Assessing the Impact of Tumor Evolution on Oncology Drug Development and Commercialization

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By Joseph P. Sterk

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This thesis investigates the commercial viability of developing and commercializing targeted oncology drugs directed at a specific tumor mutation instead of all forms and mutations of a single target. While oncologic drugs targeted to aberrant or overexpressed pro-proliferative proteins have revolutionized cancer treatment, tumors treated for long periods may mutate over time, gain resistance to these drugs and proliferate rapidly again. I hypothesize that drugs developed to inhibit specific resistant tumor genotypes can be commercially viable from a pharmaceutical manufacturer's perspective.

To assess this hypothesis empirically, I construct a patient flow model in order to quantify the treatment of CML, a relatively rare and indolent hematological malignancy with extensive clinical data available and well-delineated disease phases and response criteria. To represent the rate of diagnosis, patients are "added" to the model every month, and thereafter there is a probability that a patient may either 1) become sufficiently intolerant to his drug in order to discontinue treatment, 2) fail to respond to treatment but remain in the same disease phase, 3) fail to respond to treatment and progress to the next phase of disease, or 4) adequately respond to treatment and stay on the same drug in the same phase. Patients that fail to respond (categories 2 and 3 above) have a chance of manifesting a resistance mutation that is adequately controlled by a hypothetical drug (in addition to their current treatment) but is otherwise untreatable. The aim of this analysis is to track the number of patients that accrue the chosen resistance mutation and thus would be good candidates to receive the hypothetical drug. Patient treatment rates are converted to sales figures, and are weighed against clinical development costs, timelines, and probabilities to determine the net present value (NPV) of a project to develop the hypothetical drug. In addition, parameters are varied in order to conduct a sensitivity analysis and determine the "boundary conditions" that make a drug profitable or unprofitable.

To supplement the model results and confirm the model dynamics, I interviewed investment analysts, clinical oncology thoughtleaders, academic cancer researchers and clinical, commercial and regulatory personnel from drug manufacturers to gauge their opinions on the CML market and the hurdles particular to developing drugs aimed at resistant genotypes.

The conclusion I reach from this analysis is that development of a specific mutation-directed therapy for resistant CML is unlikely to be profitable. Given the significantly smaller patient population, favorable conditions in pricing and clinical development would be required to make the hypothetical candidate even marginally profitable.

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Author's Biography
Joseph Sterk is a Master's candidate in the Harvard-MIT Biomedical Enterprise Program and will receive his Master of Health Sciences and Technology from MIT in June 2011. He earned his MBA in June 2010 from the MIT Sloan School of Management. During his MBA program, Joseph interned at Arsenal Medical and Novartis Vaccines and Diagnostics where he worked in marketing and business development. Prior to enrolling in the Biomedical Enterprise Program, Joseph worked for Clarion Healthcare as an associate consultant, for Deutsche Bank Securities and RBC Capital Markets as an equity research associate in the biotechnology sector, and in the William C. Stanley laboratory at Case Western Reserve University as a research assistant. Joseph holds an A.B. in Biochemical Sciences from Harvard University.

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Introduction

Cancer therapy has evolved from the use of purely cytotoxic chemotherapy to a combination approach frequently combining one or more of chemotherapy and targeted inhibitors of cell proliferation, signal transduction and angiogenesis. The utility of chemotherapy was discovered during World War II, when an explosion in an Italian harbor exposed American sailors to nitrogen mustard (still used as the alkylating agent mechlorethamine) and induced profound myelosuppression[1]. Consequently, nitrogen mustard was first medically administered to a non-Hodgkin's lymphoma patient at Yale Medical Center and induced a partial tumor response.

The latter half of the 20th century saw the rational design of cytotoxic agents (including the antifolates) and use of natural products (including the vinca alkaloids and taxanes), as well as the introduction of immunotherapy. While often effective, these agents often failed due to substantial off-target effects. More recently, advances in cancer biology have led to the development of drugs that specifically target cancer cells. Many require the use of clinical biomarker testing of either patient or tumor in order to achieve a meaningful therapeutic benefit, an approach termed "stratified medicine."

Cancer treatment fulfills the three necessary conditions for stratified medicine laid out by Trusheim *et al*: a differential biological mechanism of action, multiple treatment options, and the presence of a clinical biomarker. There are 21 approved cancer therapies which either require or recommend a biomarker/diagnostic before prescription, comprising nearly two-thirds of all biomarker/diagnostic therapies[2]. Moreover, the high cost (often greater than $100,000 for a single course or year of treatment) and rate of severe toxicities in cancer treatment, and the

differential benefit between patient populations, can incentivize payers to reimburse diagnostics which can cost thousands of dollars[3].

While targeted therapies have had a significant impact and even transformed some cancers into chronic "maintenance" conditions, many tumors relapse and become symptomatic despite optimal treatment. Causes of relapse include:

- Drug modification (chemically altering the drug to an inert substance)
- Prevention of drug uptake (often a down-regulation of carrier proteins)
- Drug efflux (extruding the drug from the cytosol and preventing the attainment of therapeutic concentrations)
- Increased repair of drug damage (undoing the damage done by chemotherapy)
- Substrate alteration (preventing the drug from binding its intended target)
- Insensitivity to apoptosis (reducing susceptibility to chemotherapy)
- Proliferation through a new pathway (necessitating at least one new therapy)[4]

A mutation that causes a tumor to resist treatment that it had previously responded to is hereafter referred to as an "escape mutation" and the ongoing process of drug-induced genetic change as "tumor evolution."

One of the greatest successes of targeted therapy was the introduction of Novartis' Gleevec (imatinib mesylate), a tyrosine kinase inhibitor (TKI) that targets the cause of most CML, the BCR-ABL kinase. It was approved in May 2001 for the treatment of chronic myeloid leukemia

(CML)[5] and transformed not only the clinical treatment of the disease but the economics of treatment. A relatively small disease (5,000 new U.S. patients per year) could be treated as a near-lifelong chronic condition with premium pricing, translating to mega-blockbuster revenues (estimated worldwide sales of $3.2 billion in CML in 2010)[6]. Longer-term data have borne out the promise of Gleevec, with a majority of patients still adequately treated at seven years from disease diagnosis. In the meantime, two more TKIs have been approved for CML: Novartis' Gleevec follow-on Tasigna (nilotinib) and Bristol-Myers Squibb's Sprycel (dasatinib). Both garnered approval for later-line disease before moving into the 1st-line setting. However, some mutations confer resistance to Gleevec, Tasigna and Sprycel, most notably the T315I mutation in the BCR-ABL kinase domain.

While the 1st-line market may be the largest and most profitable segment of CML treatment, a considerable unaddressed market for 1st-line failures will emerge over time. Moreover, a drug manufacturer seeking a label for patients in later-line settings may gain approval with smaller and shorter studies, and enjoy premium pricing and regulatory treatment (such as orphan drug status). Given the presence of resistance mutations in 2nd- and 3rd-line disease, a label to treat CML with certain particularly difficult-to-treat mutations could theoretically gain rapid adoption. It remains to be seen if the streamlined clinical and regulatory path and premium pricing can outweigh the smaller patient population and requirement for a companion diagnostic.

I examine this idea through the following methods:

1. Deep-dive case study in CML. Most patients who receive any one of the three approved TKIs at the earliest ("chronic phase") stage will have well-controlled disease for many years, while others will either lose response or progress to a more advanced phase of disease. A subset of these will manifest mutations that render their tumor resistant to all three drugs. I use published data on the epidemiology of CML, analyst sales estimates, peer-reviewed efficacy and safety data, and parameter estimates from thoughtleaders to construct a state-transition model of the diagnosis, treatment and prognosis of CML. This is then translated to a profit and loss statement (for commercialization in the US and Europe) to determine the net present value (NPV) of a hypothetical drug geared to treat CML with an otherwise untreatable resistance mutation.

2. Sensitivity analyses. Using the model developed in the first part, I modify certain key inputs in order to determine which factors most influence the profitability of the hypothetical candidate. Key factors including frequency of the untreatable mutation, drug pricing, discount rate, development conditions and long-term data associated with the three approved agents can greatly influence the profitability of the hypothetical candidate.

3. Qualitative supplement. In addition to providing modeling estimates, interviews with various constituencies served to confirm the critical dynamics around the CML market and provide qualitative insight. Interviews were conducted with leading clinicians, investment analysts, key clinical, regulatory, and commercial personnel at biopharmaceutical companies, payers and basic scientific researchers.

4. Extensions and applications. I conclude by discussing the further uses of a transition-state patient flow model. Many subacute and chronic diseases are divided into stages with differential prognoses for death, complication, progression and recovery, and long-term data could allow for modeling in the same fashion as this model does for CML.

Scientific overview

Targeted therapies have advanced hand-in-hand with cancer biology in general and knowledge of perturbations in cancer signaling pathways in particular. Over time, many tumors overcome signaling pathway inhibition through resistance mutations. Certain evolved genotypes are increasingly recognized as problematic and possibly worthy of investment. I examine the science of cancer signaling, inhibition and escape from inhibition, with a focus on the biology and treatment of CML.

Importantly, the forthcoming modeling analysis takes a "black box" approach to the development of resistance. The timing (i.e. prevalent at diagnosis or developed during treatment) and precise causes of resistant mutations are unknown and current diagnostics are inadequate to detect all potential clones in a tumor sample. Moreover, mutational analysis is not conducted in trials until failure or progression (defined later in this section) occur. Thus, the modeling and analysis do not depend on how a mutation arose, but only on the fact that a mutation arose during serial treatment.

Implications of cancer as a genetic disease

Dr. I. Bernard Weinstein describes tumorigenesis as a sequential process involving the mutational activation of growth-promoting genes (oncogenes) and mutational inactivation of growth-suppressing genes (tumor suppressors), as well as epigenetic (non-mutational) abnormalities that lead to increased or decreased expression of these genes[7]. This process has been shown to occur in reverse as well, as studies in multiple tumor types have shown that turning off critical oncogenes (including *myc*, *Her-2/neu*, K-*ras* and cyclin D1) or introducing

natural tumor suppressors (including *p53*, retinoblastoma suppressor (*Rb*) and *APC*) causes cancer cells to cease proliferating and undergo apoptosis. Together, these observations reinforce the scientific view of cancer as a disease of uncontrolled cell growth secondary to abnormal genetic changes.

The nature of escape mutations

While patients with advanced and highly resistant solid tumors show drastic responses to single pathway inhibitors, many of these tumors rapidly recover after several months on therapy. The precise nature of a tumor's "escape" from therapy has not yet been fully elucidated, but many theories exist.

A tumor will have accrued many mutations and lack many safeguards against further DNA mutations by the time it becomes clinically symptomatic. Therefore, it is likely to continually accrue new mutations as well as aneuploidy (changes in chromosomal number), endoreduplication (duplication of the genome without mitosis), chromosomal deletions and chromosomal translocations as it grows and spreads[8]. If a given mutation compromises essential cellular machinery or otherwise impairs survival, the cell will die. If not, a given mutation may be categorized as a "driver" mutation (which drives cell proliferation) or a "passenger" mutation (which does not).

The nature and genesis of escape mutations has not been determined and is a topic of scientific debate. One hypothesis holds that a tumor presents clinically as a homogeneous entity without the resistant clone present, while the resistant mutation that evades treatment occurs only after

selection pressure is provided via the drug. Another assumes a heterogeneous tumor with a large burden of wildtype cells and a small but undetectable number of resistant cells that proliferate only after the drug reduces the wildtype tumor burden. More sensitive tumor assays at baseline that can detect minute quantities of heterogeneous tumor cells would be necessary to distinguish the two.

In addition, there is a population of "stem cells" that breed further leukemia cells that persist even with targeted therapy. The "log-kill" hypothesis of cell-killing agents states that each dose of medication kills a fixed percentage of cells; under this hypothesis, leukemic stem cells are simply *BCR-ABL*-expressing hematopoietic progenitors (in contrast to the more differentiated tumor cells observed in CML) that do not receive adequate levels of TKI. Moreover, it has been shown that *BCR-ABL*-expressing progenitor cells persist even in patients who respond to Gleevec[9]. Another hypothesis is that leukemic stem cells express *BCR-ABL* but have some other characteristic that renders them insensitive to TKIs. For example, one study suggests that stem cells undergo autophagy (a state of metabolic inertia in which a cell degrades internal components) that renders them resistant to TKIs[10].

While cancer stem cells have been best characterized in hematologic malignancies, similar observations have been made in solid tumors. For example, samples of breast cancer tissue revealed a subset of cells with characteristics of bone marrow stem cells (bone marrow stem cells may proliferate in conditions of both normal physiology and cancer)[11].

Evidence of oncogene addiction

It has been observed that inhibition of even one mutation that the tumor depends on to stay malignant can be sufficient to inhibit profoundly or even eradicate the tumor[12]. The theory of oncogene addiction postulates that although tumor cells may have many genetic aberrations, inhibiting one gene or pathway can prevent the cell from proliferating further.

Further evidence of oncogene addiction lies in the fact that so-called "escape mutations" (that is, mutations that allow a tumor to evade therapy) most frequently occur in the original mutated pathway[13,14]. In particular, studies of CML and epidermal growth factor receptor (EGFR)-overexpressing non-small-cell lung cancer are associated with specific resistance mutations that confer insensitivity to pathway inhibitors. For example, resistance to TKIs in CML is commonly associated with specific mutations in the BCR-ABL kinase, and several tumor types develop resistance to EGFR inhibition by gaining constitutive activity of the downstream signaling molecule Ras.

While the precise molecular and cellular mechanisms of oncogene addiction have not been determined, several theories exist as to why it has been observed. Dr. Restifo details three major theories:

- **"Dominant oncogene"**: One of the first theories of oncogene addiction held that tumor cells receive growth signals through multiple pathways but preferentially proliferate through a single pathway. Over time, mutations and epigenetic changes silence other

pathways and leave it dependent on one. Thus, inhibition of the dominant pathway renders the cell unable to proliferate and leads to apoptosis.

- **"Cumulative mutations"**: In this theory, some driver mutations are beneficial in the presence of a certain second mutation, but harmful on their own. In this case, inhibiting one mutated pathway leaves the cell with a harmful mutation that leads to senescence or death.

- **"Oncogene amnesia"**: This theory holds that there is a balance of pro- and anti-apoptotic factors in the cell, with the latter mediated by oncogenes and overriding the former during proliferation. Therefore, once the oncogene is inhibited, the balance tilts in favor of pro-apoptotic factors and leads to cell death.

It logically follows that a drug which inhibits the responsible pathway can significantly slow or even halt tumor growth, thus potentially 1) allowing the immune system to better control the tumor burden; 2) reducing the rate of tumor replication, mutation, and resistance development; and 3) increasing the efficacy of other anticancer therapies. In particular, combinations of pathway inhibitors which cover the original tumor and likely mutations could work synergistically to delay the time to drug resistance, similar to the use of combination therapy to treat HIV or tuberculosis.

Scientific case study: CML

The "arms race" of cell proliferation, pathway inhibition and escape mutation has been well-studied in CML, a slow growing hematologic cancer characterized by abnormal proliferation of myeloid cells and progenitors. The availability of long-term outcomes data, its well-characterized three phases of disease and problems of specific drug-resistant genotypes permit use of a transition state model to study a clinically and commercially relevant question.

CML is associated with a mutated gene knows as the breakpoint cluster region-Abelson leukemia virus (*BCR-ABL*) fusion oncogene, the result of a translocation between chromosomes 9 and 22 [t(9; 22)(q34;q11)] termed the "Philadelphia chromosome" (Ph+) [15]. Alone, the ABL tyrosine kinase is highly regulated; coupled to BCR, the fused oncogene encodes for a constitutively active 210 kDa tyrosine kinase. The BCR-ABL kinase phosphorylates many downstream signaling molecules, including those in the Ras/Raf/MEK/ERK, Jak/Stat and phosphoinositol-3-kinase (PI3K)/Akt signaling pathways[16]. This activity within a hematopoietic stem cell (HSC) allows it to proliferate and displace normal HSCs and is sufficient to render the HSC cancerous[17].

Though 95% of CML cases express *BCR-ABL*, the two are not synonymous. So-called "Atypical CML" presents without detectable *BCR-ABL*, although many of these patients have other chromosomal rearrangements that could inhibit detection of the actual t(9; 22) translocation, and it is debated whether the remainder have CML or a different myeloproliferative disorder known as myelodysplastic syndrome. Additionally, *BCR-ABL* may be present in a B-cell acute

lymphocytic leukemia (ALL) termed Ph+ ALL which carries an especially poor prognosis and requires intense multi-year chemotherapy[18].

The disease progresses in three phases, with an average untreated survival of approximately three years from diagnosis:

- The **chronic phase (CP)** involves the transformation of an HSC and increase in the number of myeloid cells within the appropriate hematopoietic tissues (blood, liver, spleen, bone marrow). Compared to other leukemias, these cells are relatively mature with predominant neutrophils, and lesser quantities of basophils and eosinophils. Clinically, most chronic phase patients present with left upper quadrant pain, splenomegaly, pallor, loss of appetite, fatigue, and bone pain of slow onset. Diagnosis is confirmed by laboratory abnormalities include progressively increased white blood cell count, elevated platelet count, hypercellular bone marrow with Philadelphia chromosome-positive cells, and blasts in the peripheral blood. Approximately 90% of patients present in this stage, and this fraction is likely increasing due to earlier diagnosis.

- **Accelerated phase (AP)** disease is poorly defined, and occasionally argued to be an early form of blast crisis[19]. Patients often develop a fever and night sweats, and additional cytogenetic abnormalities. Most notably, increases in activity of the Wnt pathway (through beta-catenin) and the hedgehog pathway have been observed, as are trisomy 8, trisomy 19, additional copies of the Philadelphia chromosome and isochromosome 17q.

- The final stage of disease is the **blast crisis (BC)**, in which a high percentage of blasts occur in the peripheral blood. This stage resembles an acute leukemia and may be either myeloid or lymphoid in appearance. Genetic aberrations include those observed in AP disease as well as dominant negative mutations in transcription factors required for differentiation, mutated p53, *c-Myc* amplification, and *Rb* deletion.

Table 1: WHO definitions of accelerated phase and blast crisis[20]

Accelerated Phase	Blast Crisis
Blasts (myeloid or lymphoid progenitor cells) comprising 10-19% of peripheral white blood or bone marrow cells Basophils comprising ≥20% of peripheral white blood cells Platelet abnormalities: thrombocytopenia (platelets <100,000/μl) unrelated to therapy or thrombocytosis (platelets >1,000,000/μl) unresponsive to therapy Increasing spleen size and white blood cell count despite therapy Clonal evolution	Blasts comprising ≥20% of peripheral white blood or bone marrow cells Clusters of blasts in the bone marrow Development of a solid focus of leukemia cells outside the bone marrow

CML treatment before and after targeted therapy

CML treatment has evolved significantly over time. Since the 1950s, traditional cytotoxics including busulfan (an alkylating agent) and hydroxyurea (a ribonucleotide reductase inhibitor) were used to lower white blood cell counts, and are occasionally still used today in blast crisis, later-line patients, or to bring white blood cell counts under control prior to initiating targeted therapy[21]. Immunotherapy was introduced with trials of interferon-α in the 1980s, both alone and in combination with cytosine arabinoside (termed "ara-C", an antimetabolite). This combination was the CML standard of care before the introduction of targeted therapy.

The first approved targeted therapy for CML was Novartis' Gleevec (imatinib mesylate), approved in May 2001. A competitive inhibitor of the ATP binding site of the BCR-ABL kinase (with activity against platelet derived growth factor (PDGF) receptor and c-Kit), Gleevec quickly became the new standard of care after showing significant benefits over interferon-α + ara-C. This benefit has since been shown to be durable (81.2% v. 60.6% progression free survival at seven years, defined as freedom from death, loss of response, progression to AP/BC, or increasing white blood cell count)[22], with a generally tolerable side effect profile that includes edema, cramps and rash, with approximately 4% of patients discontinuing treatment. These strong efficacy results were reproduced even in clonally evolved accelerated phase and blast crisis disease, lending further weight to the hypothesis of oncogene addiction.

The second BCR-ABL kinase inhibitor approved was Bristol-Myers Squibb's Sprycel (dasatinib), approved in June 2006. In addition to binding BCR-ABL kinase with 325-fold potency compared to Gleevec, Sprycel binds SRC family kinases and may theoretically prevent tumors from developing resistance through this pathway. Its pivotal trial in chronic phase CML showed improved rates of complete cytogenetic response (77% v. 66%) and major molecular response (46% v. 28%), two important measures of response, compared to Gleevec[23]. The major side effect of Sprycel is pleural effusion, and approximately 6% of patients discontinued treatment.

The most recent drug approved for CML was Novartis' Tasigna (nilotinib), which was approved in October 2007. Unlike Gleevec, Tasigna binds to and stabilizes the inactive conformation of

the BCR-ABL kinase (20-30-fold affinity relative to Gleevec) and like its predecessor also inhibits PDGF receptor, c-Kit, colony stimulating factor-1 (CSF-1) receptor, and discoidin domain receptor (DDR). It also showed superiority to imatinib in complete cytogenetic response (80% v. 65%) and major molecular response (44% v. 22%)[24]. Like the others, Tasigna is well tolerated, although the drug has to be taken twice daily, and is known to prolong the QT interval and thus be potentially arrhythmogenic.

These three drugs are approved to treat all phases of disease, with the latter two recently earning approval as first-line treatment for chronic phase disease[25].

Table 2: NCCN response criteria[26]

Complete Hematologic Response (CHR)	Normalization of peripheral blood counts with white blood cell count < 10,000/μl Platelet count < 450,000/μl No immature cells in peripheral blood No signs of disease including palpable splenomegaly
Partial Hematologic Response (PHR)	Same as Complete Hematologic Response, except: Immature cells in peripheral blood Platelet count <50% of pretreatment count but <450,000/μl Palpable splenomegaly <50% of pretreatment extent
Cytogenetic Responses (CyR)	Relates to fraction of Philadelphia-chromosome positive chromosomes (observed at metaphase): Complete – 0% (CCyR) Partial – ≤ 35% (PCyR) Major – CCyR or PCyR Minor – ≤ 65% (mCyR)
Complete Molecular Response (CMR)	No BCR-ABL mRNA detectable by RT-PCR
Major Molecular Response (MMR)	≤0.1% ratio of BCR-ABL mRNA to housekeeping genes

Table 3: Treatment goals[27]

	Optimal (continue treatment as is with periodic monitoring)	**Suboptimal** (variable—switch patient if significant adverse events)	**Failure** (re-evaluate, test for mutations and switch treatments)
3 mos	CHR + mCyR (or better)	CHR without CyR	Less than CHR
6 mos	PCyR (or better)	CyR less than PCyR	No CyR
12 mos	CCyR (or better)	PCyR	Less than PCyR
18 mos	MMR (or better)	CCyR without MMR	No CCyR
At any time	Stable or improving MMR	Loss of MMR, clonal evolution	Loss of CHR, loss of CCyR, clonal evolution

Tackling resistance

While these targeted therapies have eclipsed older chemo- and immunotherapies in both efficacy and safety, resistance remains a problem. Bixby *et al* detail several potential causes[28]:

- **BCR-ABL kinase domain mutations:** It is believed that most patients who develop resistance do so because of BCR-ABL kinase domain mutations (approximately 50% of patients with CML resistant to Gleevec). In chronic phase, mutations develop over a period of years (16% over 42 months in one study); in accelerated phase and blast crisis, mutations become clinically apparent much sooner[29]. However, the precise causes of mutation have not been determined (though are speculated to include induced expression of mutagenic enzymes, altered mechanisms of DNA repair or generation of reactive oxygen species).

- **BCR-ABL mutations outside the kinase domain:** Half of patients who fail TKI treatment do not show mutations in the BCR-ABL kinase domain, and many are believed to have mutations elsewhere in the gene.

- **BCR-ABL amplification:** While some studies have shown increased expression of the *BCR-ABL* gene, and Gleevec dose escalation is often used when the initial dose fails to produce a desired response, this is believed to be relatively uncommon.

- **Drug efflux:** BCR-ABL kinase inhibitors act within the cell, and imatinib, dasatinib and nilotinib are all known to be substrates of drug efflux pump P-glycoprotein[3031]. However, P-glycoprotein expression has not been observed to predict resistance in human studies.

- **Other signaling pathways:** Cancer signaling pathways are often complex and aberrant, and several mutations have been observed in BCR-ABL kinase inhibitor resistant CML including Lyn, Src, and Erk2.

- **Epigenetic alterations:** Since the BCR-ABL gene is commonly methylated, physicians will occasionally use hypomethylating agents such as Eisai's Dacogen (decitabine) to treat accelerated phase disease[32]. Small studies of decitabine showed some hematologic and cytogenetic responses in Gleevec-resistant disease across all disease phases[33].

Resistance mutations

The most commonly observed mutations occur in the ATP binding domain and affect residues which can either block the drug from binding or fail to form crucial hydrogen bonds with the drug. The most clinically concerning mutation is the T315I mutation, in which the bulky isoleucine side chain blocks the site to which TKIs bind and renders patients resistant to all three.

Others of note include M244V, G250E, E255K/V, M351T and F359V, which together account for an estimated 85% of resistance mutations[34].

Scientific case study: other solid tumors

The success of targeted therapies for several solid tumors further underlines the theory of oncogene addiction. These generally have more mutations than hematological malignancies before they become clinically apparent, but have shown susceptibility to single pathway inhibitors. Three other case studies are detailed below:

HER2

The HER2 protein (also known as ErbB-2, CD340 or p185) is a 185 kDa transmembrane growth factor receptor of the EGFR family and is overexpressed in approximately 25% of breast cancers[35]. While the EGF ligand family cannot activate HER2, other receptors in the same family can dimerize with HER2 and lead to signal transduction via the PI3K/Akt pathway and mitogen-activated protein (MAP) kinase pathway, and production of pro-angiogenic vascular endothelial growth factor (VEGF)[36]. HER2-overexpressing tumors are notoriously aggressive and insensitive to hormonal methods of treatment.

Two approved drugs are known to inhibit this pathway: Roche's Herceptin (trastuzumab, a monoclonal antibody) and GlaxoSmithKline's Tykerb (lapatinib, a small molecule dual EGFR/HER1 and HER2 tyrosine kinase inhibitor)[3738]. Herceptin was approved in 1998 and has more extensive available data, including robust efficacy in metastatic (progression free survival

of 7.2 months in combination with chemotherapy vs. 4.5 months for chemotherapy alone) and adjuvant (33-52% reduction in recurrence following surgical removal) settings.

Tykerb illustrates the utility of oncogene addiction more purely as it does not function through immunological mechanisms, and has shown efficacy in combination with chemotherapy in treating Herceptin-resistant disease.

EGFR

Often called HER1 or ErbB-1, EGFR binds a wide range of growth ligands to stimulate signal transduction and tumor proliferation. Similarly to family member HER2, EGFR signals for survival and proliferation through the PI3K/Akt and MAPK pathways. Signaling through this receptor has been implicated in non-small-cell lung cancer (NSCLC), colorectal cancer (CRC), pancreatic cancer, squamous cell carcinoma of the head and neck (SCCHN) and brain cancer.

There are four approved drugs that inhibit this pathway: two TKIs, AstraZeneca's Iressa (gefitinib, approved in 2003) and Roche/OSI's Tarceva (erlotinib, approved in 2004) and two monoclonal antibodies, Eli Lilly's Erbitux (cetuximab, approved in 2004) and Amgen's Vectibix (panitumumab, approved in 2006).

B-Raf

The evolving B-Raf inhibitor story illustrates both the promise and challenges of targeted pathway inhibitors. B-Raf is one of three Raf proteins, also known as MAP kinase kinase kinases (MAPKKK), which serve as signal transduction kinases in the MAPK pathway and regulate cell

division, differentiation and secretion[39]. Additionally, melanoma is notoriously resistant to chemotherapy—melanocytes evolved to sense and repair DNA damage and thus it is expected that a melanoma will resist DNA damaging agents effectively[40].

One of the most exciting oncology clinical candidates in development is Plexxikon's (recently acquired by Daiichi) B-Raf inhibitor PLX4032 for the treatment of metastatic melanoma with the B-Raf V600E mutation. An open label, multi-center 132 patient study shows a response rate of 52% including 2% complete response (no evidence of disease) and 50% partial response (tumor shrinkage of at least 30%), with an additional 30% showing stable disease[41]. However, many of these responses were short lived. A study by Wagle *et al.* showed that one patient developed resistance after developing a C121S mutation of the downstream signaling molecule MEK[42].

Market overview

The question that I will use the model to answer—will a hypothetical drug candidate aimed at a particular resistance mutation be sufficiently attractive to drug developers—is most relevant to a well-studied market. While some resistance mutations (including certain *K-Ras* mutations in colorectal and pancreatic cancers) are present at baseline, questions of acquired resistance are more complex and lend themselves to transition-state methodologies.

Classifications of targeted therapy

According to a Cowen & Co. analyst report, oncology/hematology is the largest single disease area by product sales with 2009 worldwide sales of $71.3 billion (20% of the worldwide biopharmaceutical market), expected to increase to 2015 worldwide sales of $97.0 billion (5% compound annual growth rate (CAGR)). Of these, targeted therapies comprise $28.4 billion or 40% of the total oncology/hematology market, the largest single share of any drug type[43]. Targeted therapies are frequently divided into monoclonal antibodies and small molecules, each with advantages and disadvantages relative to the other.

The former are very specific for the chosen protein (and thus for cells that express that receptor) and act via multiple mechanisms of action including 1) sequestering the ligand (Roche's anti-VEGF antibody Avastin (bevacizumab) is approved for several cancers including CRC, NSCLC, breast cancer, glioblastoma and kidney cancer)[44], 2) preventing the ligand from binding to the targeted receptor, 3) antibody dependent cellular toxicity (triggering tumor cell destruction by mediating phagocytosis), 4) complement dependent cytotoxicity (in which the antibody fixes complement leading to tumor cell lysis) and 5) antibodies may be conjugated to a cytotoxic or

radioactive payload to deliver a "smart bomb" (Roche's drug candidate trastuzumab-DM1 consists of Herceptin conjugated to a cytotoxic and has shown superior response rate compared to Herceptin in Phase II trials)[45]. On the other hand, these drugs must be infused over a long period of time and many risk triggering allergic reactions. With respect to efficacy, a mutation within the intracellular signaling machinery will also render the antibody ineffective. They are also generally more expensive than small molecules. Some of the greatest market successes including Roche's Rituxan (2009 worldwide sales of $5.6 billion), Roche's Herceptin (2009 worldwide sales of $4.8 billion) and Eli Lilly/Merck KGaA's Erbitux (2009 worldwide sales of $1.6 billion) come from this category[46].

Small molecules generally inhibit the intracellular signaling apparatus that triggers cancer cell survival and proliferation. Many TKIs inhibit a wide range of signaling kinases, including Pfizer's Sutent (sunitinib), which has activity against platelet derived growth factor receptors (PDGFRα and PDGFRβ), VEGF receptors 1, 2 and 3, KIT, Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor Type 1 (CSF-1R) and glial cell-line derived neurotrophic factor receptor (RET)[47], while others are much narrower in spectrum including Roche/Astellas's Tarceva (erlotinib) which only meaningfully inhibits EGFR[48]. Other small molecule targeted therapies include hormonal agents which inhibit estrogen or androgen synthesis or receptors, or immunomodulators and antiangiogenics with less-understood mechanisms of action, such as Celgene's Thalomid (thalidomide) and Revlimid (lenalidomide). While they can inhibit a broader range of kinases, this can potentially translate to side effects, and tumors may evolve to "work around" inhibition. Top sellers include Gleevec (2009 worldwide sales of $3.9 billion) and AstraZeneca's Arimidex (anastrozole, 2009 worldwide sales of $1.7 billion).

Case study: HER2-overexpressing breast cancer

One of the first success stories of stratified medicine involved the development and commercialization of Herceptin for the treatment of HER2-overexpressing breast or gastric cancer. Herceptin was first approved in the U.S. in 1998 for the treatment of metastatic HER2-overexpressing breast cancer, and U.S. sales increased at a steady rate from $184 million in 1999 to $479 million in 2004[49]. The market for metastatic breast cancer is significant for its prevalence, but only ~25% of breast cancer patients (10,000 in the U.S.) are Herceptin-eligible, and the drug is only dosed every three weeks until disease progression (6.7-7.6 months in first-line disease, and likely lower in previously treated disease)[50].

A major inflection point occurred when strongly positive results in the adjuvant setting (post-surgical, to prevent recurrence and metastasis of residual disease) drove 2005 U.S. sales to $747 million and 2006 sales to over $1.2 billion. Increased screening for breast cancer is likely to contribute to earlier detection and diagnosis in the adjuvant setting (approximately 25,000 women are believed to undergo adjuvant chemotherapy for breast cancer), and the labeled duration of treatment of 52 weeks translates to a richer market opportunity.

Case study: BCR-ABL kinase inhibitors for CML

BCR-ABL kinase inhibitors for the treatment of CML garnered an estimated $4.2 billion in 2010 worldwide sales, a seemingly disproportionate sum for a disease that affects approximately 100,000 individuals in the U.S. and EU and only 12,000 newly diagnosed individuals per year[51,52]. Despite its small size, this market has the potential to be extremely profitable due to

highly differentiated efficacy translating to premium pricing, small sales force requirements to market this class effectively, and lifelong requirement (so far) to receive the drug.

Approximately 75% of Gleevec sales (estimated $3.2 billion in 2010) come in CML, with the remainder in a sarcoma known as gastrointestinal stromal tumor (GIST) in which it functions as a c-Kit inhibitor, or in several rare hematologic malignancies. Gleevec's convenient once-daily oral dosing and demonstrated efficacy over several years of treatment have made it the standard of care for CML (especially chronic phase CML) for some time[53,54].

The second-generation TKIs Sprycel and Tasigna have been approved in 2006 and 2007 for Gleevec-resistant disease, respectively, and more recently for first-line use. Each showed superiority to Gleevec at 12 or 24 months in its Phase III chronic phase CML pivotal trial, but has not been studied long enough to show the long-term efficacy profile. Nonetheless, they are regarded as likely to prove more efficacious over the long term, and thus preferred for younger patients or more aggressive disease. In addition, both have differentiated resistance profiles compared to Gleevec, though certain BCR-ABL kinase domain mutations (most notably T315I) will render both drugs ineffective. 2010 sales of Sprycel and Tasigna were $399 million and $576 million, respectively, but are expected to increase to $1.9 billion and $1.4 billion by 2016[55].

The next wave of TKIs has been deemed "third-generation TKIs" and includes the following:

- **Pfizer's bosutinib** is a BCR-ABL and Src kinase inhibitor for which regulatory filings are expected in 2011. Trials of bosutinib in 2nd- and 3rd-line therapy showed efficacy in

chronic phase CML[56]. However, its Phase III trial in 1st-line chronic phase CML failed to show a statistically significant improvement in its primary endpoint of CCyR against Gleevec (70% vs. 68%), though it showed an improvement in MMR (39% vs. 26%)

- **Ariad's ponatinib** (formerlyAP24534) is a pan-BCR-ABL inhibitor, specifically engineered with a triple carbon bond that enables it to avoid the bulky isoleucine side chain and have activity in T315I CML[57]. It also inhibits FLT3 (common in acute myeloid leukemia) and c-Kit, with some observed activity against VEGF, PDGF and fibroblast growth factor (FGF) receptors, and the angiogenic protein Tie-2. While still early in development, Phase I data from a dose-ranging study presented at the American Society of Hematology (ASH) 2010 conference showed activity in a highly resistant population of hematologic malignancies (mostly CML, with 95% resistant to at least 2 TKIs and 65% resistant to 3 TKIs). Ponatinib induced MCyR in all 9 patients with T315I and CCyR in 8 of those, and 66% and 53% respectively in the overall chronic phase CML population despite many patients receiving less than the pivotal trial dose[58]. The pivotal Phase II PACE trail is currently enrolling patients in six cohorts, separated on the basis of disease stage and T315I mutation status.

Other drugs in the CML pipeline include the following:

- **Chemgenex' omacetaxine** (formerly homoharringtonine) is a subcutaneously-administered inhibitor of the synthesis of oncogenic proteins including Mcl-1, Cyclin D1 and c-Myc[59]. Data presented at ASH 2009 showed MCyR in 41% of chronic phase CML

patients who had failed imatinib and presented with the T3151 mutation at baseline. Regulatory filings are planned for 2H 2011.

- **Deciphera's DCC-2036** inhibits BCR-ABL, Tie-2, LYN and HCK kinases by binding the "switch region" to constrain them in an inactivate state, and thus is expected to have efficacy against mutations which renders active-site binding TKIs (including all three marketed agents) inactive[60]. A Phase I/II study in CML and Ph+ ALL is expected to enroll 45 patients and be completed in September 2011[61].

- **Other approaches.** The hedgehog pathway receptor *Smo* (smoothened) has been implicated as a cause of leukemic stem cells. A Phase I/II trial of Bristol-Myers Squibb's Smoothened inhibitor in combination with Sprycel is ongoing in patients with a suboptimal response to a prior TKI. Additional approaches include inhibitors of the aurora kinases and heat shock protein (Hsp) 90.

Implications of oncogene addiction for commercial success

While oncogene addiction is a relatively recent development in cancer biology, its implications are already widespread.

Genetically simple tumors are easier to control. One of the most important implications is the relative ease of treating certain tumor types—including more genetically simple tumors with fewer aberrations as in chronic phase CML—and the difficulty in treating more complex, heavily

mutated tumor types. It also explains the significant short-term disease control in other tumor types coupled with the likelihood of relapse.

Molecular diagnostics will become increasingly important. Drugs such as Gleevec and Herceptin require molecular diagnostics in order to be given to the right patients. However, as tumors evolve and develop resistance, new diagnostic tests will be required in order to direct the patient to the proper therapy for resistant or refractory disease. Ultimately, physician thoughtleaders believe many tumors could be controlled by the process of 1) extensively genotyping the tumor for a wide range of mutations and determining which pathways are most active, 2) prescribing a personalized cocktail of pathway inhibitors to slow the tumor's growth and impede the development of further mutations and 3) periodically checking the tumor to assure that it is under control[62].

Efficacious drugs will be used for long periods of time. CML treatment is for life—at present, physicians do not recommend stopping treatment for any reason, and 50% of patients with a CMR (no evidence of BCR-ABL mRNA in the system) will relapse if they discontinue Gleevec[63]. Thus, an orphan cancer has become a >$4 billion dollar market, possibly increasing as the Gleevec patent expires in 2015 and the more expensive Sprycel (24% price premium to Gleevec) and Tasigna (33% price premium to Gleevec) take over.

Combination therapy may be on the horizon. The paradigm of combination therapy directed as multiple aspects of an aberrant cell's machinery has been validated in infectious diseases. As

similar drug targets (often signaling molecules) are found in cancer, a personalized combination could theoretically yield the same result.

One hurdle may be the regulatory element. The FDA has only recently approved trials of two new agents in combination. Nonetheless the FDA has started to issue guidance on this matter. Additionally, orphan drug status may be questionable for biomarker-defined subsets of larger patient populations and is determined on a case-by-case basis (e.g. HER2-overexpressing breast cancer received orphan designation but another subset may not show sufficiently differential responses to be regarded as a separate indication)[64].

The model described in the next section uses CML as a model system to examine the scenarios under which drugs for certain treatment-resistant genotypes may be commercially viable.

Model structure

In order to elucidate the impact of evolving tumors, I created a Microsoft Excel transition-state model of the CML market to simulate changes in patient dynamics, drug use and physician preferences over time. In this section I will detail the rationale behind the model, the model structure, specific inputs and the reasons behind them, the model outputs, and finally the limitations and future directions that further research would entail.

Why use a model to study tumor evolution?

It is becoming a standard practice in cancer targeted therapy clinical trials to collect and genotype tumor samples. Some organizations such as Massachusetts General Hospital and the National Cancer Institute even do so outside of clinical trials in order to better understand the genetics of cancer[65]. Therefore, there is a growing database of information pertaining to evolving tumor genetics and the clinical impact of drugs on this process.

I anticipate that the concept of tumor evolution will grow in commercial importance as mechanisms of resistance to targeted therapy become elucidated. As certain drug-associated mutations or other genetic aberrations gain notoriety, pharmaceutical manufacturers will need to determine whether it may be profitable to develop a drug candidate that is effective against a specific cancer genotype, weighing the concerns of a smaller patient population and need for a companion diagnostic against the benefits of premium pricing, streamlined clinical and regulatory development and less competition within the space.

This transition-state model takes publicly-available clinical trial and market data, and uses it to quantify the market impact of evolving tumors. Additionally, a sensitivity analysis can be conducted in order to determine the impact of changes in various inputs.

Why study CML?

CML is an ideal system to study tumor evolution for many reasons. First, its biology is relatively well-understood and linked to a specific aberrant gene, of which specific mutations are associated with drug resistance and disease progression. Several of these mutations (most notably T315I) are recognized as major unmet medical needs by physicians and biopharmaceutical companies alike[66]. Thus it is an area of commercial as well as clinical interest.

Second, there is ample clinical data available on the long-term CML prognosis and the effects of treatment. Gleevec product label data on mortality, drug failure, disease progression, and tolerability extends to seven years from initial treatment, and studies on the newer agents Tasigna and Sprycel are ongoing and likely to extend just as long in order to displace Gleevec as the market leader.

Third, CML is well-suited for a transition state model. It is delineated into three phases with distinct outcomes and symptoms among each, and well-studied transition probabilities between them.

Model design

The end goal of the model is to determine the market for a hypothetical CML drug candidate that is specifically designed to treat CML non-responsive to the three currently approved agents. Inputs to the model are detailed as follows.

Table 4: Model inputs and outputs

	Inputs	Outputs
Demographics	• Disease prevalence • Disease incidence • Population growth rate	N/A
Financials	• Past drug sales, used to estimate a trajectory of use going forward • Drug prices (branded and anticipated generic prices) • Patent expiration times • Project discount rate • COGS • Estimated costs of drug marketing	• Sales of each of the three market drugs and the hypothetical candidate over time, broken down by drug, phase and line of therapy • Overall market size • Income statement translating to an NPV of the candidate
Disease State	• Disease stage at time of diagnosis • Outcomes of treatment (rate of death, progression to next phase of disease, drug failure without progression, or intolerance) over time • Rates at which patients develop the specified resistance mutation (in this case, T315I)	• Change in CML patient population over time • Number of patients receiving each drug over time
Clinical Development	• For each phase of clinical development: o Probability of advancing to the next phase o Trial costs o Duration of trial	• Estimated development costs • Risk-adjustment to NPV

Estimating the current market

The current CML patient population was obtained through published sales figures for CML treatments Gleevec (adjusted for the estimated 75% share used to treat CML, with the remaining

25% used to treat other hematologic malignancies and gastrointestinal stromal tumor), Tasigna and Sprycel, converted to estimated patient-years treated for the years 2006-2010[67]. Sales through 2011-2016 were obtained by taking consensus figures from analyst reports obtained through Investext, and incidence rates of CML starting on each drug were modified to parallel analyst estimates over this time[68] and estimated prices (to manufacturer, rather than end-user) were obtained through thoughtleader interviews. The hypothetical candidate was priced at a 30% premium to the most expensive current agent (Tasigna) to reflect its efficacy in treating a highly resistant genotype.

Similarly, patent information on each drug was readily available and incorporated into the model (assuming full conversion from patented to generic agent at the time multi-source generics enter the market and a 90% price discount from branded to multi-sourced generic agent)[69].

With respect to disease-specific figures, estimates of the prevalence and incidence of CML were obtained through thoughtleader interviews and published sources[70,71], with longer-term incidence rates assumed to grow proportionally to the expected growth rate of the 65 years of age and older patient population (1.99%)[72]. Rates of death, disease progression, drug failure without progression and intolerance leading to discontinuation were obtained from peer reviewed publications of clinical trial results or product labels. Where long-term results were not available, I extrapolated progression rates by holding the ratios of progression/intolerance rates to a drug with long-term data constant over time (that is, assuming that the drug tested has the same pattern of efficacy as its comparator). Where drug failure with progression to accelerated phase or blast crisis and drug failure without progression were not broken out, the ratio of the two was

assumed to be equal to that of the most relevant comparator (by drug and disease phase). The hypothetical candidate was assumed to be used in combination with one of the three marketed agents, and the combination was assumed to have the same efficacy against T315I disease as the least efficacious drug used for a given treatment line and disease phase, and similar safety (as measured by rates of discontinuation).

I also assume that all patients with the covered mutation receive the drug, as it would be marketed to a small specialist base that would be deeply involved with development of the drug candidate.

Patient flows

Three sheets were created, one per phase of disease. Time progresses to the right, from the start of the model in January 2007 until the end in December 2032 (representing the approximate start of multi-sourced generics for the resistant candidate). Patients are introduced into the model on diagnosis (at month zero, represented by the light green bar approximately halfway down the illustration below is repeated for every drug). The first four columns represent a treatment setting: Column A represents line of treatment (only TKIs considered), Column B represents drug received (branded agents are referred to by their proprietary name e.g. Gleevec, generic agents by their generic name e.g. imatinib), Column C represents disease phase (CP, AP, BC), and Column D represents length of time in a given treatment setting (month 0 for newly diagnosed or introduced to a given line of treatment, up to month 60+ for patients who have adequately responded to therapy for 60+ months). Each treatment setting has a unique set of associated transition probabilities.

The model assumes that the prevalent patient populations for each approved agent (Gleevec and Sprycel) at the start of the first model year (2007) were evenly distributed by month since approval. For Gleevec, chronic phase CML patients were distributed over 60 months (to represent the favorable prognosis of this phase), accelerated phase CML patients, over two years, and blast crisis CML patients, over six months (to reflect the poorer prognosis). Owing to Sprycel's recent (late 2006) approval, all patients were assumed to be evenly distributed over six months of chronic phase CML.

Every month, a patient may do one of the following:

- **Respond to treatment**, in which case she will stay in the same treatment setting (effectively moving down and to the right in the model). For example, in Figure 1 there are 708 patients in month 4 of treatment in June 2007 (6/2007), represented in cell K25. Of these, 703 maintain response to therapy and "move" to July 2007 (7/2007) and month 5 of treatment, represented in cell L26.

- **Become "intolerant."** These patients move to 2L CP treatment and are not given a probability of picking up the T315I mutation as the drug was assumed to be efficacious in suppressing disease, but not tolerable.

- **Progress to the next phase.** These move to 2L AP treatment and thus to the next tab of the spreadsheet. They have a chance to pick up the T315I mutation, which is a terminal

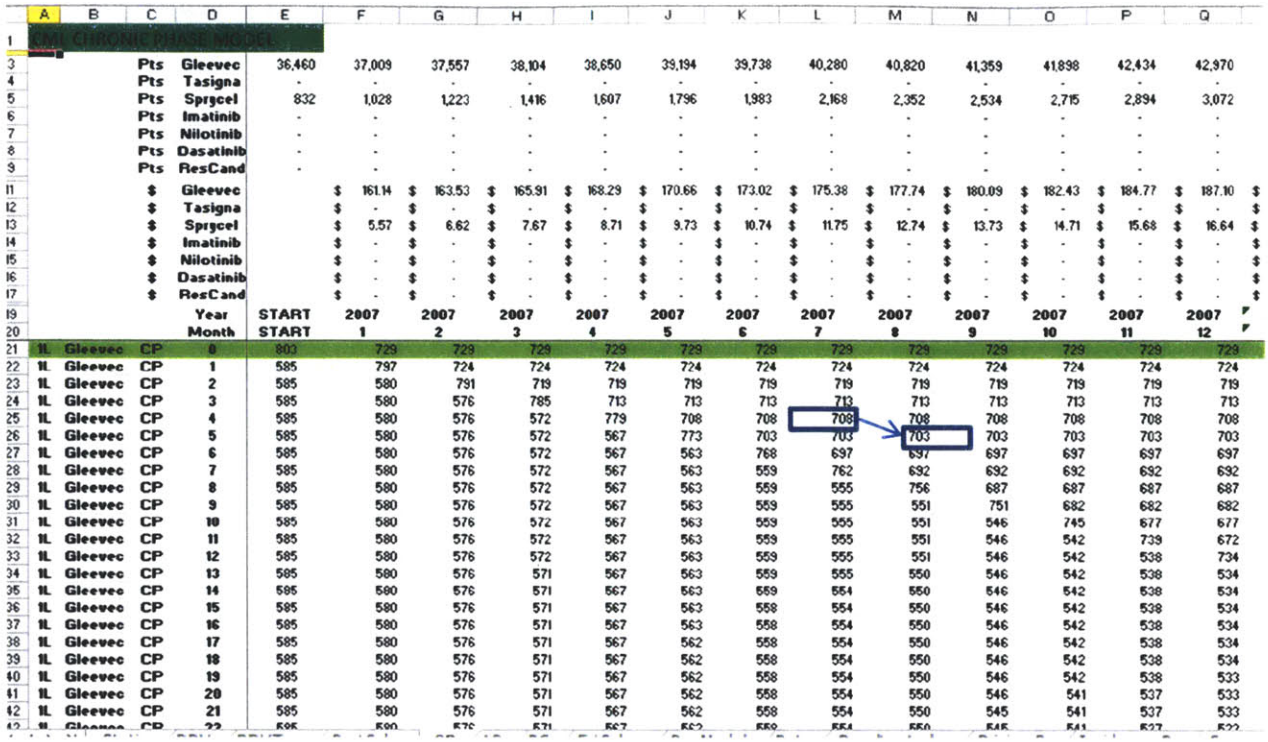
state (resistant to therapy and assumed to be treated with less-effective older therapies, hematopoietic stem cell transplant (HSCT), rescue chemotherapy, or palliative care) unless the hypothetical candidate has reached the market (in which case they are treated with the candidate + the drug to which they lost response in order to maintain selection pressure against all CML clones).

- **Fail without progression.** These patients move to 2L CP treatment and thus to a new treatment setting within the CP tab. They start over at month 0 since studies in the 2nd-line measure response, failure, and intolerance from the time second-line treatment is started, not disease diagnosis. They also have a chance to gain the T315I mutation.

Importantly, not all drugs can be used in any order. Given the resistance spectrums of these three agents, Gleevec can only be used as a 1st-line treatment for any disease phase. Sprycel and Tasigna can be used at any line of treatment.

Every month, the following statistics are tallied: number of patients receiving a drug, product revenue in that month, number of drug failures (broken down into number of deaths, progressions, failures without progression, and intolerant patients).

Figure 1: Illustrative Model Page



		Pts	Gleevec	36,460	37,009	37,557	38,104	38,650	39,194	39,738	40,280	40,820	41,359	41,898	42,434	42,970	
		Pts	Tasigna	-	-	-	-	-	-	-	-	-	-	-	-	-	
		Pts	Sprycel	832	1,028	1,223	1,416	1,607	1,796	1,983	2,168	2,352	2,534	2,715	2,894	3,072	
		Pts	Imatinib	-	-	-	-	-	-	-	-	-	-	-	-	-	
		Pts	Nilotinib	-	-	-	-	-	-	-	-	-	-	-	-	-	
		Pts	Dasatinib	-	-	-	-	-	-	-	-	-	-	-	-	-	
		Pts	ResCand	-	-	-	-	-	-	-	-	-	-	-	-	-	
		$	Gleevec		$ 161.14	$ 163.53	$ 165.91	$ 168.29	$ 170.66	$ 173.02	$ 175.38	$ 177.74	$ 180.09	$ 182.43	$ 184.77	$ 187.10	$
		$	Tasigna		$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$
		$	Sprycel		$ 5.57	$ 6.62	$ 7.67	$ 8.71	$ 9.73	$ 10.74	$ 11.75	$ 12.74	$ 13.73	$ 14.71	$ 15.68	$ 16.64	$
		$	Imatinib		$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$
		$	Nilotinib		$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$
		$	Dasatinib		$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$
		$	ResCand		$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$
			Year	START	2007	2007	2007	2007	2007	2007	2007	2007	2007	2007	2007	2007	
			Month	START	1	2	3	4	5	6	7	8	9	10	11	12	
1L	Gleevec	CP	0	803	729	729	729	729	729	729	729	729	729	729	729	729	
1L	Gleevec	CP	1	585	797	724	724	724	724	724	724	724	724	724	724	724	
1L	Gleevec	CP	2	585	580	791	719	719	719	719	719	719	719	719	719	719	
1L	Gleevec	CP	3	585	580	576	785	713	713	713	713	713	713	713	713	713	
1L	Gleevec	CP	4	585	580	576	572	779	708	708	708	708	708	708	708	708	
1L	Gleevec	CP	5	585	580	576	572	567	773	703	703	703	703	703	703	703	
1L	Gleevec	CP	6	585	580	576	572	567	563	768	697	697	697	697	697	697	
1L	Gleevec	CP	7	585	580	576	572	567	563	559	762	692	692	692	692	692	
1L	Gleevec	CP	8	585	580	576	572	567	563	559	555	756	687	687	687	687	
1L	Gleevec	CP	9	585	580	576	572	567	563	559	555	551	751	682	682	682	
1L	Gleevec	CP	10	585	580	576	572	567	563	559	555	551	546	745	677	677	
1L	Gleevec	CP	11	585	580	576	572	567	563	559	555	551	546	542	739	672	
1L	Gleevec	CP	12	585	580	576	572	567	563	559	555	551	546	542	538	734	
1L	Gleevec	CP	13	585	580	576	571	567	563	559	555	550	546	542	538	534	
1L	Gleevec	CP	14	585	580	576	571	567	563	559	554	550	546	542	538	534	
1L	Gleevec	CP	15	585	580	576	571	567	563	558	554	550	546	542	538	534	
1L	Gleevec	CP	16	585	580	576	571	567	563	558	554	550	546	542	538	534	
1L	Gleevec	CP	17	585	580	576	571	567	562	558	554	550	546	542	538	534	
1L	Gleevec	CP	18	585	580	576	571	567	562	558	554	550	546	542	538	534	
1L	Gleevec	CP	19	585	580	576	571	567	562	558	554	550	546	542	538	533	
1L	Gleevec	CP	20	585	580	576	571	567	562	558	554	550	546	541	537	533	
1L	Gleevec	CP	21	585	580	576	571	567	562	558	554	550	545	541	537	533	
1L	Gleevec	CP	22	585	580	576	571	567	562	558	554	550	545	541	537	532	

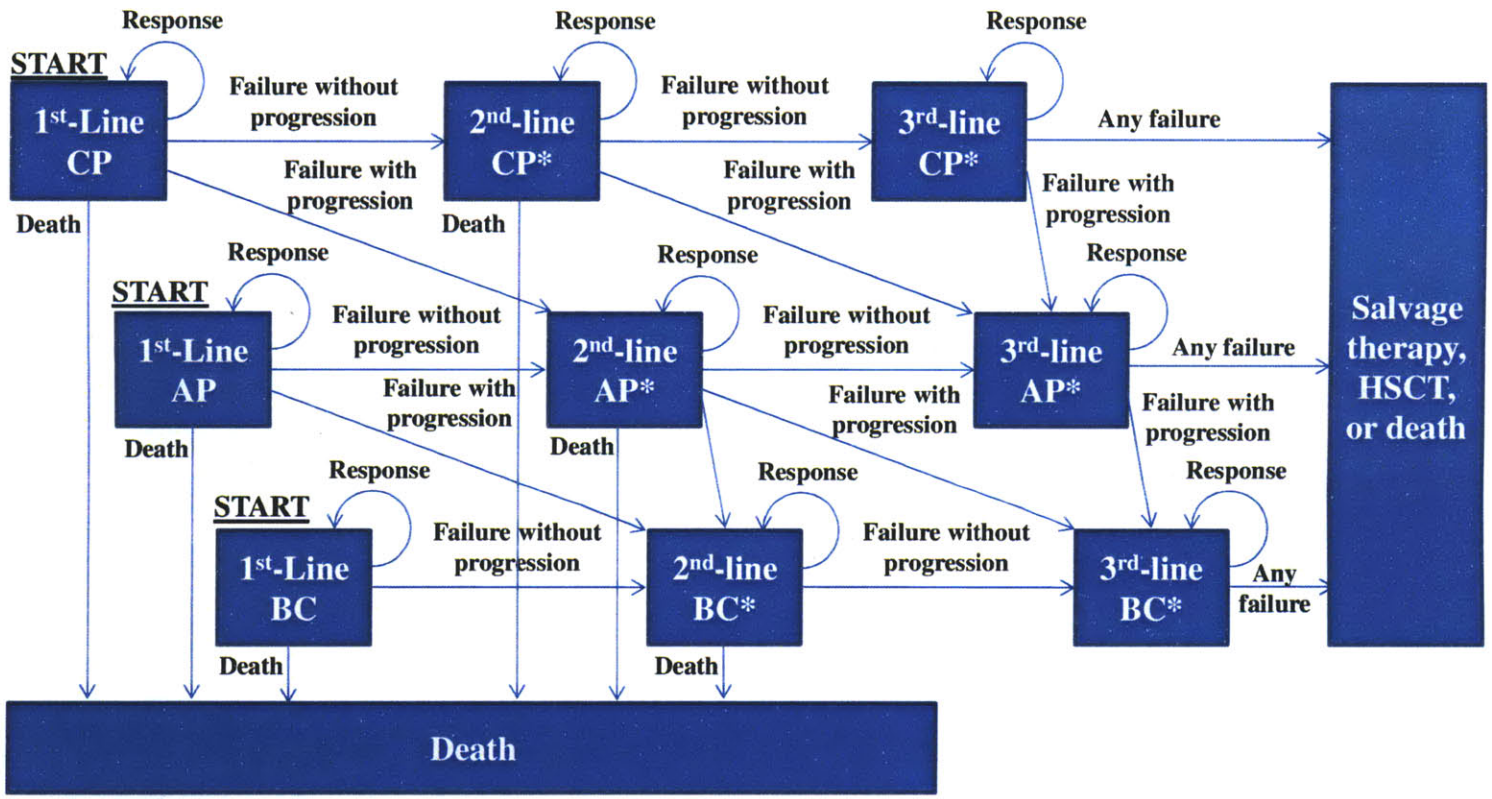


Figure 2: Patient Flow in the Model

*Any patient that fails to this line of therapy can gain the resistance mutation and become refractory to the three lines of therapy. At this point, if the hypothetical candidate is approved, the patient receives the appropriate line of therapy in combination with the hypothetical candidate. If not, the patient is refractory and placed into the absorbing state of "salvage therapy, HSCT, or death"

Hypothetical candidate development

This model assumes the "present day" to be the beginning of 2011, at which point the company is ready to initiate Phase I clinical development of both the hypothetical drug candidate and the companion diagnostic that would be required to get a label to specifically treat T315I disease.

Patient numbers and lengths of clinical trials required for approval were obtained from Sprycel FDA Oncologic Drug Advisory Committee (ODAC) briefing documents[73], Ariad Pharmaceuticals' PACE (Ponatinib Ph+ ALL and CML Evaluation) trial fact sheet[74], and Kevin Schulman's "Economics of Oncology Drug Development"[75]. Probabilities of cancer drug success were obtained from DiMasi's "Economics of New Oncology Drug Development," 76.8% in Phase I, 59.4% in Phase II and 57.1% in Phase III[76]. Given the rarity of the T315I mutation, high unmet medical need, and likely orphan drug status, I assume relatively small clinical trials (Phase I – 60 patients, Phase II – 320 patients, Phase III – 500 patients), with approval and launch occurring after Phase II (results in 2015, launch in 2016) but requiring a confirmatory Phase III to keep the drug on the market (results available at the end of 2019). I also assume an expedited regulatory review (12 months from end of Phase III to product launch) to reflect not only priority review but FDA assistance in conducting the regulatory filing. Costs of drug development were estimated on a per patient basis and assumed to be equal to the average for oncology trials and obtained from the Institute of Medicine[77]. Costs of the companion diagnostic, a relatively straightforward and already implemented quantitative reverse transcriptase polymerase chain reaction (RT-PCR), were estimated from interviews[78]. Many of these assumptions will be varied in the sensitivity analysis.

To complete the project P&L statement, the cost of goods sold (COGS) was estimated at 5%[79] (reasonable figure for a small molecule drug that does not require a complicated synthesis) and SG&A spend for a 50-member sales force (small and decreasing over time to reflect a concentrated prescriber base and increasing physician familiarity with the drug). Corporate tax was estimated at 35%, with losses in the early years offsetting profits in the hypothetical company's other operations. Profits were discounted at an appropriate real interest rate for a large pharmaceutical manufacturer (11%), although a small biotechnology firm may use a larger discount rate. This is also varied in the sensitivity analysis.

Model results

Base case results

I define the base case as the following set of variables. This represents one likely scenario that could be encountered in drug development:

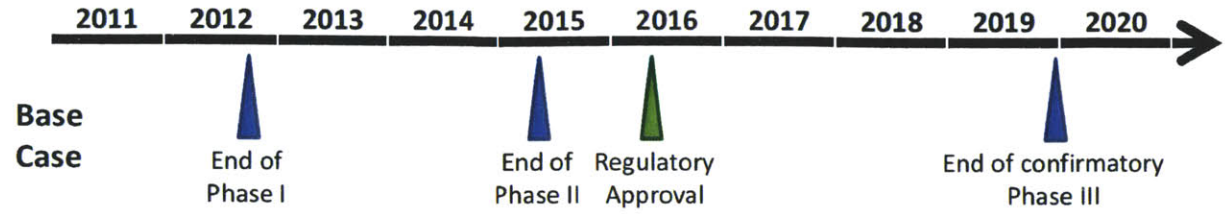
Table 5: Base case (*variable to be altered in sensitivity analysis)

	Inputs
Demographics	• 2010 CML prevalence (US/Europe): 100,000 • 2010 CML incidence (US/Europe): 12,000 • CML incidence growth: 1.99%
Financials	• Past drug sales, used to estimate a trajectory of use going forward (see graphs) • Monthly drug prices: Gleevec - $4,354 Sprycel - $5,417 Tasigna - $5,823 Candidate - $7,570* • First fully generic year: Gleevec - 2016 Sprycel - 2021 Tasigna - 2024 Candidate - 2033 • Project discount rate: 11%* • COGS: 5% • Estimated costs of drug marketing: 50 reps @ $200,000 per rep (decreasing over time)
Disease State	• Disease stage at time of diagnosis: CP - 90% AP- 5% BC - 5% • Outcomes of treatment* • Rates at which patients develop the specified resistance mutation (in this case, T315I): Following 1L - 5.16%* Following 2L - 10.32%*
Clinical Development	

	Phase I	Phase II	Phase III
Cost/patient*	$65,500	$65,500	$72,500
# patients*	60	320	500
Duration* (yrs)	1.75	2.50	3.72
Success prob*	76.8%	59.4%	57.1%

	• Time from end of Phase III to launch: 1 year • Companion diagnostic cost: $22,500,000

Figure 3: Base case development timeline



TKI use

The figure below illustrates the projected change in currently available TKI use over time, based on the preferences and perceptions of physicians interviewed and the outcomes published in peer review. Long-term data of these agents (except Gleevec) are not yet available, and pipeline agents were not factored into the analysis. Both could have a substantial impact on the results of the model.

Figure 4: Projected change in TKI use over time (arrows indicate generic entry)

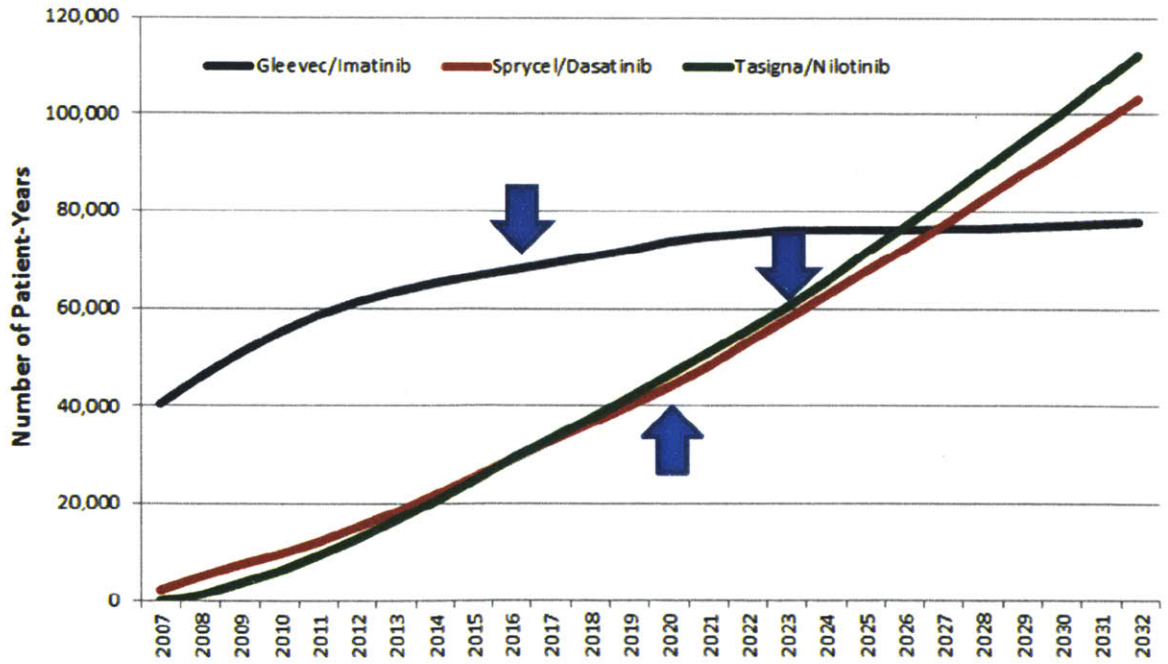
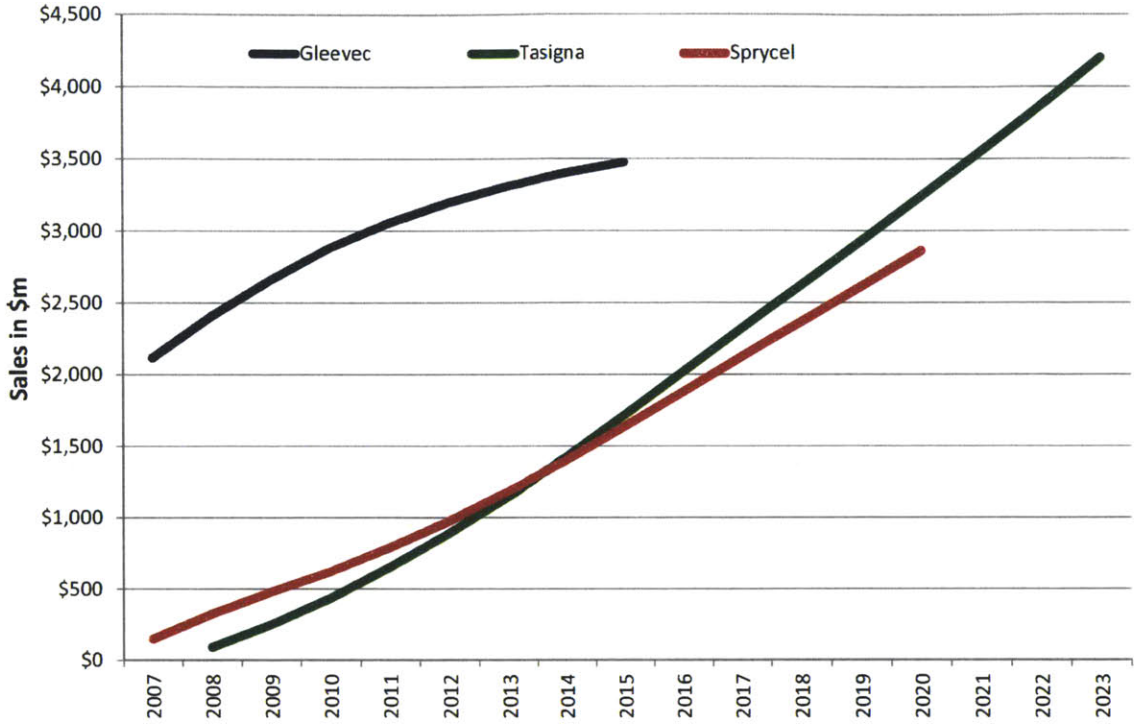


Figure 5: Projected change in branded TKI sales in CML over time (line stops at generic entry)



Change in CML population

The figure below illustrates the anticipated change in the prevalent U.S. and Europe CML population over time. The smooth, linear increase indicates the relatively long lifespan of well-treated patients with the disease. At its peak sales value (2015, with all agents available and no multi-sourced generics on the market), the market size reaches $6.8 billion with approximately 115,000 patients on therapy. If the market becomes predominantly branded again (through introduction of new therapies that significantly outclass the current drugs) at similar prices, the market could increase to more than two-and-a-half times the 2015 figure as the patient population approaches 300,000. This curve assumes that death rates observed in trials stay

constant over the long-term, when they may actually rise over time as other causes of death become more likely.

Virtually all of the increase in the CML patient population is projected to come in chronic phase disease, due to its good prognosis if properly treated and the poor prognoses of the two later phases.

Figure 6: Projected change in total CML patient population over time

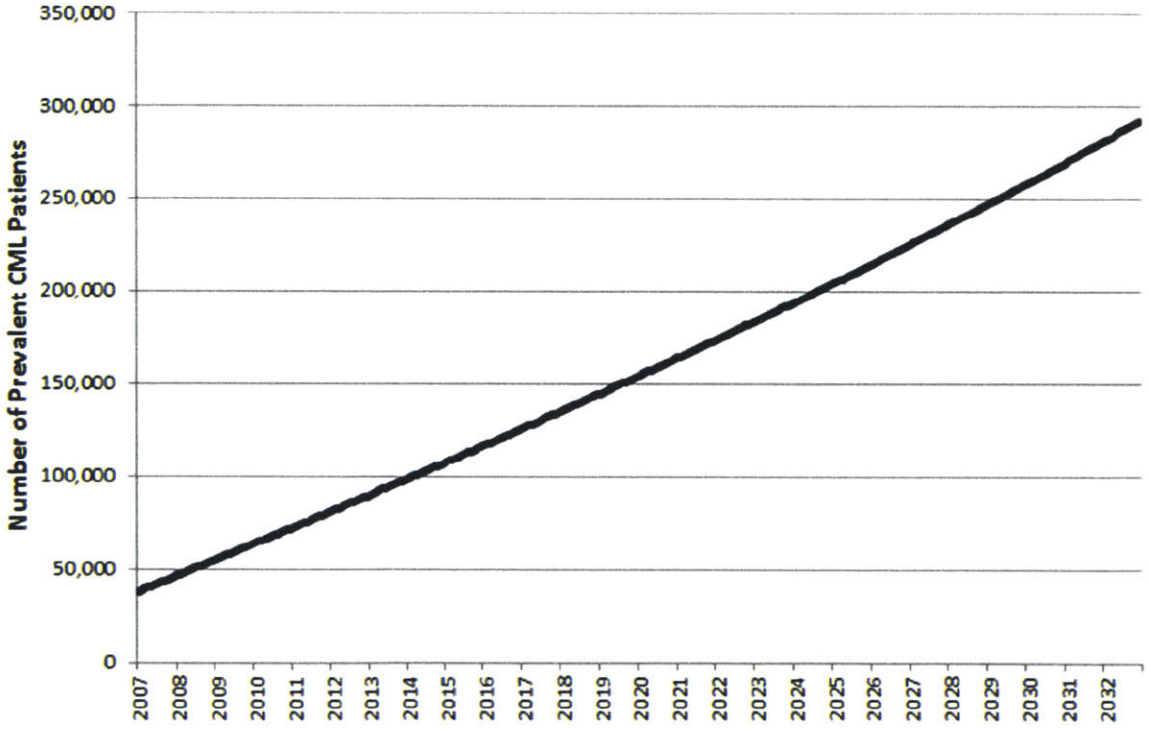
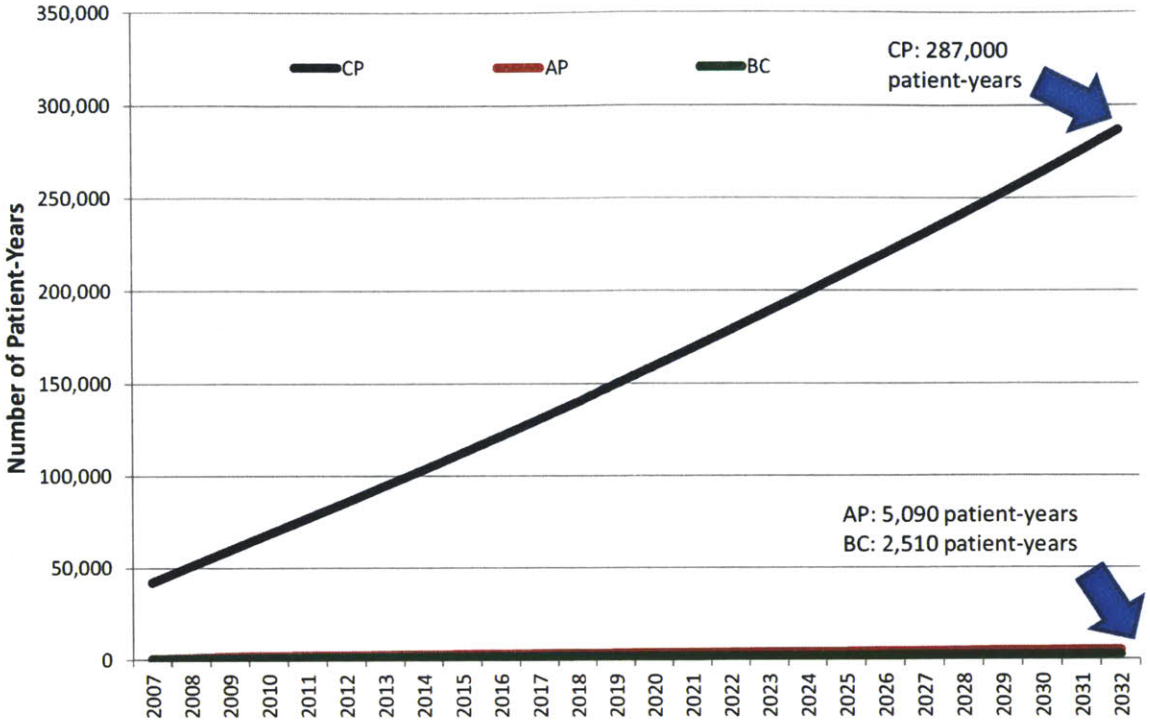
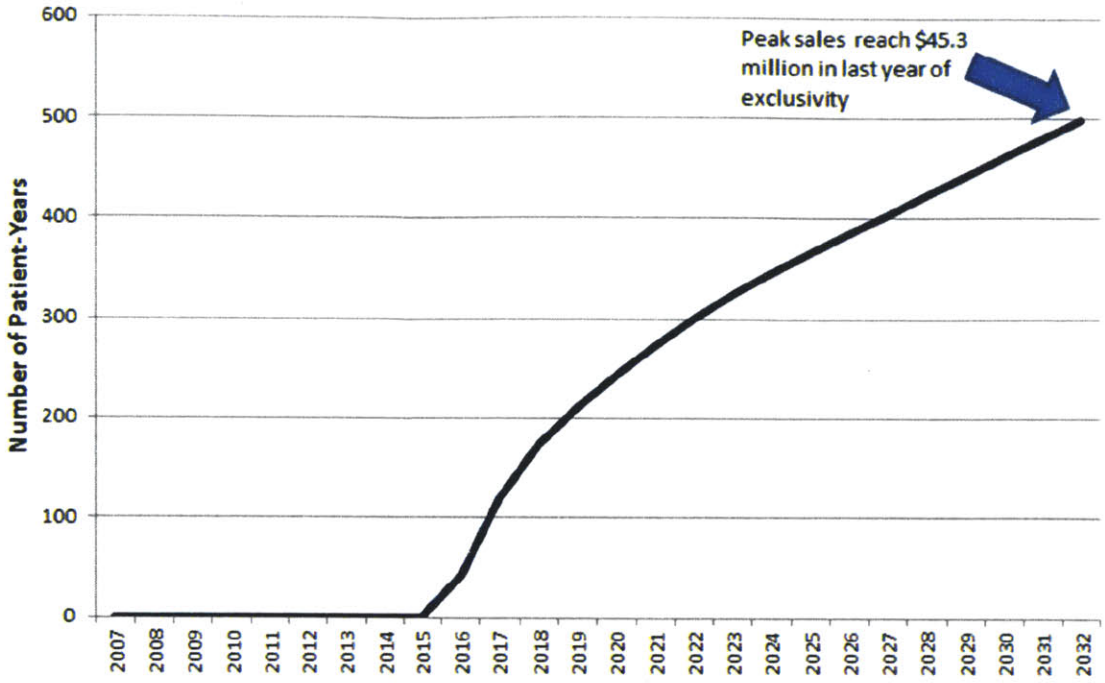


Figure 7: Projected change in CML patients by disease phase over time



The relevant population for the hypothetical drug candidate is CML patients who, following 1st-line or 2nd-line treatment, develop the T315I mutation. In 1st-line failures, this is estimated to be 5.16% of patients who develop resistance to Gleevec, in later lines of therapy, this resistant fraction increases significantly[80,81,82]. Assuming 2nd-line rate of T315I mutation equal to twice the 1st-line rate, I obtain nearly 500 patient-years of treatment in 2032, translating to a $45.3 million revenue run rate.

Figure 8: Projected change in T315I patient population over time



Financials

The "NPV rule" states that a company should invest in all projects with a positive NPV and no projects with a negative NPV. Furthermore, if there are multiple exclusive project options with a positive NPV, one should invest in the project with the highest NPV. With these assumptions, we arrive at a risk-adjusted NPV for the hypothetical candidate of -$23.4 million for the pre-tax NPV and -$15.2 million for the post-tax NPV, indicating an unprofitable project that should not be undertaken. Depending on the manufacturer's size and resources, it is likely that it may have more lucrative projects to fund than this one (e.g. spending more to boost sales of an existing drug or developing another pipeline candidate) even if the hypothetical candidate were to show a marginally positive NPV.

Sensitivity analysis

In this section, I determine the market's response to single variable changes in the model. While multiple variable changes are more likely (and discussed later), this shows the relative sensitivity to each.

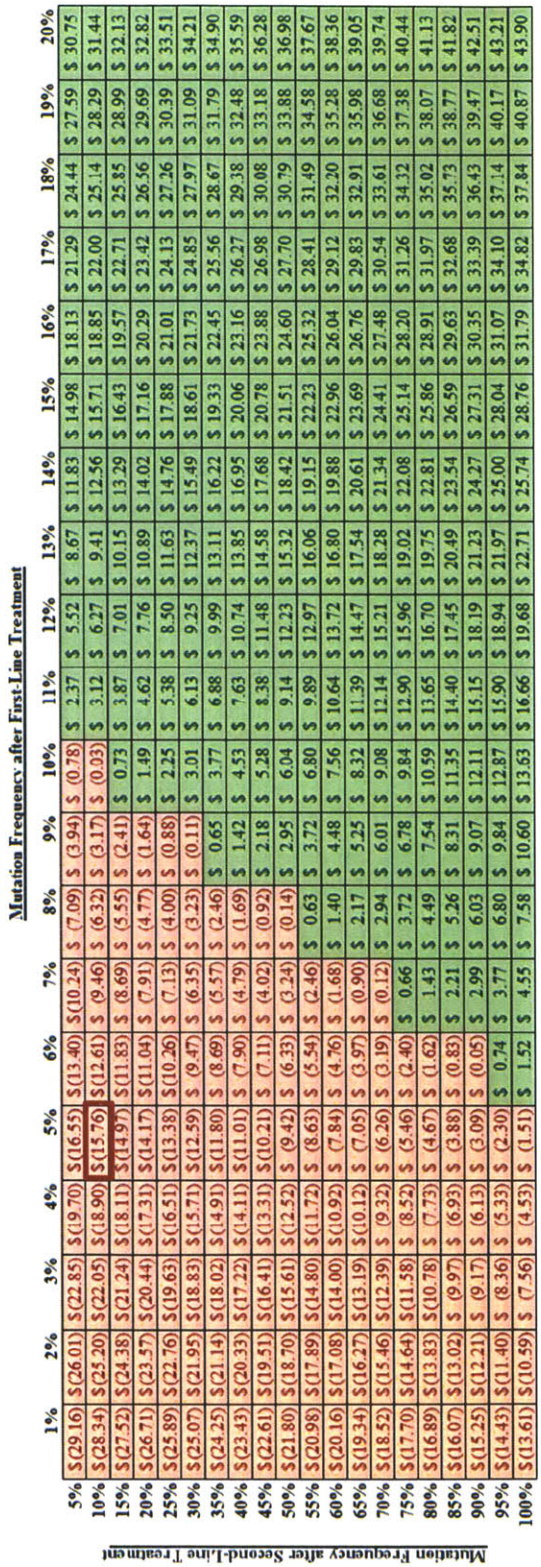
Mutation frequency

One key variable is the frequency of the targeted mutation. Rates of acquisition of T315I were determined from a Phase II study of Tasigna and may be different for other agents. Additionally, despite my choice of T315I for the hypothetical candidate (because it is recognized as an unmet medical need and a mutation that resists all three approved agents), it is unlikely that a candidate that treats a single, relatively rare mutation would be scientifically feasible (due to the nature of the BCR-ABL ATP-binding domain), let alone commercially interesting. Another scenario involves development of a TKI that covers a spectrum including T315I and several other currently unaddressed mutations. Since this is one of the most highly variable factors, I include a sensitivity analysis of NPV vs. mutation rates in most analyses where it could be expected to have a significant impact.

To account for this, I performed a sensitivity analysis in which I determine the NPV after varying the frequency of mutations "covered" by the hypothetical candidate in both the 1st and 2nd line. Since less than 50% of 1st-line "failures" (both with and without progression) have mutations in the BCR-ABL kinase domain and many of these may not be adequately treated by the hypothetical candidate, I varied the 1st-line "covered" mutation rate (as a percentage of total 1st-line failures) from 1-20%. On the other hand, 2nd-line failures are more likely to have

significant resistance mutations and so I varied this figure from 5-100% (in 5% increments). The results are indicated below:

Figure 9: Net income NPV as a function of 1st- and 2nd-line covered mutation rates



Mutation Frequency after First-Line Treatment

Mutation Frequency after Second-Line Treatment	1%	2%	3%	4%	5%	6%	7%	8%	9%	10%	11%	12%	13%	14%	15%	16%	17%	18%	19%	20%
5%	$(29.16)	$(26.01)	$(22.85)	$(19.70)	$(16.55)	$(13.40)	$(10.24)	$ (7.09)	$ (3.94)	$ (0.78)	$ 2.37	$ 5.52	$ 8.67	$ 11.83	$ 14.98	$ 18.13	$ 21.29	$ 24.44	$ 27.59	$ 30.75
10%	$(28.34)	$(25.20)	$(22.05)	$(18.90)	$(15.76)	$(12.61)	$ (9.46)	$ (6.32)	$ (3.17)	$ (0.03)	$ 3.12	$ 6.27	$ 9.41	$ 12.56	$ 15.71	$ 18.85	$ 22.00	$ 25.14	$ 28.29	$ 31.44
15%	$(27.52)	$(24.38)	$(21.24)	$(18.11)	$(14.97)	$(11.83)	$ (8.69)	$ (5.55)	$ (2.41)	$ 0.73	$ 3.87	$ 7.01	$ 10.15	$ 13.29	$ 16.43	$ 19.57	$ 22.71	$ 25.85	$ 28.99	$ 32.13
20%	$(26.71)	$(23.57)	$(20.44)	$(17.31)	$(14.17)	$(11.04)	$ (7.91)	$ (4.77)	$ (1.64)	$ 1.49	$ 4.62	$ 7.76	$ 10.89	$ 14.02	$ 17.16	$ 20.29	$ 23.42	$ 26.56	$ 29.69	$ 32.82
25%	$(25.89)	$(22.76)	$(19.63)	$(16.51)	$(13.38)	$(10.26)	$ (7.13)	$ (4.00)	$ (0.88)	$ 2.25	$ 5.38	$ 8.50	$ 11.63	$ 14.76	$ 17.88	$ 21.01	$ 24.13	$ 27.26	$ 30.39	$ 33.51
30%	$(25.07)	$(21.95)	$(18.83)	$(15.71)	$(12.59)	$ (9.47)	$ (6.35)	$ (3.23)	$ (0.11)	$ 3.01	$ 6.13	$ 9.25	$ 12.37	$ 15.49	$ 18.61	$ 21.73	$ 24.85	$ 27.97	$ 31.09	$ 34.21
35%	$(24.25)	$(21.14)	$(18.02)	$(14.91)	$(11.80)	$ (8.69)	$ (5.57)	$ (2.46)	$ 0.65	$ 3.77	$ 6.88	$ 9.99	$ 13.11	$ 16.22	$ 19.33	$ 22.45	$ 25.56	$ 28.67	$ 31.79	$ 34.90
40%	$(23.43)	$(20.33)	$(17.22)	$(14.11)	$(11.01)	$ (7.90)	$ (4.79)	$ (1.69)	$ 1.42	$ 4.53	$ 7.63	$ 10.74	$ 13.85	$ 16.95	$ 20.06	$ 23.16	$ 26.27	$ 29.38	$ 32.48	$ 35.59
45%	$(22.61)	$(19.51)	$(16.41)	$(13.31)	$(10.21)	$ (7.11)	$ (4.02)	$ (0.92)	$ 2.18	$ 5.28	$ 8.38	$ 11.48	$ 14.58	$ 17.68	$ 20.78	$ 23.88	$ 26.98	$ 30.08	$ 33.18	$ 36.28
50%	$(21.80)	$(18.70)	$(15.61)	$(12.52)	$ (9.42)	$ (6.33)	$ (3.24)	$ (0.14)	$ 2.95	$ 6.04	$ 9.14	$ 12.23	$ 15.32	$ 18.42	$ 21.51	$ 24.60	$ 27.70	$ 30.79	$ 33.88	$ 36.98
55%	$(20.98)	$(17.89)	$(14.80)	$(11.72)	$ (8.63)	$ (5.54)	$ (2.46)	$ 0.63	$ 3.72	$ 6.80	$ 9.89	$ 12.97	$ 16.06	$ 19.15	$ 22.23	$ 25.32	$ 28.41	$ 31.49	$ 34.58	$ 37.67
60%	$(20.16)	$(17.08)	$(14.00)	$(10.92)	$ (7.84)	$ (4.76)	$ (1.68)	$ 1.40	$ 4.48	$ 7.56	$ 10.64	$ 13.72	$ 16.80	$ 19.88	$ 22.96	$ 26.04	$ 29.12	$ 32.20	$ 35.28	$ 38.36
65%	$(19.34)	$(16.27)	$(13.19)	$(10.12)	$ (7.05)	$ (3.97)	$ (0.90)	$ 2.17	$ 5.25	$ 8.32	$ 11.39	$ 14.47	$ 17.54	$ 20.61	$ 23.69	$ 26.76	$ 29.83	$ 32.91	$ 35.98	$ 39.05
70%	$(18.52)	$(15.46)	$(12.39)	$ (9.32)	$ (6.26)	$ (3.19)	$ (0.12)	$ 2.94	$ 6.01	$ 9.08	$ 12.14	$ 15.21	$ 18.28	$ 21.34	$ 24.41	$ 27.48	$ 30.54	$ 33.61	$ 36.68	$ 39.74
75%	$(17.70)	$(14.64)	$(11.58)	$ (8.52)	$ (5.46)	$ (2.40)	$ 0.66	$ 3.72	$ 6.78	$ 9.84	$ 12.90	$ 15.96	$ 19.02	$ 22.08	$ 25.14	$ 28.20	$ 31.26	$ 34.32	$ 37.38	$ 40.44
80%	$(16.89)	$(13.83)	$(10.78)	$ (7.73)	$ (4.67)	$ (1.62)	$ 1.43	$ 4.49	$ 7.54	$ 10.59	$ 13.65	$ 16.70	$ 19.75	$ 22.81	$ 25.86	$ 28.91	$ 31.97	$ 35.02	$ 38.07	$ 41.13
85%	$(16.07)	$(13.02)	$ (9.97)	$ (6.93)	$ (3.88)	$ (0.83)	$ 2.21	$ 5.26	$ 8.31	$ 11.35	$ 14.40	$ 17.45	$ 20.49	$ 23.54	$ 26.59	$ 29.63	$ 32.68	$ 35.73	$ 38.77	$ 41.82
90%	$(15.25)	$(12.21)	$ (9.17)	$ (6.13)	$ (3.09)	$ (0.05)	$ 2.99	$ 6.03	$ 9.07	$ 12.11	$ 15.15	$ 18.19	$ 21.23	$ 24.27	$ 27.31	$ 30.35	$ 33.39	$ 36.43	$ 39.47	$ 42.51
95%	$(14.43)	$(11.40)	$ (8.36)	$ (5.33)	$ (2.30)	$ 0.74	$ 3.77	$ 6.80	$ 9.84	$ 12.87	$ 15.90	$ 18.94	$ 21.97	$ 25.00	$ 28.04	$ 31.07	$ 34.10	$ 37.14	$ 40.17	$ 43.21
100%	$(13.61)	$(10.59)	$ (7.56)	$ (4.53)	$ (1.51)	$ 1.52	$ 4.55	$ 7.58	$ 10.60	$ 13.63	$ 16.66	$ 19.68	$ 22.71	$ 25.74	$ 28.76	$ 31.79	$ 34.82	$ 37.84	$ 40.87	$ 43.90

Increased drug failure rates

One potential upside scenario for the hypothetical candidate would occur if long-term data for the three currently approved agents came in short of expectations. All else being equal, a higher rate of failure for other agents would increase the number of patients who develop T315I. In this scenario, I increase rates of death and failure (with or without progression) for all drugs to that of the worst drug in each line of treatment and stage of disease. In this case, the NPV with pre-tax dollars increases to -$11.5 million, and after-tax to -$7.45 million.

Notably, this scenario would significantly decrease the size of the overall market, since it would provide payers with leverage to shift new patients to the least expensive (possibly generic) treatment.

Figure 10: Net income NPV with higher drug failure rates

Mutation Frequency after Second-Line Treatment	Mutation Frequency after First-Line Treatment																			
	1%	2%	3%	4%	5%	6%	7%	8%	9%	10%	11%	12%	13%	14%	15%	16%	17%	18%	19%	20%
5%	$ (27.56)	$ (22.97)	$ (18.38)	$ (13.79)	$ (9.19)	$ (4.60)	$ (0.01)	$ 4.58	$ 9.17	$ 13.76	$ 18.35	$ 22.94	$ 27.53	$ 32.12	$ 36.72	$ 41.31	$ 45.90	$ 50.49	$ 55.08	$ 59.67
10%	$ (26.58)	$ (22.00)	$ (17.41)	$ (12.83)	$ (8.25)	$ (3.66)	$ 0.92	$ 5.50	$ 10.09	$ 14.67	$ 19.25	$ 23.84	$ 28.42	$ 33.00	$ 37.59	$ 42.17	$ 46.75	$ 51.33	$ 55.92	$ 60.50
15%	$ (25.60)	$ (21.02)	$ (16.45)	$ (11.87)	$ (7.30)	$ (2.72)	$ 1.85	$ 6.43	$ 11.00	$ 15.58	$ 20.15	$ 24.73	$ 29.30	$ 33.88	$ 38.45	$ 43.03	$ 47.61	$ 52.18	$ 56.76	$ 61.33
20%	$ (24.62)	$ (20.05)	$ (15.48)	$ (10.92)	$ (6.35)	$ (1.78)	$ 2.79	$ 7.35	$ 11.92	$ 16.49	$ 21.05	$ 25.62	$ 30.19	$ 34.76	$ 39.32	$ 43.89	$ 48.46	$ 53.03	$ 57.59	$ 62.16
25%	$ (23.64)	$ (19.08)	$ (14.52)	$ (9.96)	$ (5.40)	$ (0.84)	$ 3.72	$ 8.28	$ 12.84	$ 17.40	$ 21.96	$ 26.52	$ 31.07	$ 35.63	$ 40.19	$ 44.75	$ 49.31	$ 53.87	$ 58.43	$ 62.99
30%	$ (22.66)	$ (18.11)	$ (13.55)	$ (9.00)	$ (4.45)	$ 0.10	$ 4.65	$ 9.20	$ 13.75	$ 18.31	$ 22.86	$ 27.41	$ 31.96	$ 36.51	$ 41.06	$ 45.61	$ 50.17	$ 54.72	$ 59.27	$ 63.82
35%	$ (21.68)	$ (17.13)	$ (12.59)	$ (8.05)	$ (3.50)	$ 1.04	$ 5.58	$ 10.13	$ 14.67	$ 19.21	$ 23.76	$ 28.30	$ 32.85	$ 37.39	$ 41.93	$ 46.48	$ 51.02	$ 55.56	$ 60.11	$ 64.65
40%	$ (20.70)	$ (16.16)	$ (11.62)	$ (7.09)	$ (2.55)	$ 1.98	$ 6.52	$ 11.05	$ 15.59	$ 20.12	$ 24.66	$ 29.19	$ 33.73	$ 38.27	$ 42.80	$ 47.34	$ 51.87	$ 56.41	$ 60.94	$ 65.48
45%	$ (19.72)	$ (15.19)	$ (10.66)	$ (6.13)	$ (1.60)	$ 2.92	$ 7.45	$ 11.98	$ 16.51	$ 21.03	$ 25.56	$ 30.09	$ 34.62	$ 39.14	$ 43.67	$ 48.20	$ 52.73	$ 57.25	$ 61.78	$ 66.31
50%	$ (18.73)	$ (14.21)	$ (9.70)	$ (5.18)	$ (0.66)	$ 3.86	$ 8.38	$ 12.90	$ 17.42	$ 21.94	$ 26.46	$ 30.98	$ 35.50	$ 40.02	$ 44.54	$ 49.06	$ 53.58	$ 58.10	$ 62.62	$ 67.14
55%	$ (17.75)	$ (13.24)	$ (8.73)	$ (4.22)	$ 0.29	$ 4.80	$ 9.32	$ 13.83	$ 18.34	$ 22.85	$ 27.36	$ 31.87	$ 36.39	$ 40.90	$ 45.41	$ 49.92	$ 54.43	$ 58.94	$ 63.46	$ 67.97
60%	$ (16.77)	$ (12.27)	$ (7.77)	$ (3.26)	$ 1.24	$ 5.75	$ 10.25	$ 14.75	$ 19.26	$ 23.76	$ 28.26	$ 32.77	$ 37.27	$ 41.78	$ 46.28	$ 50.78	$ 55.29	$ 59.79	$ 64.29	$ 68.80
65%	$ (15.79)	$ (11.30)	$ (6.80)	$ (2.31)	$ 2.19	$ 6.69	$ 11.18	$ 15.68	$ 20.17	$ 24.67	$ 29.16	$ 33.66	$ 38.16	$ 42.65	$ 47.15	$ 51.64	$ 56.14	$ 60.64	$ 65.13	$ 69.63
70%	$ (14.81)	$ (10.32)	$ (5.84)	$ (1.35)	$ 3.14	$ 7.63	$ 12.11	$ 16.60	$ 21.09	$ 25.58	$ 30.07	$ 34.55	$ 39.04	$ 43.53	$ 48.02	$ 52.51	$ 56.99	$ 61.48	$ 65.97	$ 70.46
75%	$ (13.83)	$ (9.35)	$ (4.87)	$ (0.39)	$ 4.09	$ 8.57	$ 13.05	$ 17.53	$ 22.01	$ 26.49	$ 30.97	$ 35.45	$ 39.93	$ 44.41	$ 48.89	$ 53.37	$ 57.85	$ 62.33	$ 66.81	$ 71.29
80%	$ (12.85)	$ (8.38)	$ (3.91)	$ 0.56	$ 5.04	$ 9.51	$ 13.98	$ 18.45	$ 22.92	$ 27.40	$ 31.87	$ 36.34	$ 40.81	$ 45.28	$ 49.76	$ 54.23	$ 58.70	$ 63.17	$ 67.64	$ 72.12
85%	$ (11.87)	$ (7.41)	$ (2.94)	$ 1.52	$ 5.99	$ 10.45	$ 14.91	$ 19.38	$ 23.84	$ 28.31	$ 32.77	$ 37.23	$ 41.70	$ 46.16	$ 50.63	$ 55.09	$ 59.55	$ 64.02	$ 68.48	$ 72.95
90%	$ (10.89)	$ (6.43)	$ (1.98)	$ 2.48	$ 6.93	$ 11.39	$ 15.85	$ 20.30	$ 24.76	$ 29.21	$ 33.67	$ 38.13	$ 42.58	$ 47.04	$ 51.49	$ 55.95	$ 60.41	$ 64.86	$ 69.32	$ 73.78
95%	$ (9.91)	$ (5.46)	$ (1.01)	$ 3.43	$ 7.88	$ 12.33	$ 16.78	$ 21.23	$ 25.68	$ 30.12	$ 34.57	$ 39.02	$ 43.47	$ 47.92	$ 52.36	$ 56.81	$ 61.26	$ 65.71	$ 70.16	$ 74.60
100%	$ (8.93)	$ (4.49)	$ (0.05)	$ 4.39	$ 8.83	$ 13.27	$ 17.71	$ 22.15	$ 26.59	$ 31.03	$ 35.47	$ 39.91	$ 44.35	$ 48.79	$ 53.23	$ 57.67	$ 62.11	$ 66.55	$ 70.99	$ 75.43

Delayed time to market

A key downside risk to this project would occur if regulatory agencies demanded a full Phase III trial prior to approval. Even in the base case, the rarity of the covered mutation could cause delays in patient enrollment and push first product sales back from mid-2016 until the beginning of 2021. In this case, the NPV with pre-tax dollars drops to -$38.8 million, and after-tax drops to -$25.2 million, and only with much broader mutation coverage could it become even marginally profitable.

Figure 11: Development timeline with Phase III results required for approval

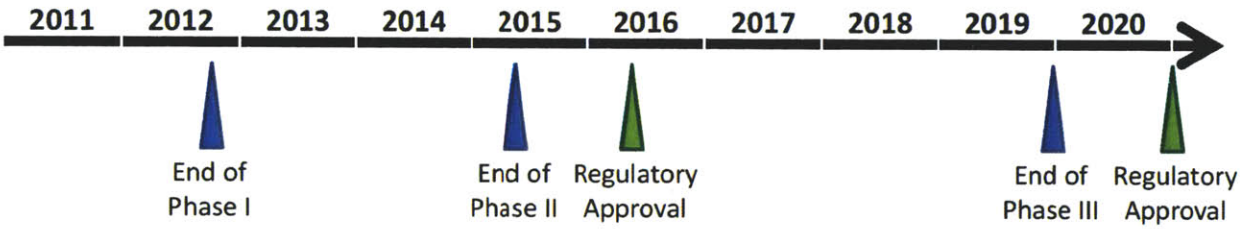
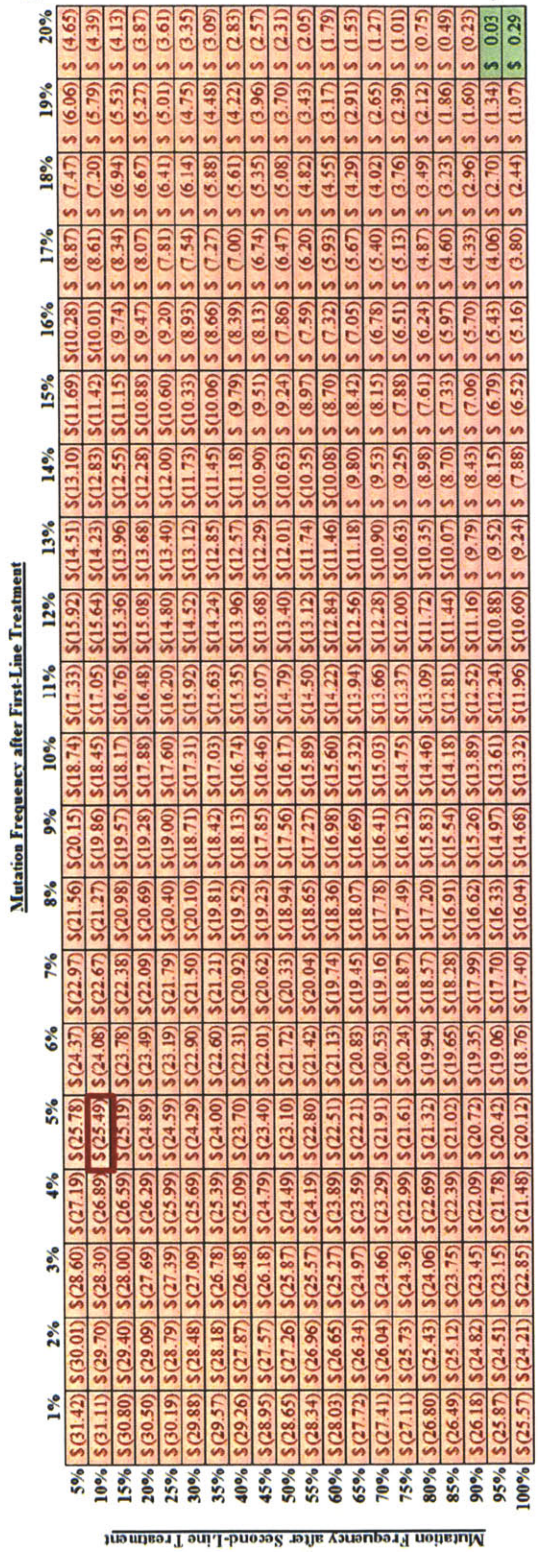


Figure 12: Net income NPV with delayed market entry



Mutation Frequency after Second-Line Treatment	Mutation Frequency after First-Line Treatment																				
	1%	2%	3%	4%	5%	6%	7%	8%	9%	10%	11%	12%	13%	14%	15%	16%	17%	18%	19%	20%
5%	$(31.42)	$(30.01)	$(28.60)	$(27.19)	$(25.78)	$(24.37)	$(22.97)	$(21.56)	$(20.15)	$(18.74)	$(17.33)	$(15.92)	$(14.51)	$(13.10)	$(11.69)	$(10.28)	$ (8.87)	$ (7.47)	$ (6.06)	$ (4.65)
10%	$(31.11)	$(29.70)	$(28.30)	$(26.89)	$(25.49)	$(24.08)	$(22.67)	$(21.27)	$(19.86)	$(18.45)	$(17.05)	$(15.64)	$(14.23)	$(12.83)	$(11.42)	$(10.01)	$ (8.61)	$ (7.20)	$ (5.79)	$ (4.39)
15%	$(30.80)	$(29.40)	$(28.00)	$(26.59)	$(25.19)	$(23.78)	$(22.38)	$(20.98)	$(19.57)	$(18.17)	$(16.76)	$(15.36)	$(13.96)	$(12.55)	$(11.15)	$ (9.74)	$ (8.34)	$ (6.94)	$ (5.53)	$ (4.13)
20%	$(30.50)	$(29.09)	$(27.69)	$(26.29)	$(24.89)	$(23.49)	$(22.09)	$(20.69)	$(19.28)	$(17.88)	$(16.48)	$(15.08)	$(13.68)	$(12.28)	$(10.88)	$ (9.47)	$ (8.07)	$ (6.67)	$ (5.27)	$ (3.87)
25%	$(30.19)	$(28.79)	$(27.39)	$(25.99)	$(24.59)	$(23.19)	$(21.79)	$(20.40)	$(19.00)	$(17.60)	$(16.20)	$(14.80)	$(13.40)	$(12.00)	$(10.60)	$ (9.20)	$ (7.81)	$ (6.41)	$ (5.01)	$ (3.61)
30%	$(29.88)	$(28.48)	$(27.09)	$(25.69)	$(24.29)	$(22.90)	$(21.50)	$(20.10)	$(18.71)	$(17.31)	$(15.92)	$(14.52)	$(13.12)	$(11.73)	$(10.33)	$ (8.93)	$ (7.54)	$ (6.14)	$ (4.75)	$ (3.35)
35%	$(29.57)	$(28.18)	$(26.78)	$(25.39)	$(24.00)	$(22.60)	$(21.21)	$(19.81)	$(18.42)	$(17.03)	$(15.63)	$(14.24)	$(12.85)	$(11.45)	$(10.06)	$ (8.66)	$ (7.27)	$ (5.88)	$ (4.48)	$ (3.09)
40%	$(29.26)	$(27.87)	$(26.48)	$(25.09)	$(23.70)	$(22.31)	$(20.92)	$(19.52)	$(18.13)	$(16.74)	$(15.35)	$(13.96)	$(12.57)	$(11.18)	$ (9.79)	$ (8.39)	$ (7.00)	$ (5.61)	$ (4.22)	$ (2.83)
45%	$(28.95)	$(27.57)	$(26.18)	$(24.79)	$(23.40)	$(22.01)	$(20.62)	$(19.23)	$(17.85)	$(16.46)	$(15.07)	$(13.68)	$(12.29)	$(10.90)	$ (9.51)	$ (8.13)	$ (6.74)	$ (5.35)	$ (3.96)	$ (2.57)
50%	$(28.65)	$(27.26)	$(25.87)	$(24.49)	$(23.10)	$(21.72)	$(20.33)	$(18.94)	$(17.56)	$(16.17)	$(14.79)	$(13.40)	$(12.01)	$(10.63)	$ (9.24)	$ (7.86)	$ (6.47)	$ (5.08)	$ (3.70)	$ (2.31)
55%	$(28.34)	$(26.96)	$(25.57)	$(24.19)	$(22.80)	$(21.42)	$(20.04)	$(18.65)	$(17.27)	$(15.89)	$(14.50)	$(13.12)	$(11.74)	$(10.35)	$ (8.97)	$ (7.59)	$ (6.20)	$ (4.82)	$ (3.43)	$ (2.05)
60%	$(28.03)	$(26.65)	$(25.27)	$(23.89)	$(22.51)	$(21.13)	$(19.74)	$(18.36)	$(16.98)	$(15.60)	$(14.22)	$(12.84)	$(11.46)	$(10.08)	$ (8.70)	$ (7.32)	$ (5.93)	$ (4.55)	$ (3.17)	$ (1.79)
65%	$(27.72)	$(26.34)	$(24.97)	$(23.59)	$(22.21)	$(20.83)	$(19.45)	$(18.07)	$(16.69)	$(15.32)	$(13.94)	$(12.56)	$(11.18)	$ (9.80)	$ (8.42)	$ (7.05)	$ (5.67)	$ (4.29)	$ (2.91)	$ (1.53)
70%	$(27.41)	$(26.04)	$(24.66)	$(23.29)	$(21.91)	$(20.53)	$(19.16)	$(17.78)	$(16.41)	$(15.03)	$(13.66)	$(12.28)	$(10.90)	$ (9.53)	$ (8.15)	$ (6.78)	$ (5.40)	$ (4.02)	$ (2.65)	$ (1.27)
75%	$(27.11)	$(25.73)	$(24.36)	$(22.99)	$(21.61)	$(20.24)	$(18.87)	$(17.49)	$(16.12)	$(14.75)	$(13.37)	$(12.00)	$(10.63)	$ (9.25)	$ (7.88)	$ (6.51)	$ (5.13)	$ (3.76)	$ (2.39)	$ (1.01)
80%	$(26.80)	$(25.43)	$(24.06)	$(22.69)	$(21.32)	$(19.94)	$(18.57)	$(17.20)	$(15.83)	$(14.46)	$(13.09)	$(11.72)	$(10.35)	$ (8.98)	$ (7.61)	$ (6.24)	$ (4.87)	$ (3.49)	$ (2.12)	$ (0.75)
85%	$(26.49)	$(25.12)	$(23.75)	$(22.39)	$(21.02)	$(19.65)	$(18.28)	$(16.91)	$(15.54)	$(14.18)	$(12.81)	$(11.44)	$(10.07)	$ (8.70)	$ (7.33)	$ (5.97)	$ (4.60)	$ (3.23)	$ (1.86)	$ (0.49)
90%	$(26.18)	$(24.82)	$(23.45)	$(22.09)	$(20.72)	$(19.35)	$(17.99)	$(16.62)	$(15.26)	$(13.89)	$(12.52)	$(11.16)	$ (9.79)	$ (8.43)	$ (7.06)	$ (5.70)	$ (4.33)	$ (2.96)	$ (1.60)	$ (0.23)
95%	$(25.87)	$(24.51)	$(23.15)	$(21.78)	$(20.42)	$(19.06)	$(17.70)	$(16.33)	$(14.97)	$(13.61)	$(12.24)	$(10.88)	$ (9.52)	$ (8.15)	$ (6.79)	$ (5.43)	$ (4.06)	$ (2.70)	$ (1.34)	$ 0.03
100%	$(25.57)	$(24.21)	$(22.85)	$(21.48)	$(20.12)	$(18.76)	$(17.40)	$(16.04)	$(14.68)	$(13.32)	$(11.96)	$(10.60)	$ (9.24)	$ (7.88)	$ (6.52)	$ (5.16)	$ (3.80)	$ (2.44)	$ (1.07)	$ 0.29

Favorable development with smaller trials

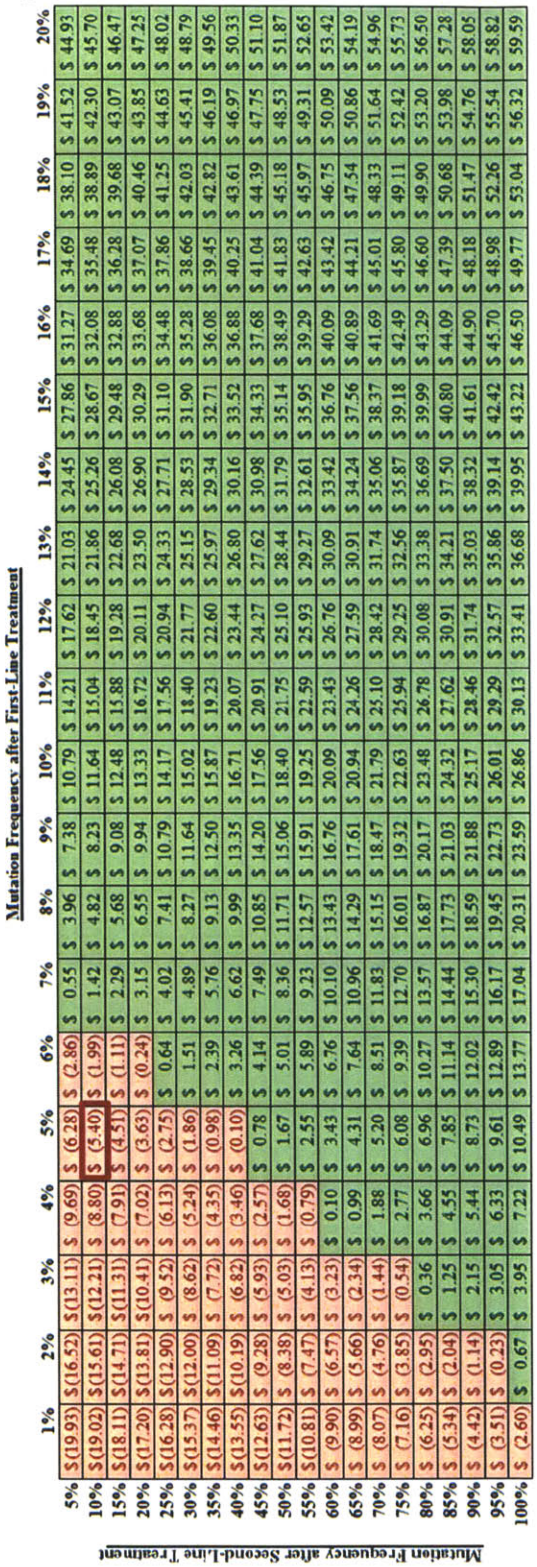
In the converse of the last scenario, the project could become more profitable if trial sizes were reduced to account for the small population or the drug were shown to be so efficacious in a pivotal trial that an interim data safety monitoring board halted the trial on the grounds that it is unethical to administer placebo. To test a "favorable" scenario, I reduce Phase I, II and III study populations by at least 50% (from 60 to 30, from 320 to 120, and from 500 to 200), and reduce trial durations by 25% to account for the smaller populations.

As a trial halt for extreme efficacy (i.e. a data safety monitoring board rules that it is unethical to administer the placebo or comparator treatment) is rare and difficult to predict, I do not incorporate this.

Figure 13: Favorable development timeline

Under this scenario, the drug is launched in early 2015, and the NPV increases to -$7.38 million pre-tax and -$4.79 million post-tax. Varying the mutation rate yields the following.

Figure 14: Net income NPV with smaller trials



Mutation Frequency after First-Line Treatment

Mutation Frequency after Second-Line Treatment	1%	2%	3%	4%	5%	6%	7%	8%	9%	10%	11%	12%	13%	14%	15%	16%	17%	18%	19%	20%
5%	$(19.93)	$(16.52)	$(13.11)	$ (9.69)	$ (6.28)	$ (2.86)	$ 0.55	$ 3.96	$ 7.38	$ 10.79	$ 14.21	$ 17.62	$ 21.03	$ 24.45	$ 27.86	$ 31.27	$ 34.69	$ 38.10	$ 41.52	$ 44.93
10%	$(19.02)	$(15.61)	$(12.21)	$ (8.80)	$ (5.40)	$ (1.99)	$ 1.42	$ 4.82	$ 8.23	$ 11.64	$ 15.04	$ 18.45	$ 21.86	$ 25.26	$ 28.67	$ 32.08	$ 35.48	$ 38.89	$ 42.30	$ 45.70
15%	$(18.11)	$(14.71)	$(11.31)	$ (7.91)	$ (4.51)	$ (1.11)	$ 2.29	$ 5.68	$ 9.08	$ 12.48	$ 15.88	$ 19.28	$ 22.68	$ 26.08	$ 29.48	$ 32.88	$ 36.28	$ 39.68	$ 43.07	$ 46.47
20%	$(17.20)	$(13.81)	$(10.41)	$ (7.02)	$ (3.63)	$ (0.24)	$ 3.15	$ 6.55	$ 9.94	$ 13.33	$ 16.72	$ 20.11	$ 23.50	$ 26.90	$ 30.29	$ 33.68	$ 37.07	$ 40.46	$ 43.85	$ 47.25
25%	$(16.28)	$(12.90)	$ (9.52)	$ (6.13)	$ (2.75)	$ 0.64	$ 4.02	$ 7.41	$ 10.79	$ 14.17	$ 17.56	$ 20.94	$ 24.33	$ 27.71	$ 31.10	$ 34.48	$ 37.86	$ 41.25	$ 44.63	$ 48.02
30%	$(15.37)	$(12.00)	$ (8.62)	$ (5.24)	$ (1.86)	$ 1.51	$ 4.89	$ 8.27	$ 11.64	$ 15.02	$ 18.40	$ 21.77	$ 25.15	$ 28.53	$ 31.90	$ 35.28	$ 38.66	$ 42.03	$ 45.41	$ 48.79
35%	$(14.46)	$(11.09)	$ (7.72)	$ (4.35)	$ (0.98)	$ 2.39	$ 5.76	$ 9.13	$ 12.50	$ 15.87	$ 19.23	$ 22.60	$ 25.97	$ 29.34	$ 32.71	$ 36.08	$ 39.45	$ 42.82	$ 46.19	$ 49.56
40%	$(13.55)	$(10.19)	$ (6.82)	$ (3.46)	$ (0.10)	$ 3.26	$ 6.62	$ 9.99	$ 13.35	$ 16.71	$ 20.07	$ 23.44	$ 26.80	$ 30.16	$ 33.52	$ 36.88	$ 40.25	$ 43.61	$ 46.97	$ 50.33
45%	$(12.63)	$ (9.28)	$ (5.93)	$ (2.57)	$ 0.78	$ 4.14	$ 7.49	$ 10.85	$ 14.20	$ 17.56	$ 20.91	$ 24.27	$ 27.62	$ 30.98	$ 34.33	$ 37.68	$ 41.04	$ 44.39	$ 47.75	$ 51.10
50%	$(11.72)	$ (8.38)	$ (5.03)	$ (1.68)	$ 1.67	$ 5.01	$ 8.36	$ 11.71	$ 15.06	$ 18.40	$ 21.75	$ 25.10	$ 28.44	$ 31.79	$ 35.14	$ 38.49	$ 41.83	$ 45.18	$ 48.53	$ 51.87
55%	$(10.81)	$ (7.47)	$ (4.13)	$ (0.79)	$ 2.55	$ 5.89	$ 9.23	$ 12.57	$ 15.91	$ 19.25	$ 22.59	$ 25.93	$ 29.27	$ 32.61	$ 35.95	$ 39.29	$ 42.63	$ 45.97	$ 49.31	$ 52.65
60%	$ (9.90)	$ (6.57)	$ (3.23)	$ 0.10	$ 3.43	$ 6.76	$ 10.10	$ 13.43	$ 16.76	$ 20.09	$ 23.43	$ 26.76	$ 30.09	$ 33.42	$ 36.76	$ 40.09	$ 43.42	$ 46.75	$ 50.09	$ 53.42
65%	$ (8.99)	$ (5.66)	$ (2.34)	$ 0.99	$ 4.31	$ 7.64	$ 10.96	$ 14.29	$ 17.61	$ 20.94	$ 24.26	$ 27.59	$ 30.91	$ 34.24	$ 37.56	$ 40.89	$ 44.21	$ 47.54	$ 50.86	$ 54.19
70%	$ (8.07)	$ (4.76)	$ (1.44)	$ 1.88	$ 5.20	$ 8.51	$ 11.83	$ 15.15	$ 18.47	$ 21.79	$ 25.10	$ 28.42	$ 31.74	$ 35.06	$ 38.37	$ 41.69	$ 45.01	$ 48.33	$ 51.64	$ 54.96
75%	$ (7.16)	$ (3.85)	$ (0.54)	$ 2.77	$ 6.08	$ 9.39	$ 12.70	$ 16.01	$ 19.32	$ 22.63	$ 25.94	$ 29.25	$ 32.56	$ 35.87	$ 39.18	$ 42.49	$ 45.80	$ 49.11	$ 52.42	$ 55.73
80%	$ (6.25)	$ (2.95)	$ 0.36	$ 3.66	$ 6.96	$ 10.27	$ 13.57	$ 16.87	$ 20.17	$ 23.48	$ 26.78	$ 30.08	$ 33.38	$ 36.69	$ 39.99	$ 43.29	$ 46.60	$ 49.90	$ 53.20	$ 56.50
85%	$ (5.34)	$ (2.04)	$ 1.25	$ 4.55	$ 7.85	$ 11.14	$ 14.44	$ 17.73	$ 21.03	$ 24.32	$ 27.62	$ 30.91	$ 34.21	$ 37.50	$ 40.80	$ 44.09	$ 47.39	$ 50.68	$ 53.98	$ 57.28
90%	$ (4.42)	$ (1.14)	$ 2.15	$ 5.44	$ 8.73	$ 12.02	$ 15.30	$ 18.59	$ 21.88	$ 25.17	$ 28.46	$ 31.74	$ 35.03	$ 38.32	$ 41.61	$ 44.90	$ 48.18	$ 51.47	$ 54.76	$ 58.05
95%	$ (3.51)	$ (0.23)	$ 3.05	$ 6.33	$ 9.61	$ 12.89	$ 16.17	$ 19.45	$ 22.73	$ 26.01	$ 29.29	$ 32.57	$ 35.86	$ 39.14	$ 42.42	$ 45.70	$ 48.98	$ 52.26	$ 55.54	$ 58.82
100%	$ (2.60)	$ 0.67	$ 3.95	$ 7.22	$ 10.49	$ 13.77	$ 17.04	$ 20.31	$ 23.59	$ 26.86	$ 30.13	$ 33.41	$ 36.68	$ 39.95	$ 43.22	$ 46.50	$ 49.77	$ 53.04	$ 56.32	$ 59.59

Favorable development with smaller trials and increased likelihood of success

In addition to reducing trial size and duration, this scenario increases the probability of trial success by 10% at Phase I (to reflect the already high likelihood of Phase I success) and 20% at Phase II and Phase III. Using these parameters and the base case mutation rate, I obtain a pre-tax NPV of $0.88 million and a net income NPV of $0.57 million. This is nominally positive but contains no "margin of error."

Figure 15: Net income NPV with smaller trials and increased likelihood of success

Mutation Frequency after Second-Line Treatment	Mutation Frequency after First-Line Treatment																			
	1%	2%	3%	4%	5%	6%	7%	8%	9%	10%	11%	12%	13%	14%	15%	16%	17%	18%	19%	20%
5%	$(22.93)	$(17.63)	$(12.33)	$ (7.03)	$ (1.73)	$ 3.57	$ 8.87	$ 14.17	$ 19.47	$ 24.77	$ 30.07	$ 35.37	$ 40.67	$ 45.97	$ 51.27	$ 56.57	$ 61.87	$ 67.17	$ 72.47	$ 77.76
10%	$(21.52)	$(16.23)	$(10.94)	$ (5.65)	$ (0.36)	$ 4.92	$ 10.21	$ 15.50	$ 20.79	$ 26.08	$ 31.37	$ 36.65	$ 41.94	$ 47.23	$ 52.52	$ 57.81	$ 63.10	$ 68.38	$ 73.67	$ 78.96
15%	$(20.10)	$(14.83)	$ (9.55)	$ (4.27)	$ 1.00	$ 6.28	$ 11.56	$ 16.83	$ 22.11	$ 27.39	$ 32.66	$ 37.94	$ 43.22	$ 48.49	$ 53.77	$ 59.05	$ 64.32	$ 69.60	$ 74.88	$ 80.16
20%	$(18.69)	$(13.43)	$ (8.16)	$ (2.90)	$ 2.37	$ 7.64	$ 12.90	$ 18.17	$ 23.43	$ 28.70	$ 33.96	$ 39.23	$ 44.49	$ 49.76	$ 55.02	$ 60.29	$ 65.55	$ 70.82	$ 76.08	$ 81.35
25%	$(17.28)	$(12.02)	$ (6.77)	$ (1.52)	$ 3.74	$ 8.99	$ 14.24	$ 19.50	$ 24.75	$ 30.01	$ 35.26	$ 40.51	$ 45.77	$ 51.02	$ 56.28	$ 61.53	$ 66.78	$ 72.04	$ 77.29	$ 82.55
30%	$(15.87)	$(10.62)	$ (5.38)	$ (0.14)	$ 5.10	$ 10.35	$ 15.59	$ 20.83	$ 26.07	$ 31.32	$ 36.56	$ 41.80	$ 47.04	$ 52.29	$ 57.53	$ 62.77	$ 68.01	$ 73.26	$ 78.50	$ 83.74
35%	$(14.45)	$ (9.22)	$ (3.99)	$ 1.24	$ 6.47	$ 11.70	$ 16.93	$ 22.16	$ 27.40	$ 32.63	$ 37.86	$ 43.09	$ 48.32	$ 53.55	$ 58.78	$ 64.01	$ 69.24	$ 74.47	$ 79.70	$ 84.94
40%	$(13.04)	$ (7.82)	$ (2.60)	$ 2.62	$ 7.84	$ 13.06	$ 18.28	$ 23.50	$ 28.72	$ 33.94	$ 39.16	$ 44.37	$ 49.59	$ 54.81	$ 60.03	$ 65.25	$ 70.47	$ 75.69	$ 80.91	$ 86.13
45%	$(11.63)	$ (6.42)	$ (1.21)	$ 4.00	$ 9.21	$ 14.41	$ 19.62	$ 24.83	$ 30.04	$ 35.25	$ 40.45	$ 45.66	$ 50.87	$ 56.08	$ 61.29	$ 66.49	$ 71.70	$ 76.91	$ 82.12	$ 87.33
50%	$(10.21)	$ (5.02)	$ 0.18	$ 5.38	$ 10.57	$ 15.77	$ 20.97	$ 26.16	$ 31.36	$ 36.56	$ 41.75	$ 46.95	$ 52.15	$ 57.34	$ 62.54	$ 67.73	$ 72.93	$ 78.13	$ 83.32	$ 88.52
55%	$ (8.80)	$ (3.61)	$ 1.57	$ 6.76	$ 11.94	$ 17.13	$ 22.31	$ 27.50	$ 32.68	$ 37.87	$ 43.05	$ 48.24	$ 53.42	$ 58.61	$ 63.79	$ 68.98	$ 74.16	$ 79.35	$ 84.53	$ 89.72
60%	$ (7.39)	$ (2.21)	$ 2.96	$ 8.13	$ 13.31	$ 18.48	$ 23.65	$ 28.83	$ 34.00	$ 39.18	$ 44.35	$ 49.52	$ 54.70	$ 59.87	$ 65.04	$ 70.22	$ 75.39	$ 80.56	$ 85.74	$ 90.91
65%	$ (5.97)	$ (0.81)	$ 4.35	$ 9.51	$ 14.67	$ 19.84	$ 25.00	$ 30.16	$ 35.32	$ 40.49	$ 45.65	$ 50.81	$ 55.97	$ 61.13	$ 66.30	$ 71.46	$ 76.62	$ 81.78	$ 86.94	$ 92.11
70%	$ (4.56)	$ 0.59	$ 5.74	$ 10.89	$ 16.04	$ 21.19	$ 26.34	$ 31.49	$ 36.64	$ 41.79	$ 46.95	$ 52.10	$ 57.25	$ 62.40	$ 67.55	$ 72.70	$ 77.85	$ 83.00	$ 88.15	$ 93.30
75%	$ (3.15)	$ 1.99	$ 7.13	$ 12.27	$ 17.41	$ 22.55	$ 27.69	$ 32.83	$ 37.97	$ 43.10	$ 48.24	$ 53.38	$ 58.52	$ 63.66	$ 68.80	$ 73.94	$ 79.08	$ 84.22	$ 89.36	$ 94.50
80%	$ (1.73)	$ 3.39	$ 8.52	$ 13.65	$ 18.78	$ 23.90	$ 29.03	$ 34.16	$ 39.29	$ 44.41	$ 49.54	$ 54.67	$ 59.80	$ 64.93	$ 70.05	$ 75.18	$ 80.31	$ 85.44	$ 90.56	$ 95.69
85%	$ (0.32)	$ 4.79	$ 9.91	$ 15.03	$ 20.14	$ 25.26	$ 30.38	$ 35.49	$ 40.61	$ 45.72	$ 50.84	$ 55.96	$ 61.07	$ 66.19	$ 71.31	$ 76.42	$ 81.54	$ 86.65	$ 91.77	$ 96.89
90%	$ 1.09	$ 6.20	$ 11.30	$ 16.41	$ 21.51	$ 26.62	$ 31.72	$ 36.82	$ 41.93	$ 47.03	$ 52.14	$ 57.24	$ 62.35	$ 67.45	$ 72.56	$ 77.66	$ 82.77	$ 87.87	$ 92.98	$ 98.08
95%	$ 2.50	$ 7.60	$ 12.69	$ 17.78	$ 22.88	$ 27.97	$ 33.06	$ 38.16	$ 43.25	$ 48.34	$ 53.44	$ 58.53	$ 63.62	$ 68.72	$ 73.81	$ 78.90	$ 84.00	$ 89.09	$ 94.18	$ 99.28
100%	$ 3.92	$ 9.00	$ 14.08	$ 19.16	$ 24.25	$ 29.33	$ 34.41	$ 39.49	$ 44.57	$ 49.65	$ 54.74	$ 59.82	$ 64.90	$ 69.98	$ 75.06	$ 80.14	$ 85.23	$ 90.31	$ 95.39	$ 100.47

Pricing

Newer targeted cancer drugs are known for a very high price point. Some new drugs are priced at over $100,000 per year, often with a marginal median survival benefit. A drug like the hypothetical candidate which has strong efficacy in a small subset of the CML population is less likely to be prescribed off-label and could command premium pricing. On the other hand, payers could regard it as another cancer drug and either refuse to reimburse (in some countries) or place onerous restrictions including prior authorization.

In the base case, I assume the hypothetical candidate is priced at $7,570 per month ($90,840 per year, translating to a 30% premium over the most expensive branded agent), with the net income NPV at certain price points detailed below. Under the base case, an additional $1,000 per patient per month adds $2.33 million to the NPV, with the NPV reaching zero at a price of $13,987 per patient per month.

Figure 16: Net income NPV with varied pricing

$ 3,000	$ 4,000	$ 5,000	$ 6,000	$ 7,000	$ 8,000	$ 9,000	$ 10,000
$(26.03)	$(23.66)	$(21.29)	$(18.96)	$(16.55)	$(14.18)	$(11.81)	$ (9.45)

Discount rate

A commonly used real discount rate for large biopharmaceutical companies is 11%, as in the base case[83]. However, smaller companies may have more restricted access to capital. Below, I vary the cost of capital from 11-20%.

Figure 17: Net income NPV with varied discount rate

11%	12%	15%	18%	20%
$(15.20)	$(16.04)	$(17.46)	$(17.79)	$(17.64)

Multiple factor sensitivity

Generating a "clear winner"

Few of the above scenarios have a positive NPV, and those that do are only marginally positive. To account for the "margin of safety" that most biopharmaceutical manufacturers would require in order to invest in a project, I combine several of the positive factors discussed above including price, discount rate, drug failure rates, favorable clinical development probabilities and trial sizes. This will inform what assumptions are required in order to generate a highly positive NPV. In this section, cells with an NPV over $100 million are indicated with blue text on a blue background.

Positive drug failure rates, clinical development probabilities and trial sizes

Of the potential deviations from the base case, I view these three as the most likely as the most likely to deviate in a manner that favors the hypothetical candidate. Under this case, the pre-tax NPV rises to $20.7 million and the after-tax NPV rises to $13.5 million. Thus, the hypothetical candidate would be a questionable investment (positive but small margin of safety) in the base case, but an agent with broader coverage could be a clear winner in the later-line setting.

Figure 18: Net income NPV with positive drug failure rates, clinical development probabilities and trial sizes

Mutation Frequency after Second-Line Treatment \ Mutation Frequency after First-Line Treatment	1%	2%	3%	4%	5%	6%	7%	8%	9%	10%	11%	12%	13%	14%	15%	16%	17%	18%	19%	20%
5%	$ (20.26)	$ (12.57)	$ (4.88)	$ 2.81	$ 10.49	$ 18.18	$ 25.87	$ 33.56	$ 41.25	$ 48.94	$ 56.63	$ 64.32	$ 72.01	$ 79.70	$ 87.38	$ 95.07	$102.76	$110.45	$118.14	$125.83
10%	$ (18.57)	$ (10.89)	$ (3.22)	$ 4.46	$ 12.13	$ 19.81	$ 27.48	$ 35.16	$ 42.83	$ 50.51	$ 58.18	$ 65.86	$ 73.53	$ 81.21	$ 88.88	$ 96.56	$104.23	$111.91	$119.59	$127.26
15%	$ (16.88)	$ (9.22)	$ (1.55)	$ 6.11	$ 13.77	$ 21.43	$ 29.09	$ 36.75	$ 44.41	$ 52.08	$ 59.74	$ 67.40	$ 75.06	$ 82.72	$ 90.38	$ 98.05	$105.71	$113.37	$121.03	$128.69
20%	$ (15.19)	$ (7.54)	$ 0.11	$ 7.76	$ 15.40	$ 23.05	$ 30.70	$ 38.35	$ 46.00	$ 53.64	$ 61.29	$ 68.94	$ 76.59	$ 84.24	$ 91.88	$ 99.53	$107.18	$114.83	$122.48	$130.12
25%	$ (13.50)	$ (5.86)	$ 1.77	$ 9.41	$ 17.04	$ 24.68	$ 32.31	$ 39.94	$ 47.58	$ 55.21	$ 62.85	$ 70.48	$ 78.12	$ 85.75	$ 93.38	$101.02	$108.65	$116.29	$123.92	$131.55
30%	$ (11.80)	$ (4.18)	$ 3.44	$ 11.06	$ 18.68	$ 26.30	$ 33.92	$ 41.54	$ 49.16	$ 56.78	$ 64.40	$ 72.02	$ 79.64	$ 87.26	$ 94.88	$102.50	$110.12	$117.74	$125.36	$132.99
35%	$ (10.11)	$ (2.51)	$ 5.10	$ 12.71	$ 20.32	$ 27.92	$ 35.53	$ 43.14	$ 50.74	$ 58.35	$ 65.96	$ 73.56	$ 81.17	$ 88.78	$ 96.38	$103.99	$111.60	$119.20	$126.81	$134.42
40%	$ (8.42)	$ (0.83)	$ 6.77	$ 14.36	$ 21.95	$ 29.54	$ 37.14	$ 44.73	$ 52.32	$ 59.92	$ 67.51	$ 75.10	$ 82.70	$ 90.29	$ 97.88	$105.48	$113.07	$120.66	$128.25	$135.85
45%	$ (6.73)	$ 0.85	$ 8.43	$ 16.01	$ 23.59	$ 31.17	$ 38.75	$ 46.33	$ 53.91	$ 61.49	$ 69.06	$ 76.64	$ 84.22	$ 91.80	$ 99.38	$106.96	$114.54	$122.12	$129.70	$137.28
50%	$ (5.04)	$ 2.53	$ 10.09	$ 17.66	$ 25.23	$ 32.79	$ 40.36	$ 47.92	$ 55.49	$ 63.05	$ 70.62	$ 78.18	$ 85.75	$ 93.32	$100.88	$108.45	$116.01	$123.58	$131.14	$138.71
55%	$ (3.35)	$ 4.21	$ 11.76	$ 19.31	$ 26.86	$ 34.41	$ 41.97	$ 49.52	$ 57.07	$ 64.62	$ 72.17	$ 79.73	$ 87.28	$ 94.83	$102.38	$109.93	$117.49	$125.04	$132.59	$140.14
60%	$ (1.65)	$ 5.88	$ 13.42	$ 20.96	$ 28.50	$ 36.04	$ 43.58	$ 51.11	$ 58.65	$ 66.19	$ 73.73	$ 81.27	$ 88.80	$ 96.34	$103.88	$111.42	$118.96	$126.50	$134.03	$141.57
65%	$ 0.04	$ 7.56	$ 15.09	$ 22.61	$ 30.14	$ 37.66	$ 45.18	$ 52.71	$ 60.23	$ 67.76	$ 75.28	$ 82.81	$ 90.33	$ 97.86	$105.38	$112.91	$120.43	$127.95	$135.48	$143.00
70%	$ 1.73	$ 9.24	$ 16.75	$ 24.26	$ 31.77	$ 39.28	$ 46.79	$ 54.30	$ 61.82	$ 69.33	$ 76.84	$ 84.35	$ 91.86	$ 99.37	$106.88	$114.39	$121.90	$129.41	$136.92	$144.44
75%	$ 3.42	$ 10.92	$ 18.41	$ 25.91	$ 33.41	$ 40.91	$ 48.40	$ 55.90	$ 63.40	$ 70.89	$ 78.39	$ 85.89	$ 93.39	$100.88	$108.38	$115.88	$123.38	$130.87	$138.37	$145.87
80%	$ 5.11	$ 12.60	$ 20.08	$ 27.56	$ 35.05	$ 42.53	$ 50.01	$ 57.50	$ 64.98	$ 72.46	$ 79.95	$ 87.43	$ 94.91	$102.40	$109.88	$117.36	$124.85	$132.33	$139.81	$147.30
85%	$ 6.80	$ 14.27	$ 21.74	$ 29.21	$ 36.68	$ 44.15	$ 51.62	$ 59.09	$ 66.56	$ 74.03	$ 81.50	$ 88.97	$ 96.44	$103.91	$111.38	$118.85	$126.32	$133.79	$141.26	$148.73
90%	$ 8.49	$ 15.95	$ 23.41	$ 30.86	$ 38.32	$ 45.78	$ 53.23	$ 60.69	$ 68.14	$ 75.60	$ 83.06	$ 90.51	$ 97.97	$105.42	$112.88	$120.34	$127.79	$135.25	$142.70	$150.16
95%	$ 10.19	$ 17.63	$ 25.07	$ 32.51	$ 39.96	$ 47.40	$ 54.84	$ 62.28	$ 69.73	$ 77.17	$ 84.61	$ 92.05	$ 99.49	$106.94	$114.38	$121.82	$129.26	$136.71	$144.15	$151.59
100%	$ 11.88	$ 19.31	$ 26.74	$ 34.16	$ 41.59	$ 49.02	$ 56.45	$ 63.88	$ 71.31	$ 78.74	$ 86.16	$ 93.59	$101.02	$108.45	$115.88	$123.31	$130.74	$138.17	$145.59	$153.02

All positive factors

Under these circumstances, the pre-tax NPV rises to $42.0 million and the post-tax NPV to $27.3 million. Even in this scenario, broader mutational coverage in 2nd- and 3rd-line setting is required to for the hypothetical candidate to be significantly profitable.

Comparing this table to any of the previous tables, it appears as though multiple synergistic factors would be required to generate a "significantly profitable" project. Given the superior data on newer CML TKIs, a pricing/payer environment (particularly in Europe) that could exert downward pressure over time and probable difficulties in enrolling sufficient numbers of patients for a clinical trial, I believe it is highly unlikely that the hypothetical candidate be deemed sufficiently profitable for investment.

Figure 19: Net income NPV with all favorable factors

Mutation Frequency after Second-Line Treatment	Mutation Frequency after First-Line Treatment																			
	1%	2%	3%	4%	5%	6%	7%	8%	9%	10%	11%	12%	13%	14%	15%	16%	17%	18%	19%	20%
5%	$ (17.25)	$ (7.09)	$ 3.07	$ 13.23	$ 23.38	$ 33.54	$ 43.70	$ 53.85	$ 64.01	$ 74.17	$ 84.33	$ 94.48	$104.64	$114.80	$124.95	$135.11	$145.27	$155.43	$165.58	$175.74
10%	$ (15.01)	$ (4.87)	$ 5.27	$ 15.41	$ 25.55	$ 35.68	$ 45.82	$ 55.96	$ 66.10	$ 76.24	$ 86.38	$ 96.52	$106.66	$116.80	$126.94	$137.07	$147.21	$157.35	$167.49	$177.63
15%	$ (12.78)	$ (2.66)	$ 7.47	$ 17.59	$ 27.71	$ 37.83	$ 47.95	$ 58.07	$ 68.19	$ 78.31	$ 88.43	$ 98.55	$108.68	$118.80	$128.92	$139.04	$149.16	$159.28	$169.40	$179.52
20%	$ (10.54)	$ (0.44)	$ 9.66	$ 19.77	$ 29.87	$ 39.97	$ 50.08	$ 60.18	$ 70.28	$ 80.38	$ 90.49	$100.59	$110.69	$120.80	$130.90	$141.00	$151.10	$161.21	$171.31	$181.41
25%	$ (8.31)	$ 1.78	$ 11.86	$ 21.95	$ 32.03	$ 42.12	$ 52.20	$ 62.29	$ 72.37	$ 82.46	$ 92.54	$102.62	$112.71	$122.79	$132.88	$142.96	$153.05	$163.13	$173.22	$183.30
30%	$ (6.07)	$ 3.99	$ 14.06	$ 24.13	$ 34.19	$ 44.26	$ 54.33	$ 64.39	$ 74.46	$ 84.53	$ 94.59	$104.66	$114.73	$124.79	$134.86	$144.93	$154.99	$165.06	$175.13	$185.19
35%	$ (3.84)	$ 6.21	$ 16.26	$ 26.31	$ 36.36	$ 46.40	$ 56.45	$ 66.50	$ 76.55	$ 86.60	$ 96.65	$106.70	$116.74	$126.79	$136.84	$146.89	$156.94	$166.99	$177.04	$187.08
40%	$ (1.60)	$ 8.43	$ 18.46	$ 28.49	$ 38.52	$ 48.55	$ 58.58	$ 68.61	$ 78.64	$ 88.67	$ 98.70	$108.73	$118.76	$128.79	$138.82	$148.85	$158.88	$168.91	$178.94	$188.98
45%	$ 0.63	$ 10.64	$ 20.66	$ 30.67	$ 40.68	$ 50.69	$ 60.70	$ 70.72	$ 80.73	$ 90.74	$100.75	$110.77	$120.78	$130.79	$140.80	$150.82	$160.83	$170.84	$180.85	$190.87
50%	$ 2.86	$ 12.86	$ 22.85	$ 32.85	$ 42.84	$ 52.84	$ 62.83	$ 72.82	$ 82.82	$ 92.81	$102.81	$112.80	$122.80	$132.79	$142.79	$152.78	$162.77	$172.77	$182.76	$192.76
55%	$ 5.10	$ 15.08	$ 25.05	$ 35.03	$ 45.00	$ 54.98	$ 64.96	$ 74.93	$ 84.91	$ 94.89	$104.86	$114.84	$124.81	$134.79	$144.77	$154.74	$164.72	$174.69	$184.67	$194.65
60%	$ 7.33	$ 17.29	$ 27.25	$ 37.21	$ 47.17	$ 57.12	$ 67.08	$ 77.04	$ 87.00	$ 96.96	$106.91	$116.87	$126.83	$136.79	$146.75	$156.71	$166.66	$176.62	$186.58	$196.54
65%	$ 9.57	$ 19.51	$ 29.45	$ 39.39	$ 49.33	$ 59.27	$ 69.21	$ 79.15	$ 89.09	$ 99.03	$108.97	$118.91	$128.85	$138.79	$148.73	$158.67	$168.61	$178.55	$188.49	$198.43
70%	$ 11.80	$ 21.72	$ 31.65	$ 41.57	$ 51.49	$ 61.41	$ 71.33	$ 81.26	$ 91.18	$101.10	$111.02	$120.94	$130.87	$140.79	$150.71	$160.63	$170.55	$180.48	$190.40	$200.32
75%	$ 14.04	$ 23.94	$ 33.84	$ 43.75	$ 53.65	$ 63.56	$ 73.46	$ 83.36	$ 93.27	$103.17	$113.08	$122.98	$132.88	$142.79	$152.69	$162.59	$172.50	$182.40	$192.31	$202.21
80%	$ 16.27	$ 26.16	$ 36.04	$ 45.93	$ 55.81	$ 65.70	$ 75.59	$ 85.47	$ 95.36	$105.24	$115.13	$125.01	$134.90	$144.79	$154.67	$164.56	$174.44	$184.33	$194.21	$204.10
85%	$ 18.51	$ 28.37	$ 38.24	$ 48.11	$ 57.98	$ 67.84	$ 77.71	$ 87.58	$ 97.45	$107.31	$117.18	$127.05	$136.92	$146.79	$156.65	$166.52	$176.39	$186.26	$196.12	$205.99
90%	$ 20.74	$ 30.59	$ 40.44	$ 50.29	$ 60.14	$ 69.99	$ 79.84	$ 89.69	$ 99.54	$109.39	$119.24	$129.09	$138.94	$148.78	$158.63	$168.48	$178.33	$188.18	$198.03	$207.88
95%	$ 22.98	$ 32.81	$ 42.64	$ 52.47	$ 62.30	$ 72.13	$ 81.96	$ 91.80	$101.63	$111.46	$121.29	$131.12	$140.95	$150.78	$160.62	$170.45	$180.28	$190.11	$199.94	$209.77
100%	$ 25.21	$ 35.02	$ 44.84	$ 54.65	$ 64.46	$ 74.28	$ 84.09	$ 93.90	$103.72	$113.53	$123.34	$133.16	$142.97	$152.78	$162.60	$172.41	$182.22	$192.04	$201.85	$211.66

Limitations of the model

While systematizing published market data and clinical trial results to quantify the market is a good surrogate for the way the market may evolve, there are a number of ways in which the evolving CML market may deviate from the model.

- **The CML treatment paradigm will continue to change.** Sprycel and Tasigna have been only recently approved for 1st-line chronic phase use. While both demonstrated superiority to Gleevec in this setting (where most treatment takes place) and are perceived more favorably by oncologists, it is possible that many oncologists may continue to start patients on the more familiar drug for which they are accustomed to managing side effects[84]. Moreover, many treatment guidelines for response and failure were developed with Gleevec treatment in mind. Use of the hypothetical drug candidate would increase under slower-than-expected 2nd-generation TKI adoption due to the higher failure rate with Gleevec.

- **Data will evolve over time.** This model relies on Gleevec data up to 60 months and available Tasigna and Sprycel data up to 24 months, while the model projects the hypothetical candidate through 20 years. Given the long life expectancy of an optimally-treated CML patient, changing failure rates beyond 60 months could have a significant impact on the number of failures. Moreover, CML is a disease of the elderly and very long-term (10+ year) follow-up could yield increased rates of death from other causes. Use of the hypothetical drug candidate would decrease with better long-term efficacy of Tasigna and Sprycel.

- **Off-label treatments and clinical trials not included.** It is common practice for patients with refractory or highly resistant disease to be placed on an off-label agent such as decitabine, a chemotherapy regimen (particularly in blast crisis with rapidly-dividing, chemotherapy-sensitive cells) or into clinical trials with highly variable efficacy and safety. It would be difficult to predict and model the effects of these agents.

- **Compliance not factored in.** It is difficult to measure compliance with TKIs over time and its effect on longer-term outcomes. Just as with other agents aimed at stopping cell proliferation, a suboptimal level of drug caused by non-compliance could select for resistant clones, which then proliferate in the presence of a drug that was formerly effective. This can be particularly problematic in agents that must be taken more than once per day (such as Tasigna) or that have more immediate unpleasant side effects. Factoring in reduced compliance would increase the market for the hypothetical drug candidate, as more patients would develop resistant disease.

- **Trial enrollment could be erratic.** On one hand, a drug aimed at treating the T315I mutation could require relatively few patients in order to garner a regulatory approval, even less than the "favorable development" scenario; on the other hand, it is often difficult to predict how rapidly such a trial can enroll patients. Delays in bringing trial centers online, or a lower-than-expected T315I acquisition rate could reduce the value of the drug candidate by protracting the time to market.

- **Pipeline agents could disrupt the market.** It is difficult to predict which agents will ultimately receive regulatory approval. Pfizer's bosutinib may have activity against certain resistant BCR-ABL mutants, but failed to achieve superiority to Gleevec in its pivotal trial. Ariad's ponatinib showed strong activity against T315I mutant CML in a Phase I trial, even with many patients dosed well below the pivotal trial dose. Deciphera's DCC-2036, which binds to the kinase switch region rather than the ATP-binding domain, is also touted as having activity in T315I resistant disease[85]. If either of these latter two were to show robust efficacy in wildtype and T315I disease, the market for the hypothetical drug candidate would be effectively zero as physicians would rather prescribe one drug with a full spectrum of action.

- **Understanding of cancer biology is evolving.** While CML is a comparatively "well behaved" cancer with one principal disease-causing mutation, signaling pathways in cancer are aberrant compared to normal cells. One thoughtleader mentioned that more sensitive assays of a patient's BCR-ABL activity (by measuring levels of the phosphorylated downstream protein CrkL) would be useful to determine drug effect and direct therapy[86]. If such an assay could more effectively direct therapy, use of the hypothetical drug candidate would decrease as patients can stay on earlier lines of therapy for a longer period of time.

- **Understanding of the biology of resistant mutations in CML is evolving.** It has not been determined whether: 1) resistant mutations are present at the onset of disease but grow at a slower rate than the wildtype disease (and are suppressed by the wildtype) or 2)

only the wildtype is present at baseline, and oncogenes continually mutate and new resistant mutations constantly emerge. In scenario #1, a more sensitive BCR-ABL genotyping assay could determine which drug (or possibly a combination thereof) is most effective and which patients are more likely to develop resistant mutations. These patients could be treated with a combination of Gleevec/Tasigna/Sprycel + hypothetical candidate at 1st-line, which would greatly expand the market. Scenario #2 is more accurately reflected in the model, as it assumes a random chance at each stage that a patient will develop the resistance mutation that the hypothetical candidate covers. The oncologist and patient would need to remain constantly "on guard" for the emergence of resistant disease.

Qualitative findings

I interviewed various stakeholders to confirm the critical dynamics of the CML market that are not yet reflected in the literature, and determine what qualitative factors may come into play in the coming years. Interviews were conducted from October 2010 to March 2011 and included investment analysts, basic scientific researchers, clinical hematologist/oncologists and pharmaceutical company clinical, commercial and regulatory personnel, all with significant experience in the CML disease space. An interview guide was used (and is included in the appendix), but adapted slightly to the expertise of each particular interviewee.

Opinions of pathway inhibitors for cancer

The general stakeholder consensus regarding cancer pathway inhibitors (TKIs or antibodies that target a specific cell signaling pathway) held that they represent an important scientific advance but that research was still in relatively early stages. Certain drugs and pathways were heralded as major advances, particularly Gleevec for CML and Herceptin for HER2-overexpressing breast cancer. Others were promising but require further elucidation, such as EGFR inhibitors for lung and pancreatic tumors which were shown to be highly efficacious in a fraction of the population but much less efficacious in the remainder.

Major hurdles to pathway inhibitor development include the convoluted nature of cancer cell signaling and the adaptability of cancer cells to overcome inhibition. Certain agents have shown strong responses caused by inhibition of the dominant pathway, followed several months later by incurable relapses caused by mutations elsewhere. Interviewees cited the ability of cancer cells to

mutate further downstream in the active pathway and the ability of one pathway to "feed into" another as particularly problematic. Several specific pathways were mentioned as lucrative drug targets in development, especially the anaplastic lymphoma kinase (ALK) pathway and HER3 (ErbB3) signaling pathway.

Interestingly, interviewees were split on the utility of narrow versus broad spectrum pathway inhibitors. Those favoring the former cited differences between the structure and function of related kinases, the potential for side effects from inhibiting off-target kinases and the ability to selectively enrich patients with a certain mutation, while those favoring the latter cited the lack of clarity into which kinases drive tumor growth ("driver" versus "passenger" mutations).

> *"The drugs that work are very good—the trouble is finding drugs that work" – Commercial, large biotech*

> *"Ten years ago, we thought targeted therapy would be the magic bullet. We since learned that cancer cells are so smart at finding ways to overcome inhibition at single steps." – Clinical, large biotech*

> *"Broad-spectrum kinase inhibitors are somewhat more inelegant but have serious activity in some diseases." – Solid tumor oncologist*

> *"A better idea involves combinations of highly targeted drugs. Promiscuous kinase inhibitors have a lot of off-target effects." – Solid tumor oncologist*

Opinions of pathway inhibitors for CML

Interviewees were virtually unanimous that CML represented one of the greatest areas of success for targeted therapy. Both oncologists who treat CML and others focused on other tumor types cited CML as a relatively well-treated cancer—the unique BCR-ABL kinase is not present in normal cells and thus represents a natural target for treatment, the slow-growing nature of CML translates to a lower mutation rate and rate of drug resistance and the TKIs are well tolerated. TKIs have displaced the pre-TKI treatment regimen of interferon-α and Ara-C at all lines of therapy, and patients with chronic phase disease may be expected to survive for many years.

However, there are unmet needs in CML treatment. Oncologists cited TKIs to treat the T315I "gatekeeper" mutation as a major unmet need. Also highly desired is the ability to stop TKI therapy upon achieving a complete molecular response, whether achieved through clinical data showing that it is feasible to stop treatment, or a more sensitive measure of disease activity than levels of BCR-ABL mRNA or positive metaphases.

It is hypothesized that there is a pool of self-renewing leukemic "stem cells" with a different molecular profile than the majority of the tumor, and can continue to generate disease even in the presence of optimal TKI therapy. Several pathways have been implicated in the development of leukemic stem cells, including Wnt/β-catenin and Hedgehog pathways.

> *"Not every cancer is CML. It's relatively simple, with less genetic abnormality than other tumors." – Solid tumor oncologist*

"The guidelines for optimal response were established for imatinib. We assume they hold for the other two drugs but this is not firmly established." – CML oncologist

"We need a more sensitive test for mutations at the time of diagnosis." – R&D, large pharmaceuticals

The CML market

Interviewees agreed that the market for later-line treatment could be meaningful but is small in comparison to that for 1st-line chronic disease, citing the longer duration of response and less rapidly mutating disease. The 2nd-generation TKIs were tested in and approved for later-line treatment, then recently moved into 1st-line chronic disease where they can prevent mutations occurring in the first place. Oncologists interviewed expressed enthusiasm for agents with a broader-spectrum of action that could suppress resistant mutations from ever developing.

There was considerably less enthusiasm for the use of TKIs in later lines of therapy. Oncologists interviewed stated that TKIs could be used to reduce tumor burden as a bridge to HSCT, but were generally not sufficient to control the disease as monotherapy. Chemotherapeutics appropriate to the type of blast crisis, or hydroxyurea, are commonly used to bring down the number of tumor cells in preparation for a transplant.

"There's probably still a meaningful CML market after 1st-line use." – Research analyst

"The younger the patient is, the more years of life she has, the more dependent she will be on a drug that more completely suppresses proliferation. Therefore, we're more likely to use 2nd-generation TKIs in that case." – CML oncologist

"I won't transplant a patient in blast crisis." – CML oncologist

Combination therapy

As many infectious diseases (especially HIV and tuberculosis) are treated with combination therapy to prevent the development of resistant disease, I asked interviewees if they saw an opportunity for combinations of therapies to treat CML. Most interviewees were pessimistic that a combination of the three available TKIs would be beneficial to treat CML, citing overlapping resistance spectrums and a likely antagonistic effect as all bind to the same target. On the other hand, combinations of agents that could hit multiple targets in the same pathway for a synergistic effect could draw physician interest.

However, interviewees were decidedly more bullish on combinations of targeted therapies for solid tumors, citing the hypothesis that tumors with more mutations are less responsive to targeted therapies and would require more inhibition to achieve a meaningful benefit.

"There is no rationale to combine the three TKIs that are available right now—unlike in HIV and TB, they all hit the same target, and the additive toxicity profiles are not encouraging." – CML oncologist

"There is limited data on the use of 2 TKIs. We don't use it much clinically." – CML oncologist

"Cures in cancer result from combination therapy—look at the use of all-trans retinoic acid, ara-C and anthracyclines for acute promyelocytic leukemia." – R&D, large pharmaceuticals

"Someday, we could reach a stage where we can screen tumors for a broad array of mutations and prescribe a cocktail of specific pathway inhibitors. It could be anywhere from three to 10 inhibitors. However, there are some targets—like Ras, where the mutation renders the protein unable to turn itself off, or transcription factors— that are just not druggable." – Solid tumor oncologist

Clinical development

Interviewees generally agreed that successful development of a T315I specific agent could be performed with fewer patients than most CML trials, but that the rarity of the mutation could make trial enrollment difficult. In addition, the scientific uncertainty of whether the T315I mutation is present at baseline (albeit at lower levels than the wildtype BCR-ABL kinase) or emerges later could make it difficult to run a combination therapy trial in 1st-line disease, relegating the trial and the approved label to patients failing a TKI and limiting the upside.

"Key opinion leaders at large academic centers are aware of T315I, but a lot of community oncologists may not be. If I had a T315I-specific agent, I'd talk about a

'broad mutational profile that covers the hardest to treat mutations'" – Commercial, large pharmaceuticals

"You could get a partial approval based on complete cytogenetic response, but the FDA may want full survival for approval. It also may be difficult to show survival in a small trial." – Commercial, large pharmaceuticals

Pricing and reimbursement

With respect to pricing, interviewees believe that the hypothetical drug candidate could command a premium to other marketed TKIs, with responses ranging from 20% to 50% of the price of the highest broad-spectrum agents. Payers are expected to continue to reimburse efficacious agents, particularly in the U.S.

However, there are global trends towards reduced willingness to pay a premium for cancer drugs, and a "per patient" view of costs that could impede combination therapy with expensive agents. For example, a country that caps reimbursement for one CML patient at 50,000 Euros per year would preclude the use of combination therapy.

"For example, the problem isn't paying for Herceptin, but people who aren't HER2-positive getting the drug." — Payer

"In the case of [Drug A], they knew the data wasn't so great and went for last-line therapy at a 10-15% premium. In rare cases you can command a 50% premium." – Commercial, large pharmaceuticals

Discussion and conclusion

Hypothetical candidate is unlikely to be developed

In this instance, it is doubtful that the hypothetical drug candidate for CML will be purposefully developed. The existence of a small and relatively well-treated CML population and the rarity of this particular mutation will severely limit the size of the market and thus the expected NPV and the expedited development process will not adequately compensate for this. There is the additional factor of opportunity cost: a company faced with this question may have several projects more deserving of manpower and effort.

At the start of this work, I thought that a genotype-directed therapy for CML could be a viable clinical development option. Many targeted cancer therapy development programs successfully conceded a large share of the patient population in exchange for premium pricing, expedited development and more robust efficacy. The particular case of a narrow-spectrum T315I CML drug illustrates the limits of this approach, since the mutation is too rare to support a market on its own. It is more likely that this combination therapy approach (T315I BCR-ABL kinase inhibitor in combination with a marketed 1st-line agent) would be used only to salvage a drug candidate that had failed in a broader treatment population.

On the other hand, CML is an atypical cancer—it is rare and well-treated—and so genotype-directed therapies may yet prove profitable in other indications. A more prevalent cancer or specific resistant genotype could represent a commercially viable market, especially if it represents a major treatment advance (in efficacy or safety) over its comparators and patients will stay on drug for a long period of time. As more pathway inhibitors are approved, it is likely

that they will be associated with specific resistance mutations and that some of these will represent clinically and commercially viable drug targets.

Broader applications and extensions of this work

The goal of the model was to systematize available data on drug sales, efficacy and tolerability profiles, and disease biology and epidemiology to come to a relatively rigorous view of the CML market. While I chose CML for several reasons including the availability of data, clearly delineated disease phases, and demonstrated commercial interest, "state-transition" models of the sort that I created could be used to describe patient progress and outcomes for many chronic diseases and have been used for such for some time[87].

Further extensions of the model work could include:

- **Testing implications of how and when resistance mutations become apparent.** Improved mutation detection and the presence of resistance mutation at baseline would permit early treatment to suppress all clones of the disease, improve prognosis, and allow use of the hypothetical candidate in the first line. On the other hand, acquisition of mutations during treatment, or leukemic stem cells that resist TKI therapy would not open up the 1st-line market.
- **Genotype-directed therapy as salvage.** I treated the hypothetical candidate as a drug candidate tailored to a resistant genotype. In this scenario, if the hypothetical candidate would be geared towards 1st-line disease but rather than "succeed or fail" in clinical trials, there could be a third probability that the drug fail in the broader trial population but succeed in in a select genotype (as determined by post hoc analysis and be tested only in

this select population going forward), the drug's value proposition could change significantly.

- **Market effect of a curative therapy.** Much of the value of the CML market results from patients being on TKI therapy for the rest of their lives. If one of the three marketed CML TKIs, or a new agent, could be stopped upon achieving a given efficacy threshold, the market dynamics could change dramatically. The curative therapy could justify greater pricing but sharply curtail duration of therapy.
- **Simulation.** Ability to test for mean and variance of NPV (rather than just an expected NPV) will affect the company's ability to value and "de-risk" the development program.
- **Other tumor types.** Any tumor for which 1) 1st-line targeted therapy delays disease progression for a significant interval and is unlikely to be displaced by the hypothetical agent, 2) resistance is associated with a specific, druggable mutation and 3) long-term data is available could be addressed with a similar model.

The model could be easily applied to other types of cancer, with modifications. Most malignancies would lack the equivalent of a "chronic phase" and be diagnosed only after a significant tumor burden and clonal evolution develops, and patients would start at an "accelerated phase." Tumors with an especially poor prognosis such as advanced non-small-cell lung cancer or pancreatic cancer will show similar survival rates to a CML blast crisis. Similarly, adjuvant treatment could be modeled by an "adjuvant" phase and a risk of relapse or diagnosis of metastasis at a given time point.

Conclusion

The first TKI for CML, Gleevec, not only revolutionized the CML treatment paradigm, but also conjured widespread hope that cancer could be cured or halted with a pill[88]. One interviewee specifically cited Gleevec as one of the foremost examples of academic scientists and pharmaceutical companies collaborating effectively (as contrasted with expensive agents that are hailed as an advance but only confer small therapeutic benefit). This work both advanced the understanding of cancer and transformed the lives of a small but underserved patient population. While better understanding of cancer biology and signaling has tempered the expectation that all cancers could be managed with a single pill, targeted therapies remain one of the most important areas in cancer research.

Just as Gleevec transformed CML from an inexorable disease to a chronic, manageable condition, new markets for resistant disease have similarly transformed CML with certain Gleevec-resistant mutations into a chronic disease. This process of "covering" specific mutations can be expected to continue as long as a reasonable profit may be made in doing so—at some point, the number of patients with important unaddressed BCR-ABL kinase mutations in CML may be too few to proceed with further development. The hypothetical drug candidate tested in the model is one such example.

It is possible that several such markets may evolve at once as inhibitors of other pathways become commercially available for solid tumors, are used simultaneously, and resistance mutations start to develop. This raises the question of how signaling molecules and pathways interact with one another, the exploration of which is still in early stages. As our understanding

of these interactions evolves, the market is likely to change in ways that are difficult to anticipate. This will require increasing collaboration between clinical oncologists, basic scientific researchers, industry and regulators to advance the state of cancer treatment.

Appendix

Interview guides

Investment analysts

1. What stocks in the oncology treatment space do you cover and why did you choose to cover them? How do you (and your clients) view oncology companies focused on tyrosine kinase inhibitors? How has the level of interest changed in recent years?

2. Walk me through your model of CML, and specifically how the drug for refractory/T315I disease fits in. If possible, how do you view the potential use of this drug in chronic phase, accelerated phase, blast crisis, and Ph+ AML? What efficacy (major cytogenetic response for chronic phase, complete hematologic response for later phases)/safety/dosing do you assume in the resistant setting, and how sensitive is your model to each?

3. What could move such a drug into earlier lines of therapy (e.g. ahead of Gleevec/Tasigna/Sprycel)? How costly would such a study be?

4. What other cancer indications could such an agent be useful in? How do you look at these markets?

5. How could you see these agents being used in combination with each other, or other targeted agents?

6. Do you believe it will be possible to make cancer a chronic disease that could be managed with single or combination targeted therapies alone? What are the necessary conditions for this to happen?

Commercial managers

1. In your opinion, have signaling/pathway inhibitors lived up to their promise in treating cancer? Why or why not? How has your opinion of the overall market for these agents (by small molecule, antibody, other) changed over the last 3-5 years?

2. What do you see as the benefits to broad-spectrum multi-pathway inhibition versus more targeted inhibition? How does mechanism of action play into your marketing strategy, particularly in your thoughts on the matter before Phase III data is announced?

3. How do you think about the market opportunity for therapies directed at tumors of a specific genotype in terms of patients, line of treatment, duration, pricing, and resistance mutation profile? Assuming similar efficacy/safety/dosing to currently marketed therapies for a given indication and line (or if none such as for T315I CML, to first line therapy).

4. What are the boundary conditions for #3? (i.e. at what point does the market become too small, the testing too onerous, etc)

5. How would you commercialize a drug for a specific tumor genotype differently from an "all comers" cancer drug? How would a requirement for Bcr-Abl sequencing at regular intervals affect commercialization?

6. What can you tell me about your line extension strategy? How can you see this drug being used as sequential or combination therapy, and are there trials underway (or in process, planning, etc) to achieve this end?

7. Do you believe it will be possible to make cancer a chronic disease that could be managed with single or combination targeted therapies alone (with genotyping/karyotyping/other molecular test to check for resistances, etc)? What are the necessary conditions for this to happen?

Clinical managers

1. In your opinion, have signaling/pathway inhibitors lived up to their promise in treating cancer? Why or why not? How has your opinion of the overall market for these agents (by small molecule, antibody, other) changed over the last 3-5 years?

2. What are the particular challenges of designing a clinical trial for a specific mutant genotype of tumor (e.g. T315I in CML)? How would this influence adaptive design, comparator arms, etc?

3. Do you believe it will be possible to make cancer a chronic disease that could be managed with single or combination targeted therapies alone (with genotyping, karyotyping, or other molecular test to check for resistances)? What are the necessary conditions for this to happen?

4. How would you design a trial meant to achieve this outcome differently? How would the timing of such a trial change? What is the regulatory environment towards such a trial?

5. How would the cost or size of a trial differ from published figures for oncology? What would be the impact of having to develop a diagnostic test?

Researchers

1. What is your opinion on the theory of oncogene addiction? Do you think that it is broadly applicable to many tumor types or not?

2. In your opinion, have signaling/pathway inhibitors lived up to their promise in treating cancer? Why or why not?

3. What do you see as the benefits to broad-spectrum pathway inhibition (similar to Sutent, Nexavar) versus more targeted pathway inhibition?

4. What phase of disease do you believe is best indicative of "cancer" as a whole (in terms of life expectancy, degree of genetic/karyotypic aberration, etc)?

5. How important is resistance spectrum in designing a new therapy? When does a specific mutant become problematic enough to warrant more research towards discovering a treatment?

6. What would be the considerations in designing a combination targeted therapy regimen for cancer? Optimally, what kind of effects could this have? What more do we need to understand about cancer biology to bring this about?

7. What pathways do you see as the most promising or potentially promising? If nothing has been developed to treat it, why is that the case?

8. What do you believe is the most promising general area in early stage cancer research? How close is this to yielding viable clinical/therapeutic options?

9. What are the limitations of current methodologies? What up-and-coming methodologies hold the greatest promise?

Oncologists

1. How should we think about the CML treatment paradigm? How much controversy surrounds the use of (Drug A) in a given setting?

2. What do you consider an adequate response to (Drug A) at a given timepoint?

3. In what percent of patients do you use (Drug A) at a given line of therapy? What other treatments do you use (including HSCT or off-label agents)?

4. What do you use to treat T315I CML or other highly refractory or resistant patients?

5. What sorts of treatments would you like to have available? Do you feel like current treatments are adequate for the majority of patients?

6. What are your opinions on drugs that specifically target resistant populations (such as T315I mutant tumors)? What efficacy/safety/dosing/resistance profile would you need to see?

7. Have you ever used combination therapy of BCR-ABL inhibitors? If so, what was your rationale? If not, why not? Is this a worthwhile approach to prevent escape mutants, or does this remove an option downstream? How would a genotype-specific therapy in general fit into this framework?

8. CML and other hematological malignancies often see some of the earliest breakthroughs in therapy—how representative is CML of other malignancies?

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