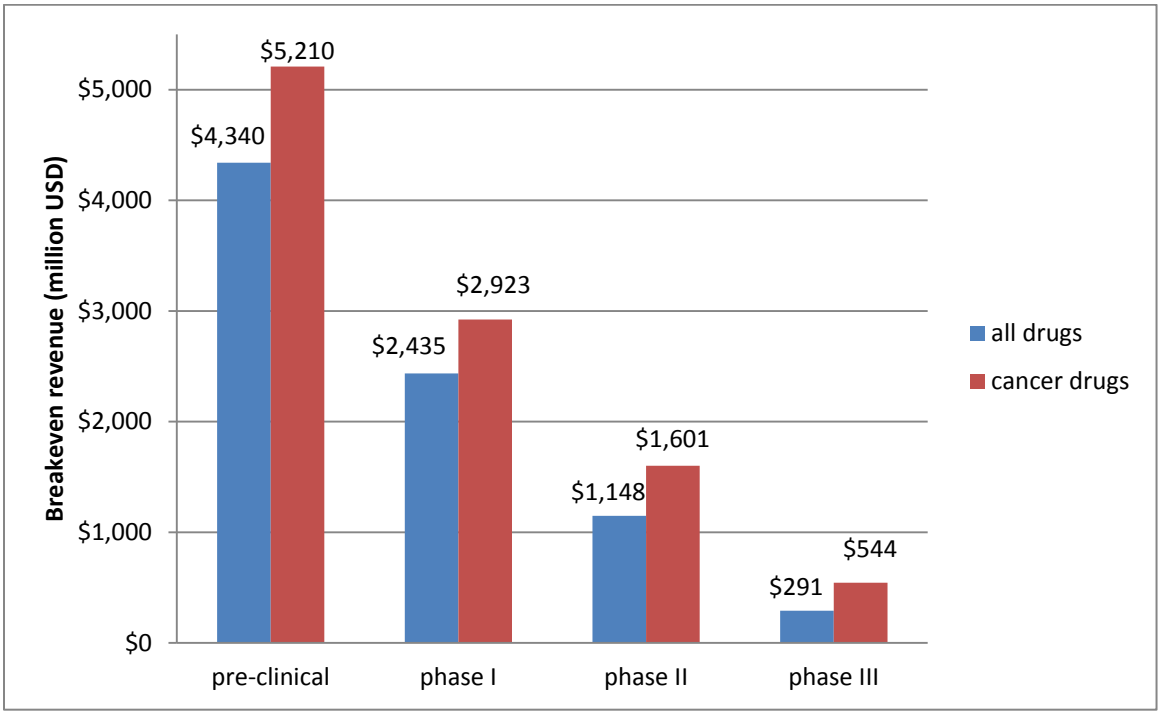
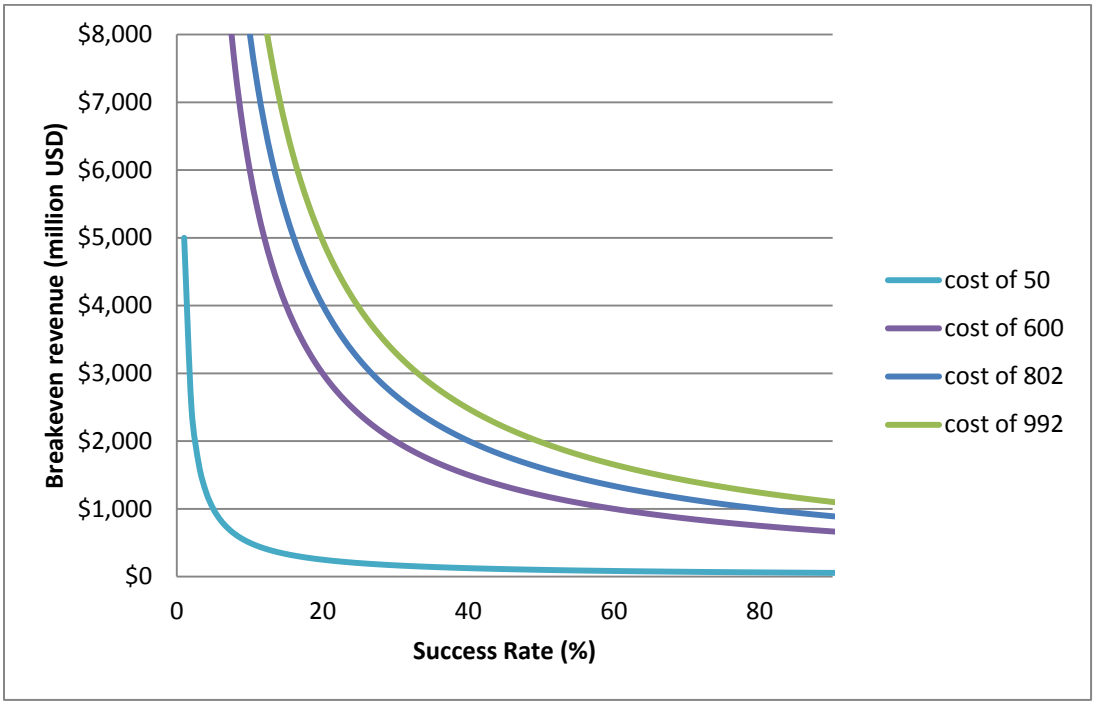


Figure 4.10. Breakeven revenue as a function of market approvals success rate for the range of potential costs of development.



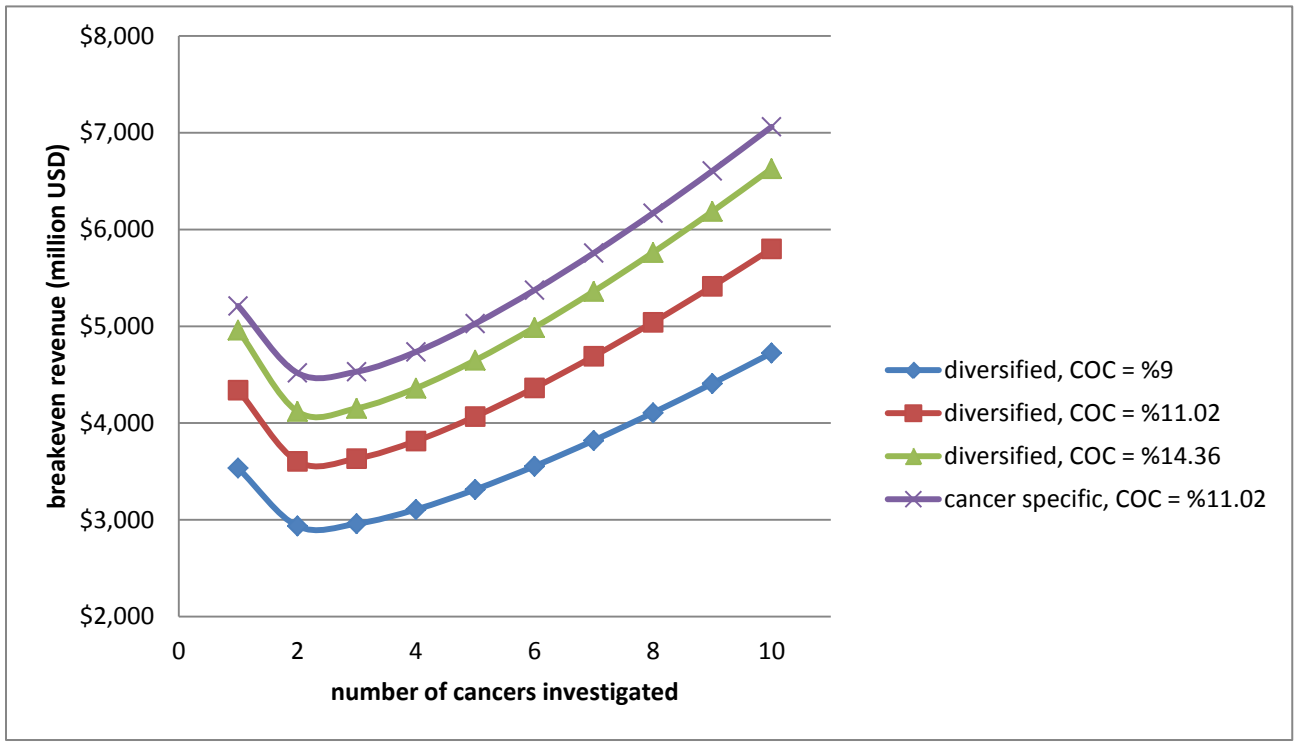
*costs are in hundred million USD

Drugs for multiple disease indications

Diversification across multiple indications provides a second opportunity for improvement in drug development efficiency over a drug designed for a single indication. When testing against independent indications, such as multiple malignancies, diversification has the potential for both improved probability of the drug receiving at least one indication for use, while simultaneously decreasing the overall cost of development per market approval by incurring the preclinical costs only once. Consequently, although an oncology-focused company producing a single therapy requires upwards of $5.21 billion USD for it to remain solvent in the long-term,

simultaneously developing it for two cancer types reduces the breakeven R&D associated revenue to $4.52 billion USD. However, in this scenario, minimum required revenue increases after the second indication; by 6 cancer types, the minimum required revenue increases over the base case by $163 million USD. Similar improvements in efficiency are achieved regardless of research and development expenditure (figure 4.11).

Figure 4.11. Minimum required revenue as a function of the number of indications attempted for a single drug.



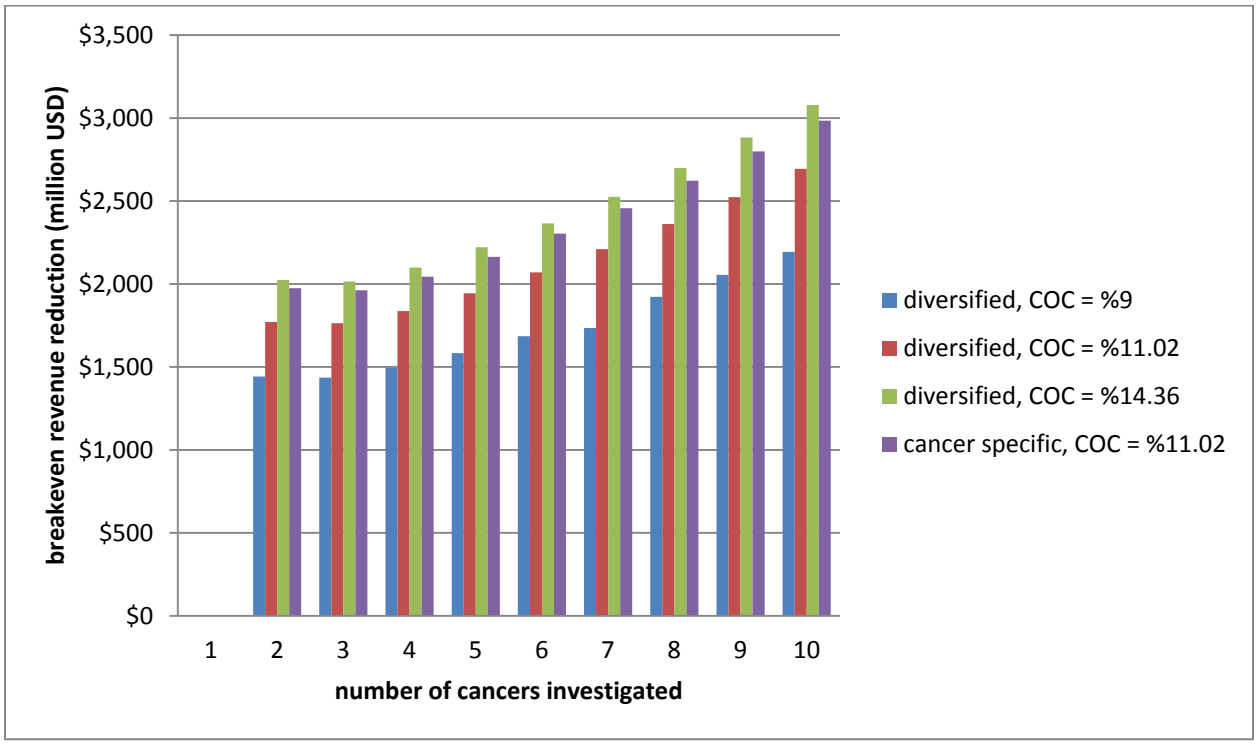
Legend:

- COC: cost of capital

Utilizing a multi-tumour phase I trial

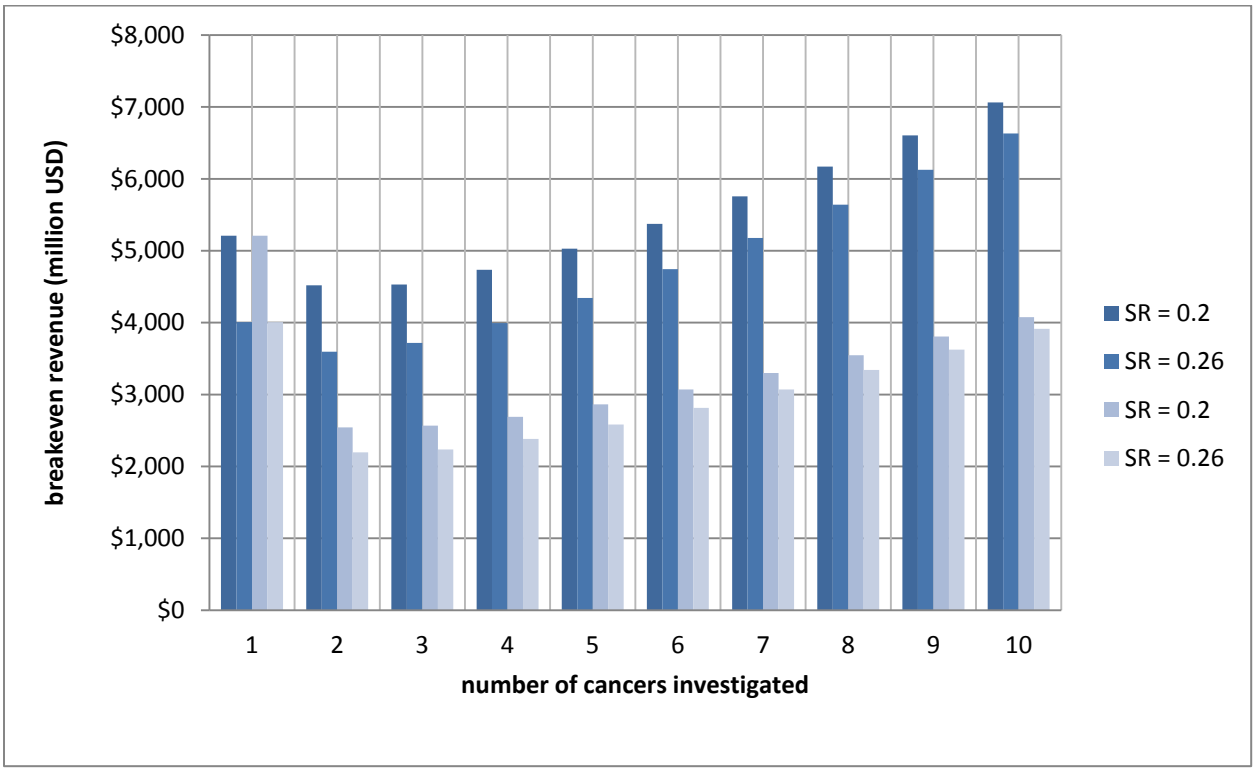
Employing a multi-indication or multi-tumour phase I trial instead of a single-tumour phase I trial, if possible, can translate to increased savings in both out-of-pocket costs and capitalized costs by limiting the number of trials needed to achieve market approval for a new pharmaceutical compound. Assuming that a single-indication and multi-indication phase I trials incur roughly equivalent out-of-pocket costs and require similar completion times, this approach to drug development results in a breakeven revenue of $1.83 billion USD instead of $3.6 billion USD required in the diversified company with a cost of capital of 11% even when only two indications are sought. Savings of minimum required revenue continue to increase as more indications are studied (figure 4.12). As the cost of capital increases, the potential reduction in minimum required revenue also increases. Moreover, because of reduced compounding cost of capital from earlier stages of drug development, the potential reductions increase as more independent indications for new medicines are sought. For oncology firms, if a multi-tumour phase I trial can be utilized in the development of a new drug, it can result in minimum breakeven revenue reductions of between $1.97 billion USD to $2.98 billion USD for 2 to 10 indications tested.

Figure 4.12. Breakeven revenue reduction by number of indications sought when switching from a single-indication to multi-indication phase I trial.



When considering different strategies of oncology research and development against the range of oncology success rates, we find required revenue to be highly variable (figure 4.13). As more indications are sought, the difference between the minimum required revenue for multi-tumour phase I and single-tumour phase I strategies continues to widen. No reductions in breakeven revenue occur for when only one indication is studied, but achieving an overall development success rate increase from 20% to 26% is associated with a steady decrease in minimum required revenue – from $1.2 billion USD initially, to $0.92 billion USD and $0.35 billion USD for single tumour and multi-tumour phase I trials respectively. A utilizing more efficient phase I strategies, when possible, dominates improvement in overall success rate.

Figure 4.13. Minimum revenue for oncology-focused firms over the full range of success rates and development strategies considered.



*note: darker bars represents a single-tumour phase I trial utilization, lighter bars represents muti-tumour phase I trial utilization.

Optimal number of indications studied

The ideal number of indications attempted is defined by economic efficiency. Industry should continue to invest in additional drug development that reduces needed revenue until the marginal benefit of an additional indication studied, the marginal decrease in minimum revenue, equals the additional cost incurred by studying the additional indication. For a single-disease phase I strategy of drug development, regardless of the cost of capital or company diversification, the marginal benefit of additional studied indications transitions from a positive

benefit to a negative benefit after a firm commits to 3 total desired indications (figure 4.14). However, for non-profit organizations that may not required a return on investment dictated by cost of capital, they may continue to capture additional marginal benefit until the firm commits to a total of 4 additional indications to be investigated. The potential number of indications studied becomes greater when a multi-indication phase I trial can be employed. Pharmaceutical firms continue to capture benefit until 7 independent indications are studied. Only diversified not-for-profit firms are able to continue to 8 investigated indications before reaching a negative marginal benefit from further study.

Figure 4.14a. marginal benefit by studying additional indications for new drugs upfront – single-tumour phase I.

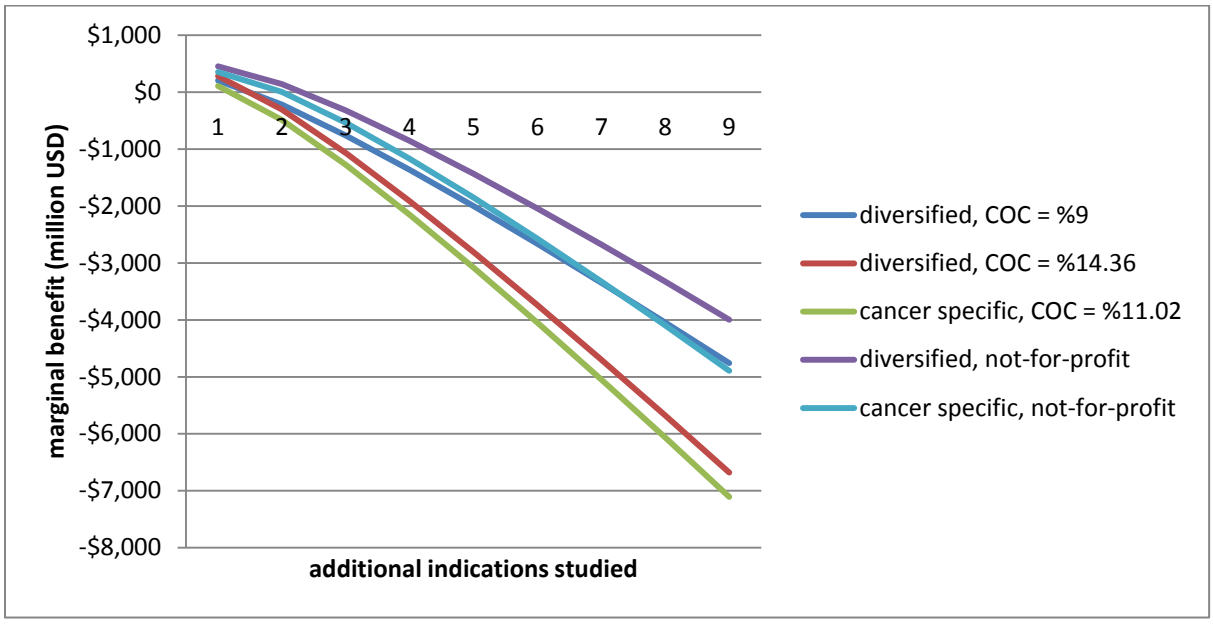
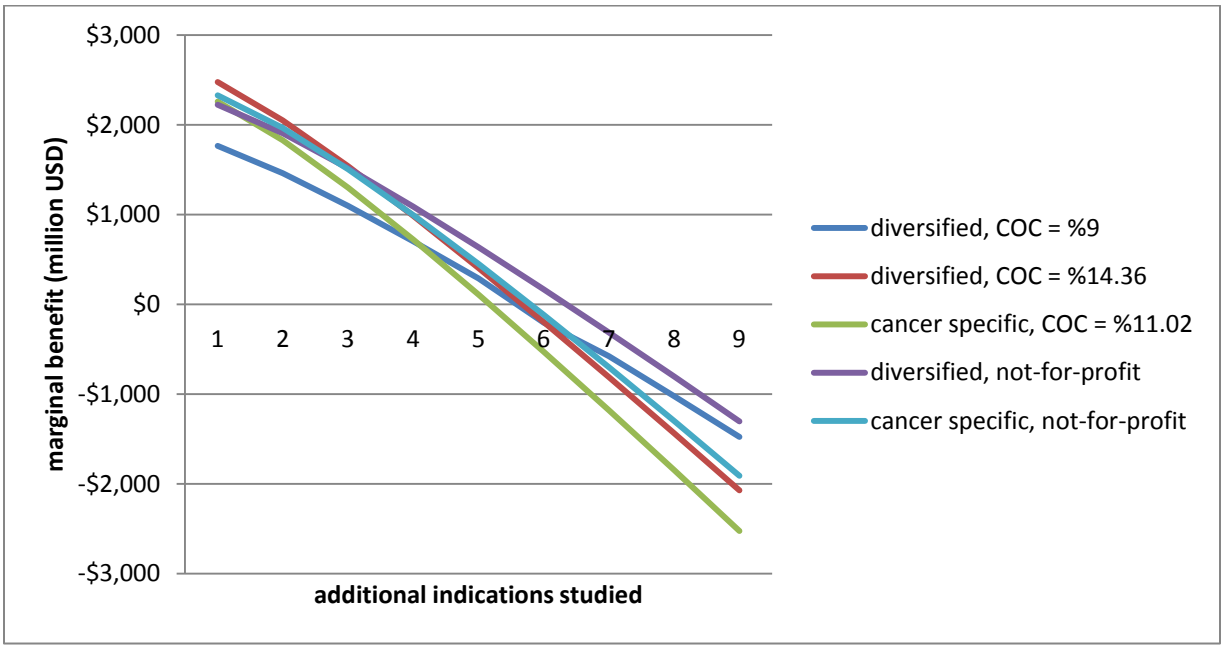


Figure 4.14b. marginal benefit recovered by studying additional indications for new drugs upfront – multi-tumour phase I.



Applying breakeven revenue to targeted therapies for incurable solid cancers

The revenue generated from the sale of a pharmaceutical may be estimated as a function of the progression free survival. For the targeted therapies captured in our systematic review, all patients were treated with the novel agent until documented disease progression. Response rates, toxicity related drop-outs, and patient adherence to the treatment are all indirectly incorporated into the final measurement of overall progression free survival (progression free survival). Equating the minimum required revenue to the progression free survival for new targeted therapeutics allows for disease-specific estimates. However, the time horizon for generating this revenue directly influences the prices set.

When considering tumour types in whom targeted chemotherapy has proven efficacious in the incurable setting in the Unites States of America marketplace (2), one can determine

revenue required per month per patient by equating the total breakeven revenue with the number of new patients that consume the therapy multiplied by the time the patient is on the drug. Firms attempting to generate their minimum required revenues over a one year time period may be subject to highly variable returns, assuming that all patients with the disease will attempt treatment (table 4.3). This assumption is likely to underestimate the breakeven revenue required per month per patient if some patients do not receive therapy. However, even for relatively toxic chemotherapy, many patients will at least attempt treatment (89). Later, we analyse the breakeven revenue per month per patient over the entire range of market penetrance.

Table 4.3. Revenue per month per patient in the USA marketplace with full drug market penetrance.

cancer type	revenue/month max	revenue/month avg.	revenue/month min
NSCLC	$11,040	$3,765	$1,735
CRC	$50,711	$9,070	$4,612
Breast cancer	$43,591	$12,183	$5,341
Pancreatic cancer	$37,754	$22,610	$14,834
Liver & bile duct	$105,968	$66,001	$37,092
RCC	$166,999	$56,754	$27,805

Legend:

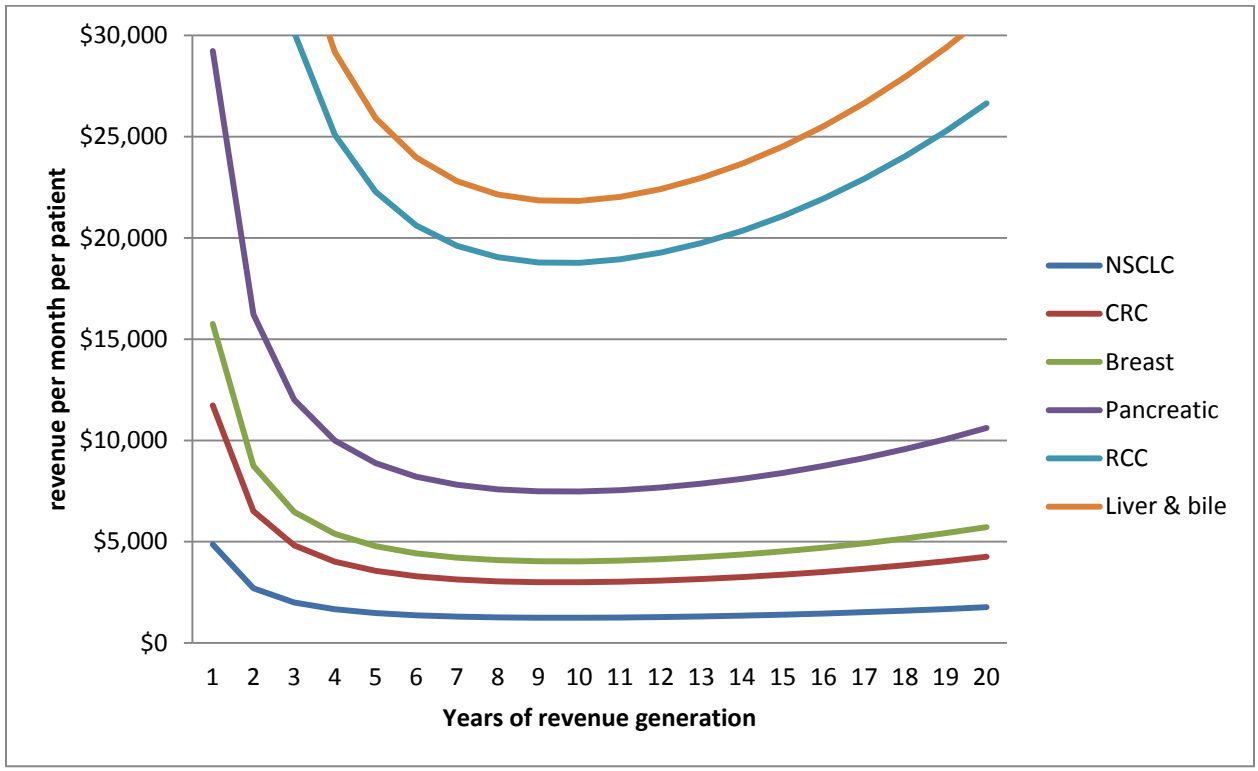
- CRC: colorectal cancer
- NSCLC: non small-cell lung cancer
- RCC: renal cell carcinoma

Maximum revenue per month per patient were calculated as a combination of the worst-case scenarios for all inputs: minimum revenue for a oncology focused company that only studied the drug in one indication and minimum progression free survival achieved by that drug. Mid-range revenue per month per patient was calculated from the an oncology focused company utilizing a single-tumour phase I trials and developing the drug for 4 indications, where the drug achieves an average progression free survival benefit considering the cancer type. And minimum revenue per month per patient was calculated from an oncology focused company utilizing a multi-tumour phase I trials and developing the drug for 4 indications, where the drug achieves the maximum progression free survival of that cancer type achieved thus far. 4 indications were chosen as the mid-point between optimal number of indications for single-tumour and multi-tumour phase I development. For non-small cell lung cancer, the most common cause of cancer death, minimum required revenue ranges from $1,600 USD to $11,000 USD per month per patient. This compared to renal cell carcinoma, a much rarer form on cancer in the United States, where the minimum required revenue ranges from $25,000 USD to $167,000 USD.

Increasing the time horizon can assist in reducing the minimum returns per month per patient. If companies are willing to recover R&D costs over a longer time period, their required returns per month per patient drop accordingly (figure 4.15). For a continued cost of capital of 11%, the minimum return per month per patient required reaches a minimum at 10 years. After 10 years, the compounding interest required by firm for expanding the time period for cost recuperation begins to dominate the reductions on revenues achieved by lengthening the time of payment. This strategy can reduce the minimum required revenue per month per patient by 74%.

This translates to a reduction in minimum required revenue per month per patient from $4,870 USD to $1,250 USD for the average case of non-small cell lung cancer. For breast cancer, the average revenue per month per patient can be reduced from $15,750 USD to $4,030 USD. And for lower prevalence cancer, like liver & bile duct cancer or renal cell cancer, the average revenue per month per patient required can be reduced from $85,330 USD to $21,830 USD and $73,370 USD to $18,770 USD, respectively

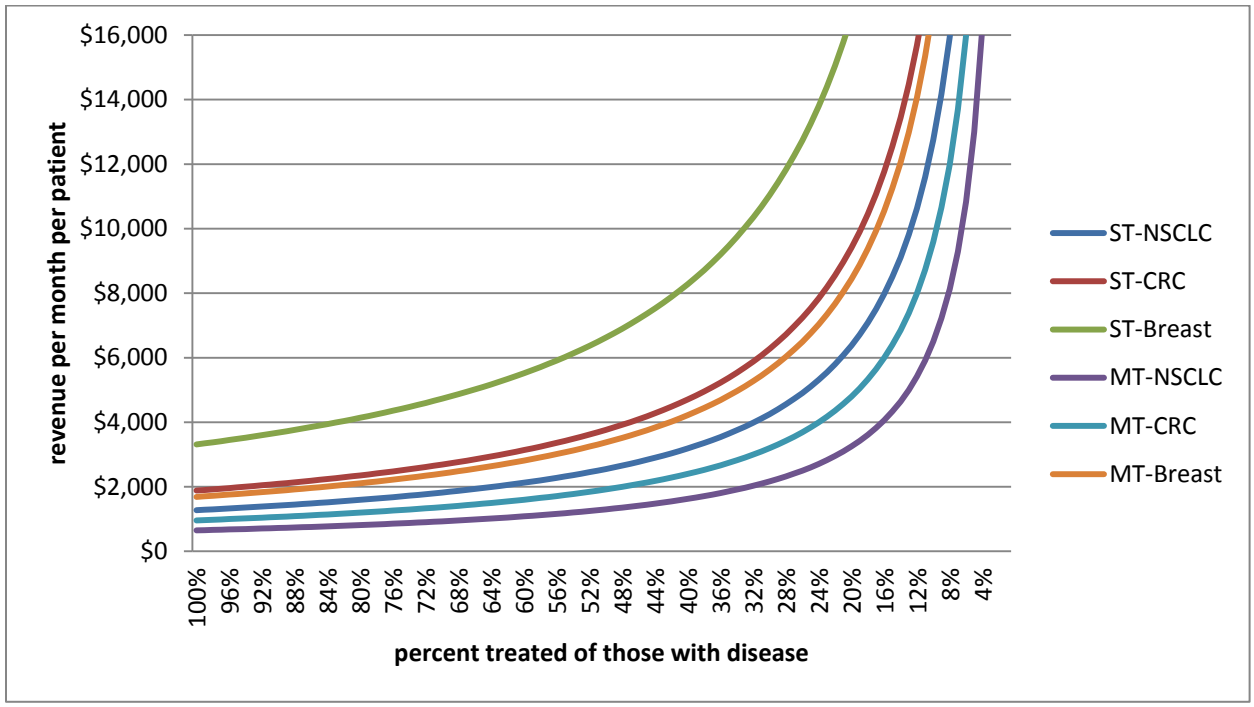
Figure 4.15. Minimum revenue required per month per patient over years of payment.



*cost of capital = 11%

Market penetrance can also influence the breakeven revenue per month per patient. As the revenues required by pharmaceutical companies are spread among fewer people, each sale is required to generate higher revenues. For the most prevalent tumours that cause death in the developed world, non-small cell lung cancer, colorectal cancer, and breast cancer (1), the greater the percent of patients treated, the lower the price need be when either a 1 year repayment or 10 year repayment arrangement (figure 4.16). The absolute effect of increasing the length of repayment on reduction in required revenue per month per patient remains, but increasing the length of repayment also changes the point at which the slope of the curves rapidly increase.

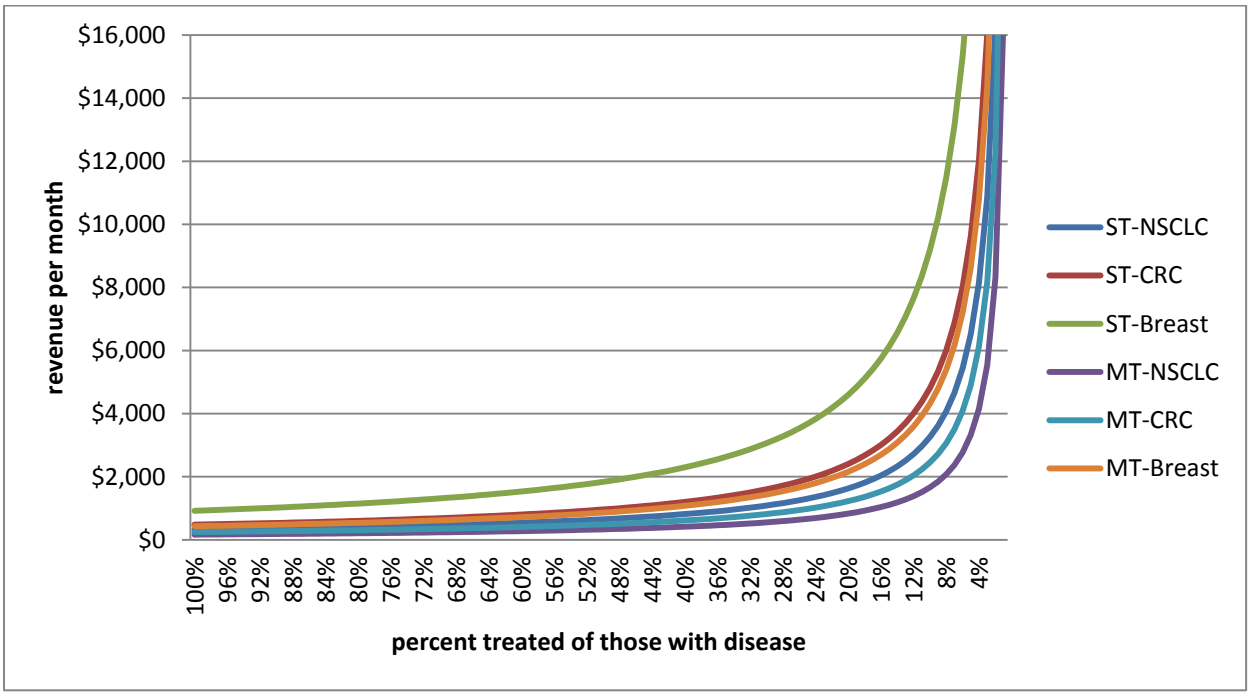
Figure 4.16a. Minimum revenue per month per patient with a cost of capital of 11% over 1 year in the developed world for a market penetrance.



Legend:

- ST: single-tumour phase I
- MT: multi-tumour phase I
- NSCLC: non-small cell lung cancer
- CRC: colorectal cancer

Figure 4.16b. Minimum revenue per month per patient with a cost of capital of 11% over 10 years in the developed world for a market penetrance.



Legend:

- ST: single-tumour phase I
- MT: multi-tumour phase I
- NSCLC: non-small cell lung cancer
- CRC: colorectal cancer

Chapter 5 – Discussion

Cancer continues to be a leading cause of death throughout the world (90-92). Its economic impact is projected to increase to $147 billion USD by 2020 in the United States of America alone, largely due to changing population demographics (93, 94). From the years 1988 to 2000, 76% to 85% of survival gains achieved for breast, lung and colon cancer were achieved through therapeutic advancement, as opposed to early detection (95). Since 2000 our understanding of cancer's biology and pathogenesis has changed substantially, with the list of fundamental cancer hallmarks increasing from 6 features to 10 (96, 97). This knowledge has led to the development of new classes of successful oncologic therapeutic agents, including small-molecule tyrosine kinase inhibitors and monoclonal antibodies. However, with these advancements has come increasing concern about the costs of treatment (98, 99). The concern for cost may be further amplified by the seemingly modest gains by some of these newer therapies over their predecessors, especially in the incurable or metastatic setting of solid cancers.

Questions on the sustainability of the rate of growth of healthcare expenditure imply questionable sustainability of the pharmaceutical industry, since drugs constitute the second largest expenditure after hospital costs (100). As societies grapple with funding decisions, investors grapple with resource allocation decisions based on the risk and return profile of the pharmaceutical industry. Whereas the maximum willingness-to-pay for new therapeutics by society may be based on value-based pricing (101), the minimum willingness-to-sell those therapeutics may be based on the minimum revenue required to cover costs. Where the value-based pricing of new drugs examines expected cost-utility achieved in a group or subgroup of patients, the expected revenue required for successfully approved drugs examines the cost to risk

ratio of future research and development. Although the costs of a pharmaceutical company are incurred through many of a firm's activities, we focused exclusively on the effect that R&D has on the needed revenue generated by new pharmaceuticals over a long-term time horizon.

Conceptually, pharmaceutical companies may choose from a variety of development pathways when attempting to take a drug from newly discovered entity to market approval, depending on a number of factors. For oncology, new pharmaceuticals are often studied in the incurable or metastatic setting, largely on account of ethical barriers to the study of these agents in patients with earlier stage disease, and thus, better prognoses. In the simplest scenario, a company specializing in oncologic therapeutics develops a new drug from pre-clinical testing through to market approval in a linear manner: from pre-clinical, through phase I, II, and III clinical trials for a specied cancer-type (102). However, once a compound has passed pre-clinical testing, multiple phase I clinical trials can be undertaken to study the drugs toxicity profile in different cancer populations. Utilizing this approach, where feasible, may reduce the variable cost of drug development by spreading the pre-clinical costs of drug research across multiple development attempts while simultaneously increasing the probability that the drug will prove successful in treating at least one tumour type. In an attempt to further reduce the costs of drug development, phase I clinical trials may include multiple tumour types so that only one such trial may be needed to launch a series of more advanced-phase trials for various tumours. However, the utilization of this strategy may be impeded for certain cancers when combinations of drugs are being studied or when pre-clinical studies demonstrate that the compound may only be efficacious in the presence of a pre-existing genetic mutation.

A shift in focus of oncology treatment from cytotoxic chemotherapy to molecularly targeted agents may have tremendous implications for the required revenues

generated by these new drugs. For drugs that are truly targeting only a specific pathway or series of pathways, pre-clinical data will need to be generated to validate the proposed drug's target and its ability to affect that target (103). Of the molecularly targeted agents approved by the Food and Drug Administration (FDA) from 1998-2009, 45% of the drugs' approval was predicated by the patients' tumour molecular biomarker status (60). Increasing the amount of data required to move from pre-clinical study to phase I clinical trials may increase the length of time a compound spends in the pre-clinical phase, the cost of the total pre-clinical research, or both. Even though current average out-of-pocket pre-clinical costs are only estimated to be $121-$133 million USD, they represent an estimated $335-$381 million USD in capitalized costs, over 40% of the total capital outlay (72, 73). Any increase in capitalized cost for pre-clinical research would hopefully be mitigated by a corresponding increase the in overall success rate of bringing new drugs to market.

The foundation for oncologic drug development comes from the cytotoxic chemotherapy experience. Historically, technology has not been sufficiently advanced to identify and target specific oncogenic pathways. Because cytotoxic chemotherapies take advantage of more rapidly dividing cancer cells or the cancer cells' retarded ability to repair DNA damage, multi-tumor phase I clinical trials are standard. If a favorable pharmacokinetic and pharmacodynamic profile is achieved by the compound being studied, it can then be advanced to the phase II setting. Which cancers to target in the phase II setting may be guided by *in-vitro* pre-clinical data, or an observation of major or minor response to therapy in the phase I setting. Whereas the purpose of the phase I trial is to assess the toxicity, safety, and recommended dose schedule for future phase II trials, the phase II trial is designed to evaluate efficacy. Phase II clinical trials can also take a multitude of forms, including single-stage, multi-stage, and sequential designs. In a single-stage

phase II clinical trial, all subjects are recruited and treated with the experimental agent(104). For cytotoxic chemotherapy, a successful phase II trial demonstrates a superior response rate to that of the current standard of care, which is estimated from previous works (105). Multi-stage designs are similar to single-stage phase II designs, except that at each stage the investigators decide whether to stop the trial, if the preliminary data support futility of continuation, or to accrue more patients to complete the study. In sequential phase II clinical trials, an analysis is performed after each individual patient experiences the pre-specified event, such a response or progression. If the test-statistic of all data accumulated to that point meets predefined stopping end-points, the trial is halted, otherwise another patient is accrued. Phase II, may also be randomized, for example to different acceptable doses, to different dosing schedules, combined with different previously-approved drugs, or against placebo, in an attempt to increase the positive predictive value of the phase II trial for phase III success (106). Phase III clinical trials, for cytotoxic chemotherapy or any drug, take a standard form: utilizing pre-specified eligibility and stratification criteria, enrolled subjects are randomized to receive one of two or more treatment regimens which are finally compared statistically at predetermined times. Phase III clinical trials are primarily concerned with effectiveness and a successful trial can be expected to translate into the market approval of the experimental compound, baring expense, logistics of delivery, or unexpected safety issues.

Molecularly targeted pharmaceuticals may also challenge the traditional phase I clinical trial paradigm developed during the cytotoxic chemotherapy era. The phase I clinical trial still aims to determine whether the safety profile of the new drug is sufficiently tolerable to allow for continued development and to inform the recommended phase II dose range (107). Unlike cytotoxic chemotherapy, where higher drug doses have been assumed to provide more anti-

tumour effect, for molecularly targeted agents, an efficacy plateau may be reached as the target receptors becomes saturated (108). This assertion is supported by evidence that suggests that in the phase I setting, patients on lower doses of the targeted treatment may not have lower survival expectations than patients being treated with higher dose levels (109). As a result of this potential property of targeted agent, computational models suggest that alternative trial designs, such as combined phase I-II trials, might be able to improve the efficiency of the overall process (110). As long as the success rate of these trials are comparable to traditional designs, their seamless transition from phase I to phase II may potentially decrease the time to market approval. However, the National Cancer Institue's Investigational Drug Steering Committee recently advised that alternative phase I trial designs may reduce the number of patients needed or the time to study completion (60).

Likely the most significant and most certain effect of focusing on molecularly targeted agents in oncology relates to the pathway of research and development required to bring these drugs to market. If the success rate of research in bringing to molecules to market remains at its historical levels, our model predicts large increases in the minimum revenue required to sustain the pharmaceutical industry as a result of risk-adjusted research and development costs. Instead of utilizing the most fiscally desirable multi-tumour phase I pathway, molecularly targeted drugs may be forced into either the single-tumour or linear pathways of development. For example, if in pre-clinical models, a drug is found to only be effective in disease X with mutation Y, it should only be studied in a linear fashion, requiring $5.2 billion dollars in revenue generation from the research and development alone, representing a more than 2 fold increase in revenue for the company to breakeven. Although the market success rate may be improved by the additional pre-clinical work, at this time it remains debatable. Vemurafenib, a selective B-RAF inhibitor

shown to be effective in the treatment of metastatic melanoma (111, 112), and vismodegib, a hedgehog pathway inhibitor effective for treating basal cell carcinoma of the skin (113, 114), have both been developed in this linear fashion and are considered very successful. But cetuximab, a monoclonal antibody that targets epidermal growth factor receptor (EGFR), and gefitinib, a tyrosine-kinase inhibitor of EGFR, were both originally reported to be most efficacious in EGFR over expressing tumours (115, 116). These assessments ultimately did not lead to FDA approvals (117-119). Only later were alternative predictive biomarkers discovered (120, 121), raising doubt about the ability of pre-clinical models to reliably identify accurate biomarkers.

Utilizing published data on cost of research and development, we set out to estimate the pharmaceutical industry's specific revenue requirements to sustain a productive research and development pipeline in the long-run. We then translated that component of revenue into an estimate of minimum revenue required per patient per month of treatment for companies that develop drugs for the treatment of incurable solid tumours dictated by the research and development process. Our analysis, to our knowledge, the first of its kind, allows for an understanding not only of the current revenue required for continued pharmaceutical development by private industry, but also provides insight into why targeted therapy for incurable solid cancer may be more costly for purchasers.

Our estimates for the component of total revenue needed to break even on the research and development component for newly approved pharmaceutical provides insight into an otherwise complicated debate around healthcare spending. The cost of research and development should be considered only a surrogate for the final drug price. Taking that cost and translating it into the corresponding component of revenue required to break even allows for a

clearer understanding of what the minimum acceptable price of a new drug may be. This in turn enables potential shareholders to judge the maximum willing-to-pay for pharmaceuticals in fundamental terms instead of thorough speculation of the potential returns for successfully approved medicines.

Our model also allows for simple, quantitative risk assessments of developing new drugs along different R&D pathways. Consider drug X, a newly invented potential targeted treatment intended for clinical use in solid tumours. From pre-clinical studies, the managing firm believes that drug X inhibits pathway X●, but also notes that it may inhibit pathways Y●, Z●, and it may inhibit other pathways, but the company did not have the time or ability to continue testing. From these same pre-clinical assessments, all three of these pathways are present to varying degrees in different tumour types, but pathway X● appears dominant in a single cancer type. In this scenario, the company can choose a wide-range of approaches to the development of this new drug: it can specifically target the tumour type where X● is most active, it can perform a series of single tumour phase I trials, perhaps targeting the tumour types where Y● or Z● are considered more active, or it can perform a multi-tumour phase I trial and disregard the X● data at this stage of development (although in all three choices, correlative biomarker studies can also be employed in an attempt to improve the potential efficacy of the drug). Holding the costs associated with each trial design constant, the firm should only switch from the multi-tumour phase I pathway to the linear pathway if drug X has a predicted 39% chance of achieving market approval, instead of the historical 20%. Similarly, if this company desires to include biomarkers to identify patients where X●, Y●, or Z● in the three different tumour types where these pathways appear active, it should only do so if the biomarker is predicted to increase the probability of acquiring an approval in a specific tumour type by 18%. However, if drug X were

undoubtedly expected to fail without the presence of X● pathway activation, then biomarkers would have to be developed to improve the probability of successful R&D and recover the cost of biomarker development, as well.

If tyrosine-kinase inhibitors and monoclonal antibodies become more selective to specific tumour types or employed to treat only patients whose tumour harbour specific mutations then we should expect the price of such drugs to increase even if the cost of producing these medications is similar to their less selective predecessors. Without a corresponding increase in the probability that such drugs will reach the market, their development would require at least an 82% increase in revenue compared to cytotoxic chemotherapy to justify such an investment.

Alone, our analysis is insufficient to determine the appropriate price for new targeted chemotherapy. The minimum price of new medications would have to incorporate both the minimum revenue required per month per patient and the total cost, both fixed and variable, of the medicine's manufacture, marketing, and general expenses associated with running a firm. The advantage of our analysis comes from the generalizability of the revenue per month per patient calculation – although the cost associated with production is specific to each pharmaceutical, the minimum revenue associate with research and development is generalizable.

For the public, the corresponding price of the drug would also have to accommodate the subsequent reduction in potential users. Take the example of the recent Food and Drug Administration (FDA)-approved tyrosine-kinase inhibitor crizotinib (122). It has been shown to be efficacious in patients suffering from non-small cell lung cancer harbouring the ALK-EML4 genetic translocation, which only occurs in approximately 4%-5% of cases (123). This reduction in potential patient volume translates to a 15 to 20 fold increase in the minimum revenue

required per month per patient in the developed world. Moreover, if industry understands that this drug is unlikely to be funded in particular markets, it would have to further increase the drug`s price. However, the speed at which crizotinib progressed through pre-clinical research to market approval is unprecedented in oncology (124). In fact, a phase III study was not even required for its approval in the United States of America because of the remarkable response rates observed in early phase trials. By avoiding the phase III portion of development, the pharmaceutical firm saved approximately $119 million USD in out-of-pocket costs. The significantly accelerated time to approval also saved the company the 11% yearly cost of capital it would have had to incur in those years that it avoided.

The crizotinib example also highlights the potential for improving the probability of successfully developing new targeted treatments in cancer if an appropriate target is identified. Crizotinib only benefits those with the pre-specified genetic mutation; identification of other mutations with drugable targets may lead to other molecules that attain similar success. However, the success rate of new drug development would have to more than double to nullify the effects of developing a single drug in a linear fashion compared to a multi-tumour phase I approach. Furthermore, this estimate does not reflect the potential increases in research cost associated with reducing the potential pool of patients, including the increased time for trial recruitment or the cost of testing the tumour for the presence of the desired target.

Although increasing the time horizon to generate the break even revenue can reduce the revenue needed per patient per month of treatment by almost 75%, the proper industry position remains unclear. Since newer, more efficacious treatments may already be in development by rival companies, there would be substantial risk that the drug in question could become obsolete prior to achieving the required financial return. Conversely, companies that accept such risk may

be rewarded by achieving funding approval in a greater number of markets or in successfully negotiating for exclusivity rights and extended patent protection. The option for extending the time horizon certainly exists and should be decided on an individual basis.

Our analysis is limited in its precision by our reliance on past data to predict future events. Although a probabilistic analysis may have been possible, it would create an artificial sense of accuracy in future predictions. The value of the deterministic model in this setting is that it provides maximum and minimum breakeven revenues per month per patient of drugs that have already been developed, with the expectation that the minimum required revenue per month per patient for a given future drug will likely fall somewhere in that range. By assuming industry flexibility in drug development and the ability to study multiple indications concurrently, this model may not applicable to small-capitalization companies who do not command the resources required to achieve that flexibility. However, this model provides a framework for how not-for-profit intervention should affect the revenue required for a sustainable pharmaceutical industry. For example, financial support from charitable organizations or government with regards to pre-clinical investigation should result in significant reductions in the final cost of drug development with relatively less out-of-pocket by saving the compounding effects of the cost of capital. Further analysis could be completed to provide estimates of the value for money of such investments.

The data used to develop these estimates seems likely to be biased in favour of industry and so would lead to an overestimate of the minimum revenue calculations by as much as 25% for linear drug development (75, 80). Unfortunately, the most significant issue is the current disagreement regarding how much of the expense of drug development is born by the firm or offset by government intervention (80, 81). This debate is beyond the scope of our analysis, but

its importance should not be understated. The greatest value of this analysis is in providing a framework for understanding a pharmaceutical firm in the context of drug price negotiation. The R&D costs of an individual firm and the support it receives from government should be explicitly considered at the time of negotiation. From an operational perspective, firms that price their products beyond what would be expected in our analysis may be doing so because of their own sub-average market success rate for new drugs, which should not be rewarded by healthcare payers covering these costs. Companies would have to explicitly provide information to payers on their R&D expenses, allowing for tailoring our analysis to a specific negotiation. In the same way, some organizations benefit from tax credits and subsidies more than others, and this too could be incorporated into a specific analysis for the purpose of negotiation. Conversely, it is conceivable that risk-adjusted breakeven revenue rises because of new required strategies in targeted cancer therapy R&D, which payers may feel is worth paying for. As the prices of oncologic therapeutics have increased over the last decade, understanding how R&D contributes to the final price and how the shift to targeted therapeutics for incurable solid cancers impacts the breakeven revenue represents an important process in mutually optimized utility for purchasers and pharmaceutical firms.

Our estimates for the minimum willingness-to-sell newly approved pharmaceutical provides insight into an otherwise complicated debate around healthcare spending. The cost of research and development should be considered only a surrogate for the final drug price. Taking that cost and translating it into the breakeven revenue to cover research and development allows for a clearer discussion of what the minimum acceptable price of a new drug may be. From the perspective of the firm, these costs can be added to the manufacturing, marketing, overhead, and other costs of doing business to determine the minimum sustainable price for a compound. This

in turn enables potential shareholders to judge the maximum willing-to-pay for pharmaceuticals in fundamental terms instead of through speculation of the potential returns for successfully approved medicines. From the payer's perspective, a similar calculation could be added to determine how far they may be able to negotiate for a price reduction without compromising other objectives, like preserving the pharmaceutical industry. . As cancer care expenses rise, a better understanding of the pharmaceutical industry and healthcare payers will pay significant dividends.

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Appendix A - Equations

Revenue Equation

In general, for a company to succeed

(1) $C < R \times Sr$

Where C is the total cost of research and development, R is revenue and Sr is the success rate of achieving those profits.

At a minimum, for a company remain solvent, equation (1) can be rearranged such that

(2) $Rmin = C / Sr$

Where Rmin is the minimum revenue required for a company to breakeven.

Assuming that research and development represents the bulk of investment, or the only significant investment, C can also be considered the firm's investment.

To simplify, if research is assumed to represent the totality of investment, the probability of achieving profit equal to the probability of having a compound achieve positive results on all of the phases of development. Therefore,

(3) $Rmin = C / [(Sr^*)x(Sr1)x(Sr2)x(Sr3)]$

Where Sr*, Sr1, Sr2, Sr3 are the success rates of pre-clinical, phase I, phase II, and phase III studies, respectively.

Expanding revenue,

(4) $Rmin = (N)x(X)x(T)x(Q)x(Qp)$

Where N is the minimum net drug revenue per treatment cycle, X is the number of cycles in a given time, T is the length of time a person remains on the drug measured in the same units as X (e.g. if X is measured as cycles per month, T must also be expressed in months), and Q is the prevalence of the disease, and Qp is the market penetrance of the drug.

Since Qp is unlikely to be independent of net drug revenue, net drug revenue (N) should be broken down into its components

(5) $N = S – E$

Where S is the price per cycle of therapy, set by the company, and E is the expense incurred by the company to make the needed drug per cycle. E should be dependent on the product of Q and Qp as a result of economies of scale.

For simplicity, since this model will only capture the needed revenue specifically associated with research and development. The minimum generated revenue must be generated over the all patients treated for the length of time that they remain on the therapy.

Costs Equation

For a forward looking industry, the average cost per drug developed is of primary importance, as it is the average cost that must be recovered by drug development.

For a single chemical, the expected cost of its development would be represented by

(1) $C = C^* + (Sr^*)\cdot C1 + (Sr^*)\cdot(Sr1)\cdot(C2) + (Sr^*)\cdot(Sr1)\cdot(Sr2)\cdot(C3)$

Where C*, C1, C2, C3 are the costs of pre-clinical, phase I, phase II, and phase III studies, respectively.

That is, the expected cost of a single attempt of developing a drug is the cost of pre-clinical development, in addition to the cost of phase I trial, in addition to the cost of a phase II trial, in addition to the cost of a phase III trial. However, since a drug may not demonstrate the properties required to move to the next phase of development, the cost of future phases should be adjusted by the probability that the cost of that phase will be incurred.

Once phases of the research and development are completed, they should be considered sunk. Therefore, the considered costs are only future costs. The total cost that should be considered is the sum of future costs multiplied by the probability of incurring those costs.

(2) $C = \sum C(x)\cdot P(x)$

Where C(x) is the cost of a phase of development and P(x) is the probability of incurring that cost.

Appendix B – Search strategies for meta-analysis of targeted therapy for incurable solid cancers.

MEDLINE search strategy

1. exp Antibodies, Monoclonal/
2. bevacizumab.mp.
3. cetuximab.mp.
4. panitumumab.mp.
5. nimotuzumab.mp.
6. trastuzumab.mp.
7. edrecolomab.mp.
8. exp Protein Kinase Inhibitors/
9. Imatinib.mp.
10. Erlotinib.mp.
11. Gefitinib.mp.
12. Lapatinib.mp.
13. Canertinib.mp.
14. semax?nib.mp.
15. vatalanib.mp.
16. soraf?nib.mp.
17. Sunitinib.mp.
18. or/1-17
19. randomized controlled trial.pt.
20. clinical trial.pt.
21. randomi?ed.ti,ab.
22. placebo.ti,ab.
23. dt.fs.
24. randomly.ti,ab.
25. trial.ti,ab.
26. groups.ti,ab.
27. or/19-26
28. animals/
29. humans/
30. 28 not (28 and 29)

31. 27 not 30
32. exp Neoplasm Metastasis/
33. exp neoplasms by site/se
34. (stage adj (IV or four)).ti,ab.
35. "stage 4".ti,ab.
36. advanced.ti,ab.
37. limit 36 to cancer
38. or/32-35,37
39. 38 and 18 and 31
40. limit 39 to english language

EMBASE search strategy

1. exp Antibodies, Monoclonal/
2. bevacizumab.mp.
3. cetuximab.mp.
4. panitumumab.mp.
5. nimotuzumab.mp.
6. trastuzumab.mp.
7. edrecolomab.mp.
8. exp Protein Tyrosine Kinase Inhibitor/
9. Imatinib.mp.
10. Erlotinib.mp.
11. Gefitinib.mp.
12. Lapatinib.mp.
13. Canertinib.mp.
14. semax?nib.mp.
15. vatalanib.mp.
16. soraf?nib.mp.
17. Sunitinib.mp.
18. or/1-17
19. exp Metastasis/
20. "Advanced Cancer"/
21. exp neoplasm/ and advanced.ti,ab.
22. (stage adj (IV or four)).ti,ab.
23. or/19-22

24. exp Controlled Clinical Trial/
25. random*.ti,ab.
26. placebo.ti,ab.
27. trial.ti,ab.
28. or/24-27
29. animals/
30. human/
31. 29 not (29 and 30)
32. 28 not 31
33. 32 and 18 and 23
34. limit 33 to english language

Cochrane Central Register of Controlled Trials search strategy

1. exp Antibodies, Monoclonal/
2. bevacizumab.mp.
3. cetuximab.mp.
4. panitumumab.mp.
5. nimotuzumab.mp.
6. trastuzumab.mp.
7. edrecolomab.mp.
8. exp Protein Kinase Inhibitors/
9. Imatinib.mp.
10. Erlotinib.mp.
11. Gefitinib.mp.
12. Lapatinib.mp.
13. Canertinib.mp.
14. semax?nib.mp.
15. vatalanib.mp.
16. soraf?nib.mp.
17. Sunitinib.mp.
18. or/1-17
19. exp Neoplasm Metastasis/
20. exp neoplasms by site/se
21. (stage adj (IV or four)).ti,ab.

22. "stage 4".ti,ab.
23. exp Neoplasm Metastasis/
24. exp neoplasms/ and (advanced or metastat*).ti,ab.
25. or/19-24
26. 25 and 18

Appendix C – References of included studies for meta-analysis

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Appendix D – Summary of included studies for meta-analysis

	Trial phase	WHO status	Cancer type	Drug name	Intervention class	Outcomes
Barrios 2010	III	<=2	breast	sunitinib	class 2	response, PFS, toxicity
Berek 2004	II	<=2	ovarian	oregovomab	class 1	PFS, toxicity
Berek 2009	III	<=2	ovarian	oregovomab	class 1	PFS, toxicity
Berek 2009a	III	<=2	ovarian	oregovomab	class 1	MS, PFS, toxicity
Blackwell 2010	III	<=2	breast	trastuzumab	class 1	MS, PFS, toxicity
Boccardo 2008	II	<=2	prostate	gefitnib	class 1	response, MS, PFS, toxicity
Bokemeyer 2009	NA	<=2	CRC	cetuximab	class 1	response, PFS, toxicity
Borner 2008	II	<=1	CRC	cetuximab	class 1	MS, PFS, toxicity
Bukowski 2007	II	<=1	RCC	erlotinib	class 1	response, PFS, toxicity
Burtness 2005	III	<=1	SCC H+N	cetuximab	class 1	MS, PFS, toxicity
Butts 2007	II	<=2	NSCLC	cetuximab	class 1	MS, PFS, toxicity, response
Cascinu 2008	II	<=2	pancreatic	cetuximab	class 1	MS, PFS, toxicity, response
Cheng 2009	III	<=2	HCC	sorafenib	class 3	MS, PFS, toxicity, response
Crino 2008	II	<=2	NSCLC	gefitnib	class 2	MS, PFS, toxicity, response, HRQL
Cristofanilli 2010	II	<=2	breast	gefitinib	class 1	response, PFS, MS
Cufer 2006	II	<=2	NSCLC	gefitnib	class 2	MS, PFS, toxicity, response
Demetri 2002	III	<=2	GIST	sunitinib	class 3	MS, PFS, toxicity
Di Leo 2008	III	<=2	breast	lapatinib	class 1	MS, PFS, toxicity, response
Escudier 2007	III	<=2	RCC	sorafenib	class 3	MS, PFS, toxicity

Escudier 2007a	III	<=2	RCC	bevacizumab	class 1	MS, PFS, toxicity
Escudier 2009	III	<=2	RCC	sorafenib	class 3	MS, PFS, toxicity
Escudier 2009a	II	<=1	RCC	sorafenib	class 2	MS, PFS, toxicity
Galal 2009	II	<=2	CRC	bevacizumab	class 1	MS, PFS, toxicity
Gasparini 2007	II	<=2	breast	trastuzumab	class 1	MS, PFS, toxicity
Gatzemeier 2004	II	<=2	NSCLC	trastuzumab	class 1	PFS, toxicity, response
Gatzemeier 2007	III	<=2	NSCLC	erlotinib	class 1	MS, PFS, toxicity, response, HRQL
Geyer 2006	III	<=1	breast	lapatinib	class 1	MS, PFS, toxicity
Giaccone 2004	III	<=2	NSCLC	gefitnib	class 1	MS, PFS, toxicity
Giantonio 2007	III	<=2	CRC	bevacizumab	class 1+2	MS, PFS, toxicity, response
Goss 2009	II	2 to 3	NSCLC	gefitinib	class 3	PFS, MS, toxicity
Hauschild 2009	III	<=1	melanoma	sorafenib	class 1	MS, PFS, toxicity
Hecht 2009	III	<=1	CRC	panitumumab	class 1	MS, PFS, toxicity, response
Herbst 2004	III	<=2	NSCLC	gefitnib	class 1	MS, PFS, toxicity, response
Herbst 2005	III	<=1	NSCLC	erlotinib	class 1	MS, PFS, toxicity, response
Heymach 2007	II	<=1	NSCLC	vandetanib	class 1	MS, PFS, toxicity, response
Heymach 2008	II	<=1	NSCLC	vandetanib	class 1+2	MS, PFS, toxicity
Hochster 2008	II	<=1	CRC	bevacizumab	class 1	MS, PFS, toxicity, response
Horti 2009	II	<=2	prostate	vandetanib	class 1	PFS, toxicity
Hudes 2007	III	<=3	RCC	temsirolimus	class 1+2	MS, PFS, toxicity
Hurwitz 2004	III	<=2	CRC	bevacizumab	class 1	MS, PFS, toxicity, response
Hurwitz 2005	III	<=2	CRC	bevacizumab	class 1	MS, PFS, toxicity

Johnson 2004	II	<=2	NSCLC	bevacizumab	class 1	MS, PFS, toxicity, response
Johnston 2009	III	<=1	breast	lapatinib	class 1	MS, PFS, toxicity
Karp 2009	II	<=1	NSCLC	CP-751871	class 1	MS, PFS, toxicity
Kabbinavar 2003	II	<=2	CRC	bevacizumab	class 1	MS, PFS, toxicity, response
Kabbinavar 2005	II	<=2	CRC	bevacizumab	class 1	MS, PFS, toxicity, response, HRQL
Kaufman 2009	III	<=1	breast	trastuzumab	class 1	MS, PFS, toxicity
Kim 2008	III	<=3	NSCLC	gefitnib	class 2	MS, PFS, toxicity
Lee 2010	III	<=2	NSCLC	gefitinib	class 2	MS, PFS, toxicity
Lilenbaum 2008	II	<=3	NSCLC	erlotinib	class 2	MS, PFS, toxicity, response, HRQL
Llovet 2008	III	<=2	HCC	sorafenib	class 3	MS, PFS, toxicity
Lorenzen 2009	II	<=1	esophageal	cetuximab	class 1	MS, PFS, toxicity
Lynch 2009	II	<=1	NSCLC	bortezomib	class 1	MS, PFS, toxicity
Lynch 2010	III	<=2	NSCLC	cetuximab	class 1	MS, PFS, toxicity
Makhija 2010	II	<=1	ovarian	pertuzumab	class 1	MS, PFS, toxicity
Marty 2005	II	<=2	breast	trastuzumab	class 1	MS, PFS, toxicity
Maruyama 2008	III	<=2	NSCLC	gefitnib	class 2	MS, PFS, toxicity
Mathew 2007	II	<=2	prostate	imatinib	class 1	PFS, toxicity
McDermott 2008	II	<=1	melanoma	sorafenib	class 1	MS, PFS, toxicity, response
Miller 2005	III	<=2	breast	bevacizumab	class 1	MS, PFS, toxicity, response
Miller 2007	III	<=1	breast	bevacizumab	class 1	MS, PFS, toxicity, response
Mitsudomi 2010	III	<=1	NSCLC	gefitinib	class 2	MS, PFS, toxicity
Mok 2009	III	<=2	NSCLC	gefitinib	class 2	MS, PFS, toxicity

Mok 2009a	II	<=1	NSCLC	erlotinib	class 1	response, PFS, MS
Moore 2007	III	<=2	pancreatic	erlotinib	class 1	MS, PFS, toxicity, response
Motzer 2007	III	<=1	RCC	sunitinib	class 2	MS, PFS, toxicity, response
Motzer 2008	III	<=2	RCC	everolimus	class 3	PFS, toxicity
Motzer 2009	III	<=1	RCC	sunitinib	class 2	MS, PFS, toxicity
Natale 2009	II	<=1	NSCLC	vandetanib	class 2	PFS, MS, toxicity
Pirker 2009	III	<=2	NSCLC	cetuximab	class 1	PFS, response, toxicity
Ratain 2006	II	<=1	RCC	sorafenib	class 3	PFS, toxicity, response
Ravaud 2008	III	<=2	RCC	lapatinib	class 2	MS, PFS, toxicity
Reck 2009	III	<=1	NSCLC	bevacizumab	class 1	PFS, toxicity, response
Rosell 2008	II	<=1	NSCLC	cetuximab	class 1	MS, PFS, toxicity, response
Saltz 2008	III	<=2	CRC	bevacizumab	class 1	MS, PFS, toxicity
Sandler 2006	III	<=1	NSCLC	bevacizumab	class 1	MS, PFS, toxicity
Santoro 2008	II	<=1	CRC	gefitnib	class 1	MS, PFS, toxicity, response
Scagliotti 2010	III	<=1	NSCLC	sorafenib	class 1	PFS, toxicity, response
Seidman 2008	III	NA	breast	trastuzumab	class 1	MS, PFS, toxicity, response
Slamon 2001	III	<=3	breast	trastuzumab	class 1	MS, PFS, toxicity
Sobrero 2008	III	<=2	CRC	cetuximab	class 1	MS, PFS, toxicity, response, HRQL
Spano 2008	II	<=2	pancreatic	axitinib	class 1	MS, PFS, toxicity
Sternberg 2010	III	<=1	RCC	pazopanib	class 3	MS, PFS, toxicity
Stewart 2009	III	<=2	H+N	gefitinib	class 2	MS, PFS, toxicity
Takeda 2010	III	<=1	NSCLC	gefitinib	class 1	MS, PFS, toxicity

Thatcher 2005	III	<=3	NSCLC	gefitnib	class 3	MS, PFS, toxicity
Tol 2009	III	<=1	CRC	cetuximab	class 1	PFS, toxicity
Van Cutsem 2007	III	<=3	CRC	panitumumab	class 3	MS, PFS, toxicity, response
Van Cutsem 2009	III	<=2	CRC	cetuximab	class 1	MS, PFS, toxicity
Van Cutsem 2009a	III	<=2	pancreatic	bevacizumab	class 1	MS, PFS, toxicity
Vermorken 2008	III	<=2	SCC H+N	cetuximab	class 1	MS, PFS, toxicity
von Minckwitz 2009	III	<=2	breast	trastuzumab	class 1	MS, PFS, toxicity
Yang 2003	II	<=2	RCC	bevacizumab	class 3	MS, PFS, toxicity
Yao 2008	II	<=2	carcinoid	bevacizumab	class 2	MS, PFS, toxicity

Legend:

CRC = colorectal cancer

NSCLC = non-small cell lung cancer

SCC H+N = squamous cell carcinoma, head and neck

RCC = renal cell carcinoma

Class 1 = chemotherapy vs. chemotherapy + targeted agent

Class 2 = chemotherapy vs. targeted agent

Class 3 = placebo vs. targeted agent