A COMPARATIVE EFFECTIVENESS ANALYSIS OF PATIENTS NEWLY INITIATING TYROSINE KINASE INHIBITOR THERAPY FOR CHRONIC MYELOID LEUKEMIA

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ABSTRACT

Melea Ward: A comparative effectiveness analysis of patients newly initiating tyrosine kinase inhibitor therapy for chronic myeloid leukemia
(Under the direction of Susan Blalock)

There are currently three tyrosine kinase inhibitors (TKI) approved for first-line treatment of chronic myeloid leukemia (CML). Historically, imatinib, a first-generation TKI (1GTKI), was the standard of care for patients with CML. Both nilotinib and dasatinab, second-generation TKIs (2GTKI), received FDA approval as first-line options for CML in 2010. This study examined the association between patients newly initiating a 1GTKI compared to a 2GTKI and treatment patterns, adherence, health services utilization and healthcare costs.

A retrospective cohort study of commercial and Medicare patients newly initiating TKI therapy between June 1, 2010 and December 31, 2011 were identified. Patients who were new users, continuously enrolled for 4 months during the baseline period, between the ages of 18 and 89 years old at the index date, and had a diagnosis for CML were included. Risk adjustment methods were used to evaluate time to treatment interruption and regimen change. Multivariate logistic regression was used to investigate the association between TKI therapy and adherence. Generalized linear models were used to examine the association between TKI therapy and (1) health services utilization and (2) healthcare costs during the 12 months follow-up period.

Of the 368 patients newly initiated on TKI therapy, 237 (64%) initiated therapy on 1GTKI. Initiating a 2GTKI was associated with a higher risk of treatment interruption (HR: 1.59, 95% CI 1.18-2.12, unadjusted model; HR: 1.48, 95% CI 1.08-2.02, multivariable model; HR 1.50, 95% CI 1.10-2.04, propensity score quintiles model). Although the majority of patients with a treatment interruption re-initiated the index medication or changed medications, 15% of patients who initiated a 1GTKI and 30%

of patients who initiated a 2GTKI discontinued treatment for the remainder of the study period. There was no association between initiating a 2GTKI versus 1GTKI and regimen change or adherence. Although mean adherence was higher for the 1GTKI cohort compared to the 2GTKI cohort, mean adherence was low in both cohorts (PDC=0.79 and PDC=0.68, respectively, p=0.007). Patients who initiated 2GTKI incurred more inpatient hospitalizations and ER visits compared to 1GTKI. Regression models demonstrated that initiating therapy with a 2GTKI was associated with higher total and TKI-related costs.

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CHAPTER I: INTRODUCTION

1.1 Overview

Chronic myeloid leukemia (CML) accounts for 15% of all leukemias, with a median age at diagnosis of 64 years.[1] In 2013, it was estimated that 5,920 people would be diagnosed with CML and 610 would die from the disease in the United States.[2] CML is classified into three phases (i.e. chronic, accelerated and blast crisis) and is typically diagnosed in the chronic phase.[3] Untreated chronic phase CML typically will evolve into advanced phase disease in 3-5 years.[4]

There are currently three oral oncology agents known as tyrosine kinase inhibitors (TKIs) approved for the first-line treatment of CML: imatinib, dasatinib, and nilotinib.[5-7] Imatinib was approved for the treatment of CML in 2001 and has been the standard of care for newly diagnosed patients. The introduction of this targeted cancer therapy changed CML from a fatal condition to one that can be managed as a chronic illness in many patients. Although this novel agent has been a significant advance in treating CML, it has some limitations. Major limitations of imatinib therapy include toxicity, lack of efficacy, and poor adherence.[8]

Dasatinib and nilotinib are second-generation TKIs, initially approved by the FDA as second-line therapy for patients with CML who are resistant or intolerant to imatinib. With the aim of improving responses achieved with first-line therapy, head-to-head randomized control trials (RCTs) were conducted to compare the second-generation TKIs to imatinib for patients newly diagnosed with chronic phase CML.[9-13] Both nilotinib and dasatinib had superior efficacy over imatinib during the first year of therapy, with higher rates of complete cytogenetic response and major molecular response and similar safety profiles.[9,11] Subsequently, nilotinib received FDA approval as a first-line option for CML in June 2010 and dasatinib received approval in October 2010.

The rationale for initiating a second-generation TKI as first-line therapy is remarkable rates of early responses, excellent event-free survival, and overall survival.[14-16] The counterargument is that approximately two-thirds of patients have an acceptable response to imatinib based on the results of the IRIS study[17] and other reports.[18,19] Regardless of what agent is chosen as first-line therapy, physicians will continue to have to consider adherence as well as cost. Long-term continuous exposure to TKI therapy is required to achieve and maintain favorable treatment outcomes. Specifically, adherence greater than 90% has been correlated with clinical end points that are associated with prolonged survival.[17,20-22]

Cost is another important consideration. The price of a 1-year supply of a first-generation TKI (i.e. imatinib) and a second-generation TKI (i.e. dasatinib, and nilotinib) is between $80,000 to $90,000 and $115,000 to $124,000, respectively.[23] These medications are typically placed in the highest tier, the specialty tier, which requires a 20% co-insurance, placing a large financial burden on the patient. Thus, member cost-share may be an important barrier to medication adherence and persistence that should be considered for treatment with TKI therapy. Cost will continue to be an important health care issue to consider when generic imatinib becomes available in 2015. The expected price differential between generic imatinib and the second-generation TKIs will be considerable ($2,000 to $10,000 vs. >$100,000, respectively).[23]

1.2 Specific Aims

Because there is no consensus on whether to start patients on a first compared to a second-generation TKI therapy as first-line therapy and there is limited ability to generalize RCT evidence to clinical practice, it is critical to use observational data to evaluate the effectiveness of first-generation TKI (i.e. imatinib) versus second-generation TKI (i.e. dasatinib and nilotinib) in patients newly initiating therapy. The proposed study used a comprehensive healthcare administrative database from Humana Inc. which is a national health plan representing over 6 million covered lives with a wide geographic

distribution covering all 50 states. The database includes the most current pharmacy claims, medical claims, and member enrollment data for all commercial fully-insured and Medicare members.

The specific aims of the study are to:

Aim 1: Identify factors associated with newly initiating therapy for CML with a second-generation versus a first-generation TKI.

Aim 2: Examine differences in treatment interruption and regimen change between patients newly initiating a second-generation versus a first-generation TKI.

Aim 3: Determine if adherence is higher among patients newly initiating a second-generation versus a first-generation TKI.

Aim 4: Determine if rates of health services utilization (i.e. number of outpatient physician visits, number of inpatient hospital admissions, length of inpatient hospital stays, and number of emergency room visits) and healthcare costs differ between patients initiating a second-generation versus a first-generation TKI.

Aim 5: Perform exploratory analyses to determine if adherence, health services utilization, and healthcare costs differ between patients newly initiating dasatinib versus nilotinib.

1.3 Significance

Although there have been clinical trials comparing each of the second-generation TKIs to imatinib in the first-line setting, no comparative effectiveness data exist comparing first and second-generation TKIs as first-line therapy using real world data. The results from the proposed study will be used to inform clinicians and payers through a comparative effectiveness analysis.

As survival increases and lifelong treatment is anticipated for the treatment of CML, payers are instituting more restrictive covered and preferred therapies. Payers may consider two strategies moving forward in managing CML treatment. First, payers may consider preferring a second-generation TKI therapy. Recent guidance issued by the National Institute for Health and Clinical Excellence (NICE) recommends imatinib and nilotinib, both made by Novartis, for first-line treatment of CML.[24] Dasatinib,

made by Bristol-Myers Squibb, is not recommended. NICE concluded from indirect comparisons that dasatinib and nilotinib could be considered equally effective in treatment of CML and accepted an undisclosed patient access scheme reducing the cost to approve nilotinib on the formulary in the United Kingdom. NICE guidance is referred to by other countries because of the perceived robust methodology of their review process. In the case of first-line use of TKI therapy for CML, there is not currently robust data to support excluding coverage for dasatinib. However, U.S. payers may consider following a similar strategy as the United Kingdom and prefer imatinib and nilotinib as first-line treatment for CML. Second, payers and oncology clinical pathway partners may consider an imanitib first strategy for patients with chronic phase CML with the availability of generic imatinib in 2015. Developing a pathway involves evaluating efficacy, tolerability, and cost. If agents are considered equally efficacious and tolerable, the least costly agent is preferred.[25]

The proposed study is a first step in evaluating treatment patterns and comparing adherence and outcomes among patients newly initiating first and second-generation TKI therapies for the treatment of CML.

CHAPTER II: LITERATURE REVIEW

2.1 Chronic Myeloid Leukemia: the disease

2.1.1 Overview

Leukemia is a cancer of the bone marrow or blood. CML is one of four major types of leukemia. It is a slow growing leukemia that results from a chromosomal translocation ultimately resulting in an increased clonal population of white blood cells that carry this genetic mutation. CML occurs in all age groups but is typically diagnosed in older adults.[26] Being exposed to high-dose radiation is the only known environmental risk factor.[27] The risk of CML has not been shown to be affected by smoking, diet, exposure to chemicals, or infections. A recent study suggests that CML may occur in at least three different settings: 1) sporadic; 2) genetic heterogeneity with polygenetic and environmental impact; and 3) a familial phenotype following an autosomal dominant inheritance.[28] Most patients do not report symptoms of the disease.[26] CML is typically detected when the patient is being tested for another disease or as part of a routine physical exam.

2.1.2 Epidemiology

2.1.2.1 Incidence

CML is a rare disease.[29] Between 2005-2009, the incidence rate of CML was 1.6 per 100,000 men and women.[30] In 2013, the American Cancer Society estimated that 5,920 people would be diagnosed with CML and 610 would die from the disease in the U.S.[2] The incidence increases with advancing age. There is some evidence suggesting CML occurs with greater frequency in men than women with a male to female incidence ratio ranging from 1.3 to 1.8.[31] The incidence of CML may also vary by race and ethnicity. In a U.S. study, the incidence of CML was lower in individuals of Asian/Pacific Islander ethnicity compared to other races.[32]

2.1.2.2 Prevalence

Little CML specific prevalence data are published because CML is often reported within the broader category of leukemia.[31] Although prevalence information is lacking, it is well accepted that patients with chronic phase CML experience long periods of disease remission on current therapies, increasing disease prevalence. Huang et al. estimated the prevalence of CML in the U.S. was 70,000 cases in 2010 and will increase to 112,000 in 2020 and 181,000 cases in 2050.[33]

2.1.2.3 Survival Outcomes

2.1.2.3.1 Definitions

There are several different survival measures assessed and reported for cancer patients. Overall survival refers to the proportion of cancer patients who survive during a specific time period beginning at the time of diagnosis (e.g. five-year period). Relative survival measures the ratio of the proportion of observed survivors in a cohort of cancer patients to the proportion of expected survivors in a comparable set of cancer-free individuals, matched on age, gender, race but not region or exposure.[30] For young persons, observed and relative survival are typically similar. However, for older persons, due to competing causes of death, relative survival rates are higher than observed survival rates. Progression-free survival (PFS) for CML has been defined as the time that elapses before a doubling of the white blood cell count to more than $20x10^9$ per liter in the absence of complete hematologic response; a loss of complete hematologic response; an increase in Philadelphia positive bone marrow metaphases to more than 35%; progression to accelerated or blast-crisis phase CML; or death from any cause.[34]

2.1.2.3.2 Overview

When evaluating cancer outcomes, it is important to consider the likely survival among the patients being studied. Imatinib was approved for the treatment of CML over a decade ago. The introduction of this targeted cancer therapy changed CML from a fatal condition to one that can be managed as a chronic illness in many patients. In newly diagnosed patients with CML, overall survival at 3 years for patients initiating therapy with imatinib, dasatinib, and nilotinib have been

above 93%.[13,35] The proposed study will follow patients for up to one year following initiation of TKI therapy. Based on the overall survival data from the clinical trial data, it is unlikely that a more than 5% of patients will die during the follow-up period.

2.1.3 Pathophysiology

In a disease-free individual, hematopoietic stem cells, which are produced in the bone marrow, eventually develop into mature blood cells. A blood stem cell may become a myeloid stem cell or a lymphoid stem cell. Lymphoid stem cells develop into T and B lymphocytes. Myeloid stem cells develop into one of the following three types of mature blood cells[36]:

- Red blood cells that carry oxygen to the tissues of the body
- Platelets that cause blood clots to form and prevent bleeding
- Granulocytes (white blood cells) that have a role in fighting infection and disease

In CML, there is an excess of clonal blood stem cells developing into abnormal granulocytes (referred to as leukemic cells).[36] These leukemic cells do not become healthy white blood cells. Instead they build up in the blood and bone marrow, leaving less room for the development of healthy white blood cells (WBCs), red blood cells, and platelets.

The buildup of leukemic cells is the result of an abnormal gene mutation causing activation of pathways that lead to increased cellular proliferation, or too many stem cells that develop into leukemic WBCs. In 95% of CML cases, patients acquire a gene mutation known as the Philadelphia chromosome and 5% have an alternative abnormal chromosomal arrangement where the Philadelphia chromosome is undetectable.[37-39] The Philadelphia chromosome is the product of reciprocal translocation (t[9;22]) that fuses the breakpoint cluster region (BCR) gene on chromosome 22 at band q11 and the Abelson murine leukemia (ABL) gene located on chromosome 9 at band q34 (t[9;22][q34;q11]), resulting in the creation of the fusion protein *BCR-ABL*.[40] Specifically, the *BCR-ABL* fusion protein contains an active tyrosine kinase region of ABL that deregulates cell growth, motility, angiogenesis, and apoptosis, leading to the development of leukemia.[41]

2.1.4 Diagnosis and staging

2.1.4.1 Diagnosis

The diagnosis of CML can be accomplished through peripheral blood. An elevated white blood cell (WBC) count with left shift (i.e. increase in the number of immature WBCs) and an enlarged spleen is suggestive of CML. In all patients with suspected CML, the initial work-up for CML consists of a bone marrow aspiration with differential count and cytogenetic analysis as well as fluorescence in situ hybridization (FISH) and polymerase chain reaction (PCR).[42] Table 2.1 describes the tests used to confirm CML diagnosis. The Philadelphia chromosome is undetectable in 5% of patients and diagnosis relies on the defection of the *BCR-ABL* fusion protein. FISH and PCR are used to detect the *BCR-ABL* fusion gene in the blood or bone marrow (preferred). PCR has the same role as FISH but quantifies the number of *BCR-ABL* transcripts. Bone marrow aspiration and cytogenetic analysis are necessary to assess staging. Additionally, cytogenetic examination is used to assess whether additional chromosomal abnormalities exist besides the Philadelphia chromosome.

Table 2.1 Tests used to Diagnose and Monitor CML

Test	Specimen Used	Purpose	Related CML Endpoint
Standard cytogenetics	Bone marrow	Detection of the Philadelphia chromosome and other abnormal chromosomal arrangements	Cytogenetic
FISH	Blood or bone marrow	Detects BCR-ABL gene	Cytogenetic
RT-PCR	Blood or bone marrow	Detects and quantifies levels of BCR-ABL transcripts	Molecular

BCR-ABL=breakpoint cluster region-Abelson murine leukemia; FISH=fluorescence in situ hybridization; RT-PCR=reverse transcriptase polymerase chain reaction
Source: National Comprehensive Cancer Network (NCCN) v3.2013

2.1.4.2 Staging

CML occurs in three phases: chronic (CP), accelerated (AP), and blast crisis (BC). The stage reflects the severity of the disease. The percentage of blast cells in the blood and bone marrow determine the phase of disease[36] (Figure 2.1). Approximately 90% of patients diagnosed with CML are diagnosed in the chronic phase by routine blood tests. Clinical presentation of symptomatic

disease includes fatigue, unexplained weight loss, night sweats, fever, splenomegaly, and bleeding.[43] In 45% of cases, CML presents asymptomatically.[44] Treatment improves WBC counts, chronic phase symptoms resolve, and patients are able to return to their usual activities. Untreated CP-CML typically leads to advanced terminal blastic phase in 3 to 6 years with signs and symptoms similar to acute leukemia.[4]

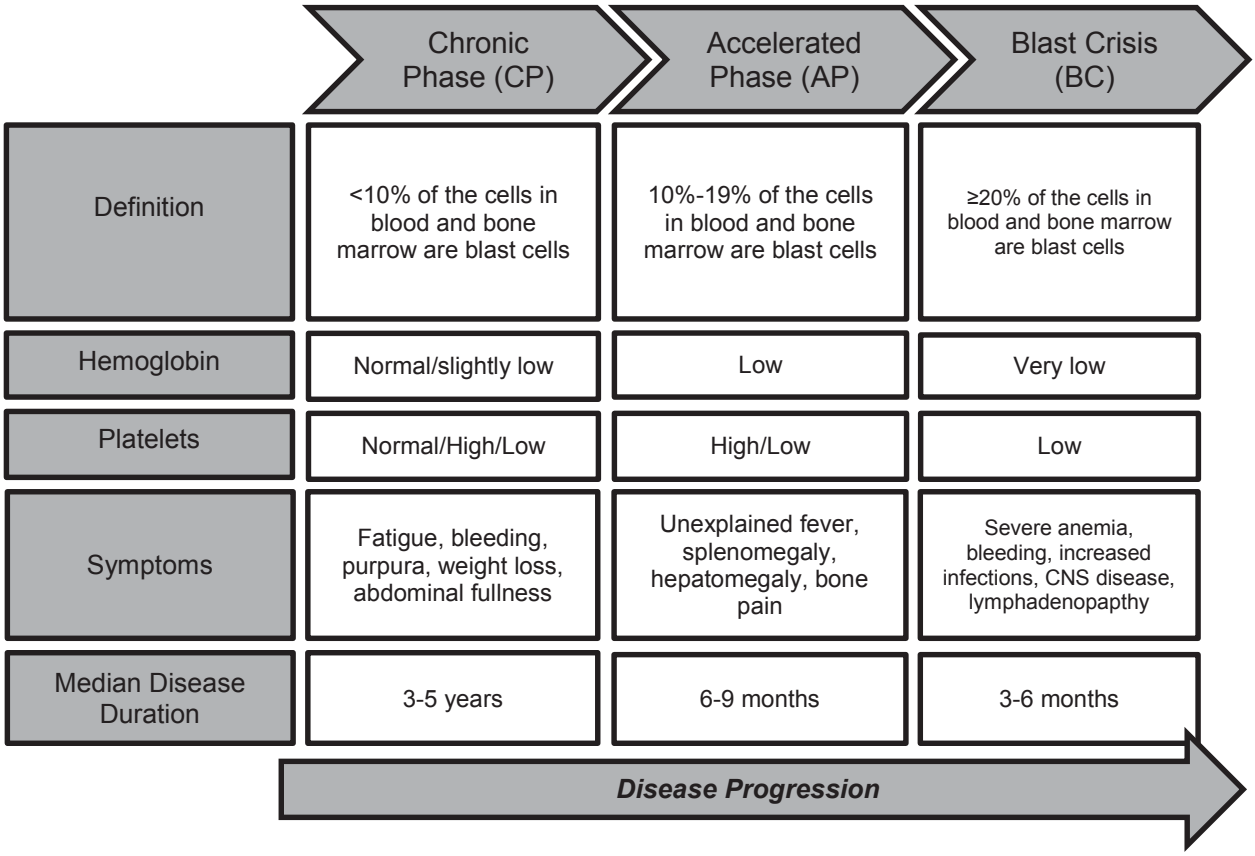

Figure 2.1 Clinical Course of Untreated CML

Note: Median duration of disease assumes the patient is left untreated
Source: Frazer et al., 2007[45]

2.1.5 Clinical Endpoints

Management of CML involves periodic disease monitoring to assess response to therapy and detection of early relapse. Three different types of responses in CML are monitored: hematologic,

cytogenetic, and molecular. Each type of response is outlined in detail in Table 2.2. Early achievement of deeper molecular and cytogenetic responses confers a favorable long-term outcome.[42] Additionally, an accepted goal of CML therapy is to achieve complete cytogenetic response (CCyR), which means no Philadelphia positive cells can be detected, within 18 months after initiating therapy.[46]

2.1.5.1 Hematologic Response

A complete hematologic response is a return of blood cells to normal levels and a disappearance of blast cells and other immature cells in peripheral blood.

2.1.5.2 Cytogenetic Response

Although a CCyR means that Philadelphia positive cells can no longer be detected, patients who achieve CCyR may still carry as many as 10^9 leukemic cells.[47] Cytogenetic response is an independent prognostic factor for improved survival and has become a therapeutic target for clinical studies.[43] Jabbour et al. reported that achievement of early CCyR is a major surrogate endpoint in patients newly diagnosed with chronic phase CML that correlates with survival improvement regardless of TKI.[48]

2.1.5.3 Molecular Response

Although the majority of patients treated with TKI therapy will achieve CCyR, a smaller proportion of patients go on to achieve complete molecular response (CMR). CMR indicates there is no detectable *BCR-ABL* mRNA. Major molecular response (MMR) indicates there is at least a 3-log reduction in *BCR-ABL* mRNA which is assessed based on the standardized baseline and not a reduction from the actual individual patient's baseline level. MMR is associated with long-term remission rates and progression-free survival (PFS). In the 5-year follow-up IRIS study, patients who achieved CCyR and MMR at 12 months did not progress to accelerated or blast crisis.[22] Additionally, molecular responses also predict the duration of CCyR.[49-52] In the 7-year follow-up IRIS study, the probability of loss of cytogenetic remission by 7 years was 3% among patients achieving MMR at 18

months compared to 26% for patients who achieved CCyR but not MMR ($p<0.001$).[49] Additionally, patients with stable MMR have a lower probability of loss of cytogenetic remission compared to unstable MMR or not achieving MMR.[51,52]

Table 2.2 National Comprehensive Cancer Network (NCCN) Response Criteria

Response Type	Degree of Response	Definitions
Hematologic	Complete	• Complete normalization of peripheral blood counts with leukocyte count < 10 x 10^9/L • Platelet count < 450 x 10^9/L • No immature cells, such as myelocytes, promyelocytes, or blasts, in peripheral blood • No signs and symptoms of disease with disappearance of palpable splenomegaly
Cytogenetic	Minor	> 35% Ph+ metaphases
	Major	0%-35% Ph+ metaphases (complete + partial)
	Partial	1%-35% Ph+ metaphases
	Complete	No Ph+ metaphases
Molecular	Major	≥3-log reduction in International Scale of BCR-ABL mRNA
	Complete	No detectable BCR-ABL mRNA by QPCR (International Scale) using an assay with a sensitivity of at least 4.5 logs below standardized baseline

BCR-ABL=breakpoint cluster region-Abelson murine leukemia; mRNA=messenger RNA; Ph+=Philadelphia chromosome-positive; QPRC=quantitative reverse transcriptase polymerase chain reaction
Source: NCCN v3.2013

2.1.6 Risk classification

Prognostic scores are used to stratify patients into risk groups based on age, spleen size, and blood cell counts. The prognostic classification systems proposed by Sokal and Hasford are used to calculate the risk of progression and death based on baseline characteristics, without consideration for treatment response.[53,54] The calculations are used to categorize patients as low, intermediate, and high risk (Table 2.3). The Sokal score predicts the likelihood of achieving CCyR at 2 years as follows: low-risk patients 91%, intermediate-risk patients 84%, and high-risk patients 69%.[55]

Table 2.3 Risk Calculations in CML

Classification System	Calculations	Risk Definition
Sokal	Exp 0.0116 x (age in years – 43.4) + 0.0345 x (spleen - 7.51) + x [(platelet count ÷ 700)^2 – 0.563] + 0.0887 x (blast cells – 2.10)	Low: < 0.8 Intermediate: 0.8-1.2 High: > 1.2
Hasford	0.666 when age ≥ 50 years + (0.042 x spleen) + 1.0956 when platelet count > 1,500 x 10^9/L + (0.0584 x blast cells) + 0.20399 when	Low: ≤ 780 Intermediate: 781-1,480 High: > 1,480

	basophils > 3% + (0.0413 x eosinophils) x 100

CML=chronic myelogenous leukemia
Note: For the equations, age is measured in years; spleen in centimeters below the costal margin; and blast cells, eosinophils, and basophils are in percents of peripheral blood differential. All factors must be collected before any treatment.
Source: National Comprehensive Cancer Network (NCCN) v3.2013

2.2 Current Approaches to Treatment

2.2.1 First-Line Therapy

2.2.1.1 Overview

There are currently three oral oncology agents known as tyrosine kinase inhibitors (TKIs) approved for the first-line treatment of CML, imatinib, dasatinib, and nilotinib (Table 2.4). In the United States, imatinib was approved for the treatment of chronic phase CML in 2002. The introduction of this targeted cancer therapy changed CML from a fatal condition to one that can be managed as a chronic illness. Although this novel agent was a significant advance in treating CML, it has some limitations, including toxicity, lack of efficacy and poor adherence.[8] Specifically, one-third of newly diagnosed CP-CML patients treated with imatinib had inadequate responses or did not experience long-term benefit in an intention-to-treat analysis.[18]

Two second-generation TKIs, dasatinib and nilotinib, were initially approved by the FDA as second-line agents for patients with CML who fail imatinib. With the aim of improving responses achieved with first-line therapy, head-to-head RCTs were conducted to compare the second-generation TKIs to imatinib for patients newly diagnosed with CP-CML.[9-13] Both nilotinib and dasatinib had superior efficacy over imatinib during the first year of therapy with higher rates of complete cytogenetic response (CCyR) and major molecular response (MMR) rate and similar safety profiles.[9,11] Subsequently, nilotinib received FDA approval as a first-line option for CP-CML in June 2010 and dasatinib received approval in October 2010. These recent changes have been reflected in *National Comprehensive Cancer Network (NCCN) Guidelines for Chronic Myelogenous Leukemia,* which has changed the landscape for treating newly diagnosed patients with CML.[56] The pivotal

trials for imatinib, dasatinib, and nilotinib in the first-line setting are described below and compared in Table 2.5.

Table 2.4 First-line treatment for CML

Current TKI Therapies	Description	Dose
	First-generation TKI	
Gleevec (imatinib)[5]	FDA approved for: Newly diagnosed Ph+ CP-CML Ph+ CML in CP, AP, BC after failure of interferon-alpha	CP: 400 mg once daily AP or BC: 600 mg one daily or 400 mg twice daily
	Second-generation TKIs	
Sprycel (dasatinib)[6]	FDA approved for: Newly diagnosed Ph+ CP-CML Ph+ CML in CP, AP, or BP, with resistance or intolerance to prior therapy, including imatinib	CP: 100 mg once daily AP or BP: 140 mg once daily
Tasigna (nilotinib)[7]	FDA approved for: Newly diagnosed Ph+ CP-CML Ph+ CML in CP or AP, resistant or intolerant to prior therapy that included imatinib	CP: 300 mg twice daily Resistant CP or BP: 400 mg twice daily

AP=accelerated phase; BC=blast crisis; BP=blast phase; CP=chronic phase; Ph+=Philadelphia chromosome-positive
Sources: FDA prescribing information

2.2.1.2 Imatinib, dasatinib, and nilotinib: pivotal trials

International Randomized Study of Interferon and STI571 (IRIS) trial

Imatinib has been the recommended first-line treatment for newly diagnosed chronic phase CML patients following FDA approval in 2002. Results from the multicenter, phase III study International Randomized Study of Interferon and STI571 (IRIS) trial established imatinib as the standard of care.[57] Patients were randomized to receive imatinb (400 mg daily) (n=553) or the previous standard of care, interferon-alfa plus low-dose cytarabine (control) (n=553). Crossover to alternative group was allowed for treatment failure or intolerance. The rates of major cytogenetic response (MCyR) at 18 months were 87.1% in the imatinib group compared to 34.7% in the control ($p<0.001$). The rates of CCyR were 76.2% in the imatinib group compared to 14.5% in the control. Imatinib was better tolerated compared to interferon-alpha plus cytarabine. Longer-term follow-up data is available from the IRIS trial.[17,22] At 5 year follow-up for patients receiving imatinib, Kaplan-Meier estimates of best rates of CCyR were 69% by 12 months and 87% by 60 months.[22] The 5 year

overall survival (OS) for patients receiving imatinib was 89%. Patients who reached CCyR or MMR had a significantly lower risk of disease progression compared to patients not achieving CCyR.

Dasatinib versus imatinib study in treatment-naïve CML (DASISION) trial

The safety and efficacy of dasatinib (100 mg daily) and imatinib (400 mg daily) in patients newly diagnosed with CP-CML were compared in a multinational study.[9] There were 259 patients randomized to the dasatinib arm and 260 patients in the imatinib arm. By 12 months of follow-up, the rates of confirmed CCyR and MMR were higher in the dasatinib arm compared to the imatinib arm (CCyR: 77% vs. 66%, p=0.007; MMR: 46% vs. 28%, p<0.0001), respectively. In addition, responses were achieved in a shorter time in patients receiving dasatinib compared to imatinib. The rate of CCyR at 3, 6, and 9 months were 54%, 73%, and 78%, respectively for the dasatinib group and 31%, 59%, and 67%, respectively for the imatinib group. The 2 year follow-up data from DASISION confirms faster and deeper responses with dasatinib compared to imatinib.[10] The median time to achieve CCyR and MMR were shorter for dasatinib than for imatinib (CCyR: 3 months vs. 6 months; MMR: 15 vs. 36 months), respectively.

Evaluating nilotinib efficacy and safety in clinical trials-newly diagnosed patients (ENESTnd) trial

In the phase III multicenter trial, patients newly diagnosed with CP-CML were randomized to receive nilotinib (300 mg or 400 mg twice daily) or imatinib (400 mg daily).[11-13] The primary endpoint was rate of MMR and the secondary endpoint was CCyR at 12 months.[11] The MMR and CCyR rates were significantly higher in nilotinib groups compared to imatinib at both 12 and 24 months.[11,12]

Table 2.5. Comparison of pivotal trials for first-line TKI therapy in patients newly diagnosed with CP-CML

	IRIS[57]		DASISION[9,10]		ENESTnd[11,12]	
Intervention	Imatinib 400 mg daily or interferon-alfa plus low-dose cytarabine		Dasatinib 100 mg daily or imatinib 400 mg daily		Nilotinib 300 mg or 400 mg twice daily or imatinib 400 mg daily	
Study Design	Multicenter, open-label, randomized, controlled phase 3 study		Multicenter, international, open-label, randomized phase 3 study		Multicenter, open-label, randomized phase 3 study	
Patient Population	N=1,106 patients newly diagnosed with CP-CML (imatinib, n=553; combination therapy, n=553)		N=519 patients newly diagnosed with CP-CML (dasatinib, n=259; imatinib, n=260)		N=846 patients newly diagnosed with CP-CML (nilotinib 300 mg, n=282; nilotinib 400 mg, n=281; imatinib, n=283)	
Primary End Point	Progression defined as death from any cause during treatment, development of AP-CML or BP-CML, loss of CHR, loss of MCyR, or increasing white counts		Confirmed CCyR by 12 months after initiation of therapy		MMR at 12 months	
Secondary End Point	• CHR • MCyR • Partial CyR		• MMR at any time • Time to CCyR and MMR • Duration of PFS and OS		• MMR by 24 months • CCyR • Time to MMR and CCyR	
Follow-up data available to date	8 years[17]		24-months[10]		3 years[13]	
Results						
Primary End Point	At 12 months, PFS was higher with imatinib than combined therapy (96.6% vs. 79.9, p<0.001), respectively		Confirmed CCyR was higher with dasatinib than imatinib (77% vs. 66%, p=0.007, respectively)		MMR was higher in patients receiving nilotinib 300 mg (44%) or 400 mg (43%) compared to those receiving imatinib (22%) (p<0.001 for both comparisons)	
Sustained Response	18 Months		24 months		24 months	
	Imatinib	**Interferon-alfa**	**Dasatinib**	**Imatinib**	**Nilotinib 300 mg and 400 mg**	**Imatinib**
CCyR, %	76.2	14.5	86	82	87, 85	77
MMR, %	NR	NR	64	46	71, 67	44
PFS, %	92.1	73.5	93.7	92.1	98, 97.7	95.2
Transformation to AP or BP, %	NR	NR	2.3	5.0	0.7, 1.1	4.2

AP=accelerated phase; BC=blast crisis; BP=blast phase; CHR=complete hematologic response; CP=chronic phase; CyR=cytogenetic response MCyR=major cytogenetic response; MMR=major molecular response; OS=overall survival; PFS=progression-free survival; NR, not reported
Clinical trial acronyms: IRIS, International Randomized Study of Interferon and STI571 (IRIS) trial; DASISION, Dasatinib versus imatinib study in treatment-naïve CML; ENESTnd, Evaluating nilotinib efficacy and safety in clinical trials-newly diagnosed patient

2.2.2 Second-line therapy

2.2.2.1 Overview

Approximately 50% of patients who develop resistance to imatinib will respond to a second-generation TKI.[58] Both dasatinib and nilotinib are approved as second-line therapies to treat CML patients who are resistant or intolerant to imatinib. Additionally, bosutinib was FDA approved in September 2012 for adult patients with CP, AP, or BP CML with resistance or intolerance to prior therapy.[59] Table 6 summarizes design, endpoints, and results for the pivotal second-line studies. Studies of nilotinib and bosutinib in the second-line setting used single-arm designs. The dasatinib study was a phase 3 dose-optimization and schedule-optimization study that investigated the effect of changing the recommended dose for chronic phase CML patients from 70 mg twice daily to 100 mg once daily.[60]

2.2.2.2 Dasatinib

Dasatinib has shown efficacy in patients with CML who are resistant or intolerant of imatinib in a series of phase II studies [SRC/ABL tyrosine kinase inhibition activity: research trials of dasatinib (START)]. In a dose optimizing study, imatinib-resistant and imatinib-intolerant patients achieved similar MCyR across all treatment arms.[60] Additionally, dasatinib produced similar CHR, MCyR, and CCyR rates across all treatment arms. Only the efficacy results for 100 mg once daily are provided in Table 2.6 as that is the recommended starting dose.

Table 2.6. Studies for second-line TKI therapy for the treatment of CML

	Dasatinib[60,61]	Nilotinib[58,62]	Bosutinib[63]
Intervention	Dasatinib 100 mg daily, 50 mg twice daily, 140 mg daily, or 70 mg daily (efficacy provided for 100 mg group only)	Nilotinib 400 mg twice daily	Bosutinib 500 mg daily
Study Design	Randomized, international, multicenter, open-label phase 3 dose-optimization and schedule-optimization study	Single-arm, open-label phase 2 study	Single-arm, open-label, phase 1/2 study
Patient Population	N=670 patients with CP-CML with resistance, intolerance, or suboptimal response to imatinib (100 mg daily, n=167; 70 mg twice daily, n=168; 140 mg daily, n=167; 50 mg twice daily, n=168)	N=321 patients with imatinib-resistant (n=226) or imatinib-intolerant (n=95) CP-CML	N=266 patients evaluated for efficacy with imatinib-resistant (n=186) or imatinib-intolerant (n=80)
Primary End Point	MCyR at 24 weeks in patients with imatinib-resistance	MCyR	MCyR at 24 weeks in patients with imatinib-resistance
Secondary End Point	• MCyR in patients with imatinib intolerance • CHR • Time and duration of MCyR and CHR • PFS and OS	• Time and duration of MCyR • Time and duration of CHR • PFS and OS	• Time and duration of MCyR • Time and duration of CHR • PFS and OS
Follow-up data available to date	2 year[61]	24-month minimum follow-up[62]	24-month follow-up
		Results	
Primary End Point	59% of patients achieved MCyR at 24 weeks	48% of patients achieved MCyR at 24 weeks	31% of patients achieved MCyR at 24 weeks
Sustained Response	24 months	24 months	24.2 months
MCyR (CCyR)	63% (50%)	59% (44%)	53% (41%)
Transformation to AP or BP	3%	3.1%	3.8%
OS	91%	87%	92%

CHR=complete hematologic response; CP=chronic phase; MCyR=major cytogenetic response; OS=overall survival; PFS=progression-free survival; Note: Cross trial comparisons pose challenges due to differences in study population and study design.

2.2.2.3 Nilotinib

The safety and efficacy of nilotinib was evaluated in a Phase II trial in imatinib resistant or intolerant CP and AP-CML patients.[58,62] Nilotinib was administered to 321 patients who were imatinib resistant (70%) or intolerant (30%) with a primary endpoint of rate of MCyR.[58] Overall, 59% of patients achieved MCyR at 24 months follow-up. Additionally, 44% achieved CCyR and the OS was 87%.

2.2.2.4 Bosutinib

The safety and efficacy of bosutinib used as a second-line therapy was evaluated in 288 patients with CP imatinib-resistant (69%) or imatinib-intolerant (31%) CML.[64] At 24 weeks, the primary end point of MCyR was achieved by 31%. After a median of 24.2 months of follow-up, 86% of patients achieved CHR, 53% had a MCyR, and 64% of those achieving CCyR had a MMR. Additionally, at 2 years, PFS was 70% and overall survival was 92%. Bosutinib had an overall acceptable safety profile with a notable increased incidence of diarrhea with 82% of patients experiencing any grade and 8% grade 3/4 diarrhea. Approximately, 21% of patients discontinued treatment due to adverse events.

2.2.3 Safety

2.2.3.1 Overview

The choice of first-line therapy depends on disease risk score, physician's experience, patient age, ability to tolerate therapy, and the presence of comorbid conditions.[46] The information presented below includes a high level overview of agent specific toxicities. The specific toxicities mentioned are included as they may be a factor influencing treatment decision. For example, if a physician is choosing to initiate a second-generation TKI therapy, nilotinib may be preferred over dasatinib for patients at risk of developing pleural effusions based on toxicity profile.[46]

2.2.3.2 Imatinib

Imatinib is generally well tolerated. The most often reported adverse reactions include gastrointestinal toxicity such as mild nausea and diarrhea, edema, rash, and musculoskeletal complaints. Frequently reported grade 3 or 4 toxicities include neutropenia and thrombocytopenia.[46] Erythropoietin and filgrastim have been used and shown effective in patients with imatinib-induced anemia and neutropenia[65,66] but are not supported by guidelines from the FDA and Centers for Medicare and Medicaid Services (CMS).[46] A recent study reported cardiotoxicity and congestive heart failure (CHF) among 10 patients with longer-term use of imatinib. Another study found that of 1,276 patients treated with imatinib, 22 patients (1.7%) developed CHF during treatment.[67,68]

2.2.3.3 Dasatinib

The most common reported adverse reactions reported in at least 10% of patients newly diagnosed with chronic phase CML include myelosuppression, fluid retention, diarrhea, headache, musculoskeletal pain, and rash. These adverse reactions as well as dyspnea and hemorrhage occur in greater frequency (≥20%) in patients with resistance or intolerance to prior imatinib therapy.[6] Quintas-Cardama et al. studied risk factors associated with dasatinib therapy after failure of imatinib.[69] Among 138 patients treated with dasatinib, 35% developed pleural effusion. Patients with a cardiac history, hypertension, receiving twice daily dosing with 70 mg are at increased risk of developing pleural effusion. Pleural effusion led to dose interruption in 83% of patients and dose reduction in 71% of patients. Management of pleural effusion includes treatment with diuretics, dose interruption, and a short course of steroids (3 days) for patients with significant symptoms.[46] After symptoms resolve, guidelines recommend that the dose should be reduced.

2.2.3.4 Nilotinib

The most commonly reported non-hematologic adverse reactions (≥10%) were rash, pruritus, headache, nausea, fatigue, myalgia, arthralgia, pyrexia, nasopharyngitis,upper respiratory tract infection, back pain, cough, asthenia, and gastrointestinal (constipation, diarrhea, abdominal pain, vomiting). Nilotinib has a black box warning for QT prolongation and sudden deaths.[7] Nilotinib

prolongs the QT interval and electrocardiograms (ECGs) should be obtained at baseline, seven days after initiation, and periodically thereafter. In clinical trials, the maximum mean QTcF change from baseline at steady state was 10 msec. Increase in QTcF > 60 msec from baseline was observed in 4.1% of the patients and QTcF of >500 msec was observed in 4 patients (<1%).[7] Nilotinib doses should be held in cases where ECGs have a QTc > 480 msec. Nilotinib should not be used in patients with hypokalemia, hypomagnesemia, or long QT syndrome. Drugs known to prolong the QT interval and strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, ritonavir) should be avoided.

2.3 Treatment Guidelines

2.3.1 First-line treatment for patients newly diagnosed with CP-CML

The National Comprehensive Cancer Network (NCCN) is a not-for-profit alliance of 21 U.S. National Cancer Institute-designated cancer centers working together to improve the quality, effectiveness, and efficiency of cancer care. NCCN guidelines are the most comprehensive and widely used oncology clinical practice guidelines in the world. NCCN guideline recommendations are accepted by the CMS and most private insurance companies.

The *NCCN Guidelines for Chronic Myelogenous Leukemia version 4.2013* recommends treatment with a tyrosine kinase inhibitor (TKI) for newly diagnosed patients with CP-CML.[56] Imatinib (400 mg once daily), nilotinib (300 mg twice daily), and dasatinib (100 mg once daily) have a category 1 recommendation for initial treatment of CML.[56] Category 1 evidence is based upon high-level evidence with uniform NCCN consensus that the intervention is appropriate. High dose imatinib (800 mg) is not currently recommended for patients newly diagnosed with CP-CML. According to the guidelines, data from DASISION[9,10] and ENESTed[11-13] suggest intermediate- and high-risk patients (based on Sokal or Hasford score) may benefit from a second-generation TKI but acknowledge longer-term follow-up is needed to determine whether second-generation TKIs should be used as standard first-line therapy.

2.3.2 Monitoring response to first-line therapy and indications of treatment change

Table 2.7 describes the NCCN's recommendations for monitoring response to first-line TKI therapy with imatinib, dasatinib, or nilotinib and indications of treatment change.[56] Patients not responding to first-line therapy with imatinib should be treated with dasatinib, nilotinib, bosutinib or ponatinib in the second-line setting.[56] Patients not responding to first-line therapy with a second-generation TKI could be treated with an alternate second-generation TKI for second-line therapy. Patients taking second-line TKI therapy with no cytogenetic response at 3 or 6 months should be considered for alternate therapies.[70]

Table 2.7 Recommendations for Follow-up Therapy

Follow-up	Response	Recommendation
3 Months	*BCR-ABL* transcript level ≤10% or PCyR	• Continue same dose of imatinib, dasatinib, or nilotinib
	BCR-ABL transcript level > 10% or less than PCyR	• Switch to alternate 2G-TKI • Evaluate for allogeneic HSCT depending on response to TKI
12 Months	CCyR	• Continue same dose of imatinib, dasatinib, nilotinib, or bosutinib
	PCyR	• Switch to alternate 2G-TKI (preferred) • Continue same dose of dasatinib, nilotinib, or bosutinib • Dose escalation of imatinib to a maximum of 800 mg, as tolerated (if not a candidate for dasatinib, nilotinib, bosutinib, ponatinib, or omacetaxine)
	Minor or no cytogenetic response	• Switch to alternate 2G-TKI (preferred) • Evaluate for allogeneic HSCT depending on response to TKI
	Cytogenetic relapse	• Switch to alternate 2G-TKI (preferred) • Dose escalation of imatinib to a maximum of 800 mg, as tolerated (if not a candidate for dasatinib, nilotinib, bosutinib, ponatinib, or omacetaxine) • Evaluate for allogeneic HSCT depending on response to TKI

18 Months	CCyR	• Continue same dose of TKI
	PCyR or cytogenetic relapse	• Switch to alternate TKI • Evaluate for allogeneic HSCT depending on response to TKI therapy

2G-TKI=second-generation TKI; CCyR=complete cytogenetic response; HSCT=hematopoietic stem cell transplantations; PCyR=partial cytogenetic response
Source: NCCN Guidelines v4.2013

2.3.3 Resistance to treatment

Patients can develop resistance to imatinib, dasatinib, and nilotinib. The mechanisms associated with treatment resistance are complex and will not be discussed in detail. Primary hematologic resistance, defined as a failure to achieve hematologic remission within 3-6 months of initiation, is rare in patients newly diagnosed with CP-CML. However, primary cytogenetic resistance, defined as failure to achieve any level of cytogenetic response at 6 months, MCyR at 12 months or CCyR at 18 months, occurs in 15-25% of patients newly diagnosed with CP-CML.[46] Secondary resistance occurs in patients who have lost a hematologic or cytogenetic response. In the case of secondary resistance, Cortes et al. recommend initiating patients on a different therapy immediately.[42] Delaying a treatment change in patients with secondary resistance causes a decreased probability of PFS.[71]

Although second-generation TKI therapies are associated with significantly lower rates of progression to accelerated phase/blast crisis, patients developing primary or secondary resistance to these agents historically did not have any therapeutic options. A major mechanism of resistance is mutation of the *BCR-ABL* kinase domain. One of the most common mutations in up to 20% of patients with TKI resistance is T315I. Ponatinib became commercially available at the beginning of 2013. It is the only oral TKI therapy with efficacy against the T315I mutation. Reports suggest that T315I mutation is associated with disease progression and poor survival.[72,73]

2.4 Medication Adherence

2.4.1 Overview

Long-term continuous exposure to TKI therapy is required to achieve and maintain favorable treatment outcomes.[17] Therefore, patient adherence, defined as the extent to which a person's lifestyle and/or medication-taking behavior corresponds with agreed upon recommendations from a health care provider,[74] is crucial. Clinical responses to therapy are measured in terms of cytogenetic (presence of Philadelphia chromosome containing cells) and molecular (presence of abnormal *BCR-ABL* genes) response. Evidence suggests adherence can promote major and complete cytogenetic response.[20,75] Similarly, adherence to TKI therapy is a critical factor for achieving major and complete molecular response.[20,75] These clinical parameters have been associated with prolonged overall and progression-free survival in patients with CML.[17,21,22]

There is a wealth of evidence supporting the benefits of adherence to TKI therapy. The following sections describe reported rates of adherence to TKI therapies, factors associated with TKI adherence, and the association of adherence with clinical responses and economic outcomes. To date, most of the literature focuses on imatinib as this was the only TKI therapy indicated for first-line treatment until recently. Since dasatinib and nilotinib received first-line indication for the treatment of patients newly diagnosed with CP-CML, no study has directly compared the three TKI therapies using clinical trial or real world data.

2.4.2 Measurement of adherence to TKI therapy in CML

2.4.2.1 Methods for measuring adherence

Varying rates of adherence to TKI therapy for the treatment of CML have been reported in the literature. Variations in reported rates may be due to variations in the methods used to assess adherence and the operational definitions. The three common methods to measure adherence include: patient self-report, pharmacy refill records, and use of electronic lids. There are limitations to each type of measurement.

Patient self-report relies on the patient's perception of medication-taking behavior and is subject to recall and reporting bias.[76] Pharmacy refill records are based on medication claims which

may not be a true reflection of medication utilization. Additional challenges of using claims data include how to best estimate adherence and determining the most appropriate threshold to define adherence.[77,78] In the CML literature using administrative healthcare databases to assess adherence to TKI therapy, a cut point of 85% is used to define adherence.[79-82] This threshold has been used because it is the midpoint of previous adherence thresholds in cancer research ranging from 80%[83] to 90%.[84] Electronic lids to capture dose and time are considered the gold standard for measuring adherence but electronic devices may not accurately capture when or how much medication was utilized.[85]

2.4.2.2 Adherence reported in prospective studies

The ADAGIO study (adherence assessment with Glivec: indicators and outcomes) examined adherence to imatinib prospectively over a 90-day period in "real practice" among 169 patients.[75] Adherence to imatinib was measured through physician-rated, patient-rated, and pill count. Physicians believed on average 92.8% of patients were adherent to imatinib during the first month after diagnosis and 87.4% remained adherent after 1 year of treatment. Based on a visual analog scale (VAS), patients reported their baseline and 90-day follow-up adherence as 95.3% and 95.7%, respectively. The percentage of imatinib taken compared to imatinib prescribed was 90.9% (range 29%-202%) during the 90-day period. Only 14.2% of patients according to pill count results were perfectly adherent to the prescribed regimen.

Marin et al. prospectively monitored adherence during long-term imatinib treatment among 87 patients using microelectronic monitoring systems (MEMS).[20] Patients were eligible for the study if they had been treated with imatinib for 2 years or longer, were able to tolerate therapy, and were in CCyR at time of enrollment. Median adherence was 97.6% over the 3-month period evaluated, 26.4% of patients had adherence $\leq$ 90%, and 14% of patients had adherence $\leq$ 80%.

2.4.2.3 Adherence reported in retrospective studies

Darkow et al. evaluated medication adherence and treatment interruptions using claims data for commercial, Medicare and Medicaid patients taking imatinib.[84] Treatment interruption was defined as failure to refill imatinib within 30 days from the run-out date of the prior prescription and adherence was measured using a medication possession ratio (MPR), calculated as total days' supply of imatinib divided by 365. Among the 267 patients included, the average MPR was 77.7% over the 12 month follow-up with 31% of patients having a treatment interruption. All patients restarted imatinib within the study period. Wu et al. and St. Charles et al. evaluated adherence to imatinib over a 12 month period using MarketScan Commercial Claims and Encounters database.[79,81] Of the 592 patients included, 59.1% were considered to have a high MPR using a cut point of ≥85% and the mean MPR was 0.79.[79]

Wu et al. evaluated adherence to dasatinib or nilotinib as second-line therapy using two large administrative claims databases, Ingenix and MarketScan Commercial Claims and Encounters Database, with a maximum follow-up of six months.[80] Patients in the dasatinib cohort were less adherent than the nilotinib cohort. The average adherence to dasatinib (n=452) and nilotinib (n=69) was 0.69 and 0.79 (p=0.007), respectively. In another retrospective claims analysis using i3's Rx Lab database, adherence to first-line imatinib and second-line dasatinib and nilotinb was evaluated over a six month period. Average adherence measured using MPR to dasatinib (n=81), nilotinib (n=15) and imatinib (n=449) was 0.75, 0.69, and 0.86, respectively.[82]

2.4.3 Factors Associated with Adherence

Several factors have been identified that are associated with poor adherence to TKI therapy for the treatment of CML. St. Charles et al. identified the following predictors of non-adherence to imatinib: younger age, shorter exposure to imatinib, starting imatinib dose ≤400 mg, longer lag between CML diagnosis to imatinib prescription fill, more concomitant prescriptions, and higher percentage of copayment.[81] Marin et al. identified lower imatinib adherence rates among younger patients, patients with common adverse events (i.e. asthenia, nausea, muscle cramps, and bone or

joint pains), patients taking imatinib independently of meals (a contributor to gastrointestinal tract upset), and unexplained five-fold increases in *BCR-ABL* transcript levels at any time during follow-up.[20]

2.4.4 Adherence and clinical response

The ADIAGO study examined whether treatment response is associated with adherence levels.[75] Pill counts were used to measure adherence, expressed as the percentage of imatinib taken to imatinib prescribed, over a 3-month period.[75] Patients treated with imatinib who had an incomplete cytogenetic response (n=15) had taken on average fewer prescribed doses compared to patients with complete cytogenetic response (n=109) (76% vs. 91%, p=0.004), respectively.

Marin et al. evaluated whether imatinib adherence correlates with degree of molecular response using MEMS.[20] Adherent patients (defined as patients who took >90% of medication as prescribe) had a significantly higher 6-year probability of achieving MMR (95% vs. 28%, respectively; p<0.001) and CMR (44% vs. 0%; p=0.002) compared to non-adherent patients (patients who took ≤90% of medication as prescribed). The probability of achieving these clinical endpoints (i.e. MMR and CMR) is associated with prolonged survival.[17,21,22]

2.4.5 Adherence and Economic Outcomes

Darkow et al. estimated the association between treatment interruptions and non-adherence among patients who newly initiated imatinib and healthcare costs over a 12 month period.[84] MPR was categorized as low (<50%), intermediate (50-89%), high (90-95%) and very high (>95%). Average number of outpatient physician visits ranged from 25.6 visits among patients with very high adherence to 39.1 visits among patients with low adherence. Only a small proportion of patients in the high and very high MPR groups were hospitalized during the year (8% and 7%, respectively), 20% of intermediate MPR patients, and more than half of the patients with low MPR (51%) were hospitalized during follow-up. There was an inverse relationship for total medication costs, with higher costs among patients with lower MPR. The lowest total healthcare costs were reported among

patients with high and very high adherence ($39,236 and $42,250, respectively), followed by patients with intermediate MPR ($54,770), and total healthcare costs were highest among patients with low MPR ($131,357). Wu et al. examined the associated between adherence to imatinib, defined as an MPR ≥ 85%, and direct healthcare costs and resource utilization over a 12 month period.[79] Patients who were more adherent to imatinib therapy had lower resource utilization and overall costs compared to those patients with lower adherence. Regression models indicated a difference of $56,324 in total non-imatinib costs (i.e medical costs plus pharmacy costs with imatinib costs excluded) between the low and high-MPR cohorts ($p<0.001$).

2.5 Summary

Although there is a wealth of evidence supporting the benefits of adherence to imatinib from a clinical, patient, and economic perspective, varying rates of adherence have been reported in the literature. For example, median adherence rates to imatinib, measured over a 3-month period using MEMS, were 97.6% (range 22.6-103.8%),[86] whereas reports of average adherence measured over a one year period using medication possession ratio were 77.7%.[84] Because outcomes associated with these therapies have focused on imatinib,[87] we know relatively little about these issues in relation to dasatinib and nilotinib. Also, in the absence of RCT data, comparative effectiveness data related to the first-line use of imatinib, dasatinib, and nilotinib in patients newly treated with CML will help inform clinicians who now have more treatment options to consider.

The proposed study is a first step in evaluating treatment patterns and comparing adherence and outcomes among patients newly initiating first and second-generation TKI therapies for the treatment of CML. The specific aims of the study are to:

Aim 1: Identify factors associated with newly initiating therapy for CML with a second-generation versus a first-generation TKI.

Aim 2: Examine differences in treatment interruption and regimen change between patients newly initiating a second-generation versus a first-generation TKI.

Aim 3: Determine if adherence is higher among patients newly initiating a second-generation versus a first-generation TKI.

Aim 4: Determine if rates of health services utilization (i.e. number of outpatient physician visits, number of inpatient hospital admissions, length of inpatient hospital stays, and number of emergency room visits) and healthcare costs differ between patients initiating a second-generation versus a first-generation TKI.

Aim 5: Perform exploratory analyses to determine if adherence, health services utilization, and healthcare costs differ between patients newly initiating dasatinib versus nilotinib.

CHAPTER III: CONCEPTUAL FRAMEWORK

This section describes the conceptual framework used to guide the proposed study by discussing the factors that may influence treatment selection, and ultimately impact medication use patterns and healthcare resource utilization and costs. The proposed framework is based on Carpenter and colleagues' conceptual model for examining data for nonexperimental cancer comparative effectiveness research.[88]

3.1 Carpenter and colleagues' conceptual model for examining non-experimental cancer comparative effectiveness research

Randomized controlled trials (RCTs) remain the gold standard in determining the efficacy of new interventions. However, RCTs are not always feasible and often do not adequately reflect patient heterogeneity due to selective inclusion criteria and therefore fall short of informing "real-world" clinical practice. Growing repositories of secondary data collected through registries, electronic health records, and administrative claims databases are being leveraged to fill gaps in knowledge through nonexperimental cancer comparative effectiveness research. Carpenter and colleagues' developed a conceptual model to better inform an evolving framework articulating cancer comparative effectiveness research data needs to be used for clinical and policy decision making (Figure 3.1).[88] This conceptual model was developed by incorporating feedback from over 70 cancer comparative effectiveness researchers. Additionally, the model reflects contemporary cancer care by characterizing cancer as a longitudinal, chronic condition rather than a single acute-care episode. This model also moves beyond the intention-to-treat principle by recognizing the potential for multiples lines of therapy, their interaction, and reciprocal feedback. Although the proposed model was developed to inform future data collection, it was also designed to serve as a template for current researchers.

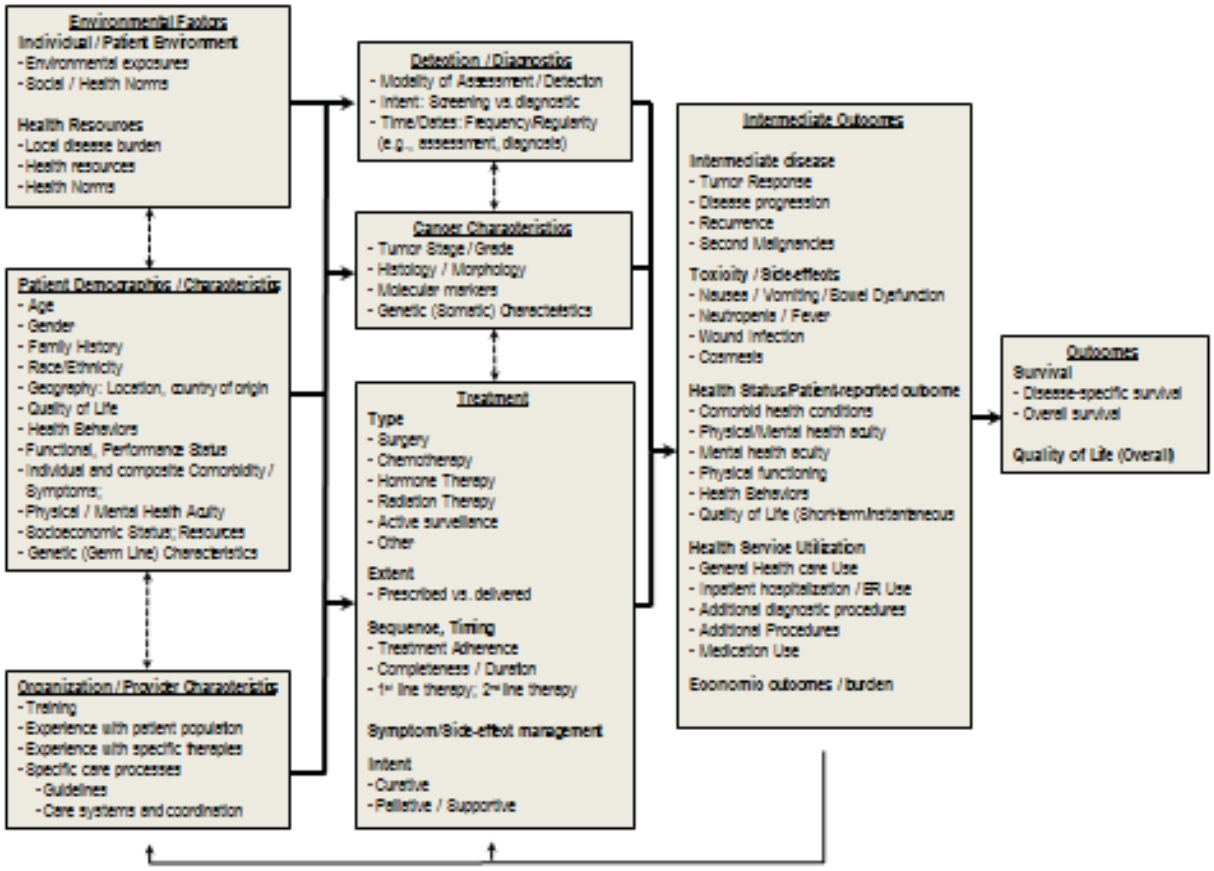

Figure 3.1 Carpenter and colleagues' conceptual model for examining data for nonexperimental cancer comparative effectiveness research
Carpenter WR, Meyer AM, Abernethy AP, Sturmer T, Kosork MR. A framework for understanding cancer comparative effectiveness research data needs, J Clin Epid. 2012;65:1150-1158.[88]

3.2 Proposed Conceptual Framework

Relevant factors influencing TKI use, balanced with information available in the dataset were used to develop a conceptual framework. The conceptual framework for the proposed study is depicted in Figure 3.2. The components from Carpenter and colleagues' conceptual model that guide the conceptual framework in the proposed study include: patient demographic, patient clinical characteristics, provider characteristics, TKI treatment choice, health behaviors, and health outcomes. The model emphasizes the direct associations between factors that predict TKI use and medication

patterns, health services utilization, and costs. Because we do not have detailed information on the interaction of patient and provider characteristics, the relationship is depicted by a dotted line with a double arrowhead rather than a solid line. Although Carpenter and colleagues included reciprocal feedback loops in their model recognizing the potential for multiples lines of therapy in cancer treatment, this study focuses on evaluating first-line treatment for CML. Therefore, reciprocal feedback loops were not included in the conceptual model for this dissertation.

There were six demographic characteristics included in the proposed framework. They include: age, gender, geographic region, type of insurance coverage, low income subsidy, and dual eligibility status. As expected, there were no differences in age between patients randomized to second versus first-generation TKI therapy in the pivotal RCTs for first-line use of nilotinib and dasatinib. [11,22] Currently, it is unknown if differences exist in age between patients who are newly initiated on second compared to first-generation TKI therapy. There is some evidence suggesting CML occurs with greater frequency in men.[31] The majority of patients included in the pivotal trials for imatinib, nilotinib, and dasatinib were male.[9,11,57] Geographic region has become a covariate often included in studies using administrative data in part because of the ability to measure it. Geographic region has not been reported in the CML literature, but geographic variation in prescribing TKI therapies likely exists. Although all the patients in the study are insured, differences in patient demographic characteristics, insurance benefits, and treatment patterns have been reported between Humana patients enrolled in a commercial versus a Medicare plan. For example, a study evaluating patterns of osteoporosis treatment demonstrated that commercial patients tended to be younger and have fewer comorbidities, and higher out-of-pocket expenses for medications.[89] The final demographic characteristics included, LIS status and dual eligibility, are only applicable to Medicare patients. To date, these characteristics have not been reported in the CML literature. However, they are included in the conceptual framework because CML is a disease that affects older adults and therefore the majority of the population was Medicare patients. Patients who have LIS status are

Medicare beneficiaries with income below 150% of poverty and are eligible for cost-share assistance for prescription medications under the Medicare Part D program.[90] LIS beneficiaries tend to have multiple chronic conditions that are controlled by adherence to many medications.[91] Dual eligibility indicates Medicare patients are also covered under Medicaid which covers ancillary services not covered under the Medicare plan. Often these patients have increased disease burden and have different healthcare utilization patterns compared to other Medicare patients.[91]

The four clinical characteristics included in the framework were: phase of disease, comorbidity, medication count, and vaccine use. Patients' starting dose of TKI therapy was assessed and used as a proxy for CML phase at the time of initiation. Long-term comorbidities have been associated with reduced adherence.[92,93] Patient's number of prescribed medications is an indicator of concomitant disease. The association reported in the literature between adherence to TKI therapy and number of medications taken is mixed. Darkow et al. reported lower adherence among patients taking more medications[84] while Noens et al. reported higher adherence among patients taking more concomitant medications.[75] Flu or pneumonia vaccine use was included because patients who are adherent may have a health-seeking tendency and may be more likely to use preventative services.[94]

Four physician characteristics were included: provider age, gender, specialty, and practice type. Provider specialty was included and classified as an oncologist or other. Practice type was classified as academic, private, and other (i.e. community hospitals, clinics, or outpatient cancer care facilities neither owned by the practicing physicians nor considered academic or university-based).[95]

The conceptual framework posits that patient demographic characteristics, patient clinical characteristics, and provider characteristics influence treatment selection. Treatment characteristics, in turn, influence medication use patterns (i.e. adherence, treatment interruption, regimen change).[87] Higher rates of adherence have been reported among patients taking imatinib 400 mg compared to doses of 600 mg and above.[20,75,84] Additionally, studies show adherence to TKI therapy decreases over time which may influence subsequent health outcomes.[81,96] There is evidence to suggest that

adherence to second-generation TKIs is higher compared to imatinib.[96]

Finally, the model suggests that the type of TKI therapy influence patients' use of health care services and the costs associated with these services. In the next section, I describe the methods that were used to examine the relationships hypothesized in this conceptual framework.

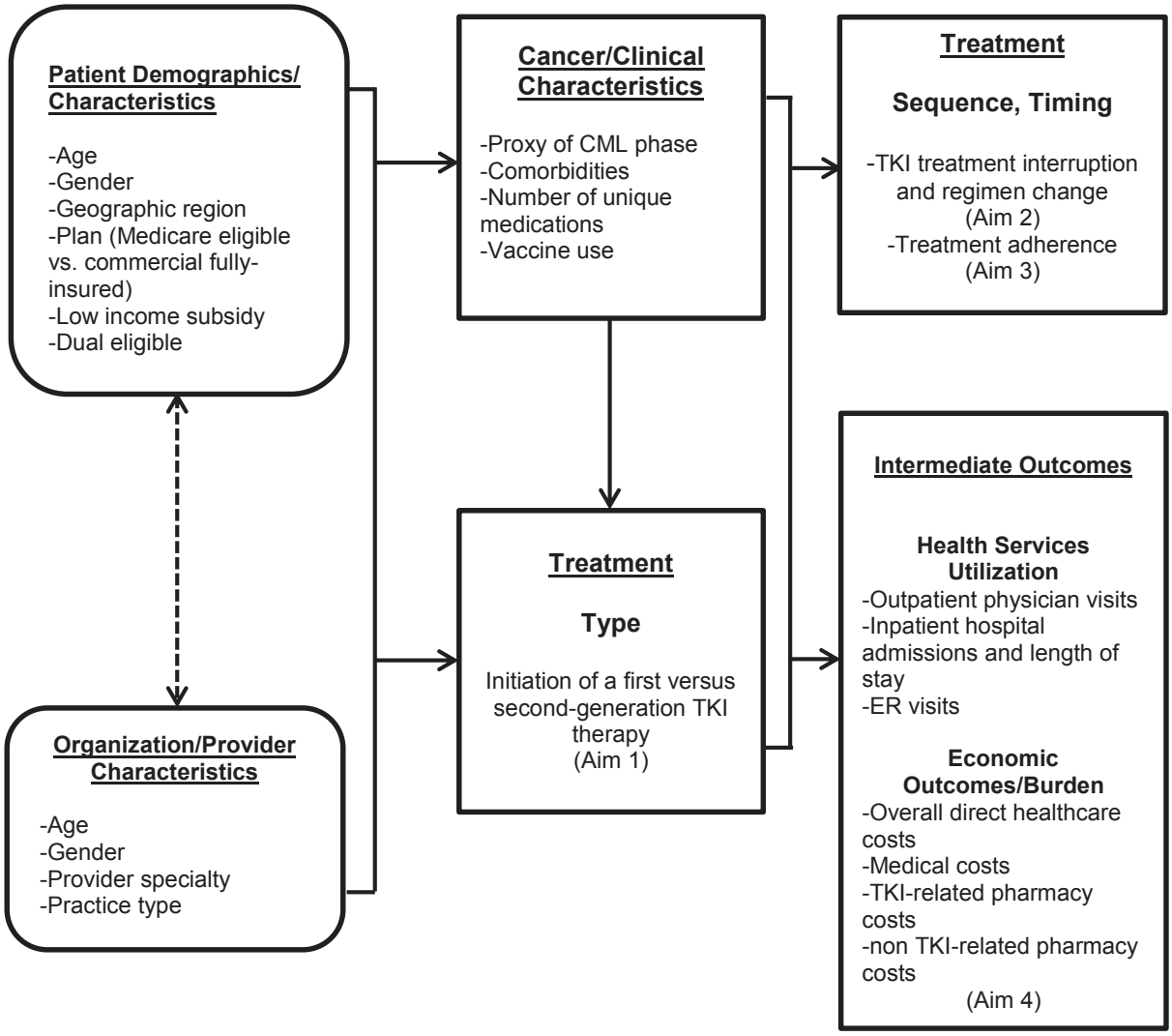

Figure 3.2 Proposed Conceptual Framework

CHAPTER IV: METHODS

4.1 Overview

The aims of this retrospective cohort study are to (1) identify factors associated with newly initiating therapy for CML with a second-generation versus a first-generation TKI; (2) examine differences in treatment interruption and regimen change between patients newly initiating a second-generation versus a first-generation; (3) determine if adherence is higher among patients newly initiating a second-generation versus a first-generation TKI; (4) determine if rates of health services utilization (i.e. number of outpatient physician visits, number of inpatient hospital admissions, length of inpatient hospital stays, and number of emergency room visits) and healthcare costs differ between patients initiating a second-generation versus first-generation TKI; and (5) perform exploratory analysis if adherence, health services utilization, and healthcare costs differ between newly initiating dasatinib versus nilotinib. This section provides a detailed description of the data sources, study design, measurements, and statistical analyses that were used to accomplish each of the specific aims. The University of North Carolina Institutional Review Board determined that the proposed study was exempt from review (Appendix 1).

4.2 Data Source

4.2.1 Overview

Data from a large health benefits carrier (Humana), representing over 6 million covered lives with wide geographic distribution covering all 50 states, was used to conduct a retrospective cohort study. The database used for the study included beneficiaries who were enrolled in a commercial fully-insured plan, a Medicare Advantage Prescription Drug (MAPD) plan, or a Medicare Part D Prescription Drug Plan (PDP). Commercial fully-insured and MAPD members have both medical and outpatient pharmacy coverage through Humana. Medicare PDP members have only Part D

(outpatient pharmacy) coverage and no medical coverage (Medicare Part A, B, or C coverage) through Humana. Table 4.1 summarizes plans offered through Humana and respective coverage.

4.2.2 Commercial fully-insured

Humana provides medical and pharmacy coverage for commercial fully-insured individuals and both large (100+ lives) and small employer groups (2 to 99 lives). The following medical services are covered for commercial fully-insured members: outpatient services (e.g. primary care, preventative care, specialist office visits, urgent care visits, and ER visits if not admitted) and inpatient hospital care (e.g. admitted hospital stay, home health care, skilled nursing facility care, inpatient mental health services or substance abuse services). Prescription drugs are covered under one of six Humana formularies. The majority of commercial members have a drug formulary with a 3 or 4 tier benefit design where patient cost-share for medications increase with increasing tier status.

4.2.3 Medicare

Medicare is a federally funded program that provides health insurance for individuals age 65 and over as well as those under 65 with end-stage renal disease (ESRD) or certain disabilities. Almost all Medicare beneficiaries receive Medicare Part A and Part B benefits. Medicare Part A provides coverage for inpatient care in hospitals and use of skilled nursing facilities, hospice, and some home health care services. Part B benefits provide coverage for outpatient care services including doctor visits, hospital outpatient care, durable medical equipment (e.g., oxygen), home health care, and some preventive services (e.g., flu shots). Part C benefits or Medicare Advantage plans are managed care plans administered by private insurance companies approved by Medicare that provide coverage for all Part A and Part B eligible services and in many cases Part D or prescription drug plan (PDP) coverage.

Before January 1, 2006, Medicare did not offer outpatient prescription drug benefits and Medicare members had to rely on other sources such as Medicaid or employer-sponsored health plans to assist in paying for outpatient medications, or pay out-of-pocket if assistance was not available.

The Medicare Prescription Drug, Improvement, and Modernization Act (MMA) was signed into federal law in 2003, establishing the voluntary Medicare outpatient prescription benefit, known as Medicare Part D, that became effective January 1, 2006 to help subsidize the costs of prescription medications for Medicare members. Additionally, Medicare has replaced Medicaid as the prime source of drug coverage for "dual eligible" members who receive both Medicare and Medicaid benefits and some low-income members who may also qualify for additional assistance with Part D plan premiums and cost-sharing responsibilities.

With the establishment of Part D, all Medicare beneficiaries are eligible to access the prescription drug benefit through enrollment into one of the private plans approved by the federal government, either as a stand-alone PDP or as part of their Medicare Advantage Prescription Drug (MAPD) plan. Plans available to beneficiaries vary in benefit design including monthly premiums and copayment structure, formulary restrictions on medications covered, cost-containment or utilization management strategies, and coverage through the coverage gap.

Table 4.1 Type of plans

Types of plans offered by Humana	Covered Lives	Coverage
Commercial fully-insured	1.5 million	Medical outpatient services, inpatient hospitalization stays, ER visits, and prescription drug plan coverage
MAPD	1.9 million	Medicare Part A, B, C, and D coverage
PDP	2.4 million	Medicare Part D (prescription drug plan) coverage only

4.2.4 Summary of data files

In the proposed study, three distinct files were merged: membership files containing demographic information (age, sex, plan enrollment information); a pharmacy claims file containing data on dispensed medications (name, dosage, quantity, day supply, cost); and a medical claims file containing up to nine International Classification of Diseases Ninth Revision, Clinical Modification (ICD-9-CM) codes per encounter. Medical claims data are only available for fully-insured commercial and MAPD plan members. A prior comparison of these data to nationally representative

samples from the Medical Expenditures Panel Survey and the Medicare 5% sample showed that the age adjusted prevalence of diseases was similar in this commercial insurance database to those in these nationally representative samples.[97]

4.3 Study Design and Selection of Participants

4.3.1 Study Design Overview

The proposed study used a retrospective cohort design involving fully-insured commercial and Medicare adult patients who newly initiated a TKI as first-line therapy for CML between June 1, 2010 and December 31, 2011 (intake period). The intake period was determined based on the FDA approval of first-line use for second-generation TKIs for the treatment of CML, allowing for at least a 1-year follow-up after TKI initiation (maximum follow-up period is December 31, 2012). Patients were identified from outpatient pharmacy claims for the initiation of therapy with the following medications, imatinib, nilotinib, or dasatinib. The date of the first pharmacy claim for the TKI therapy during the intake period was defined as the index date. An incident or new user design is preferred over prevalent user designs in comparative effectiveness research because it can reduce under ascertainment of early events and avoids the potential error of adjusting for covariates on the causal pathway or potentially introducing confounding.[98,99] No consensus exists for defining an incident user of a medication when using a secondary database.[99] Among studies utilizing a secondary database to evaluate utilization of TKI therapy for the treatment of CML, a baseline period ranging from one month to six months during which no prescriptions for TKI therapy are filled has been used to define newly treated patients.[80,82] For this study, a 4 month period prior to the index date was used to define an incident user of a TKI. This allows for a 30 day refill gap for patients who may have filled a prescription for a 90 day supply. Patients were followed for up to 12 months following the index date which was defined as the follow-up period. Figure 4.1 shows the time period that was applied for the study.

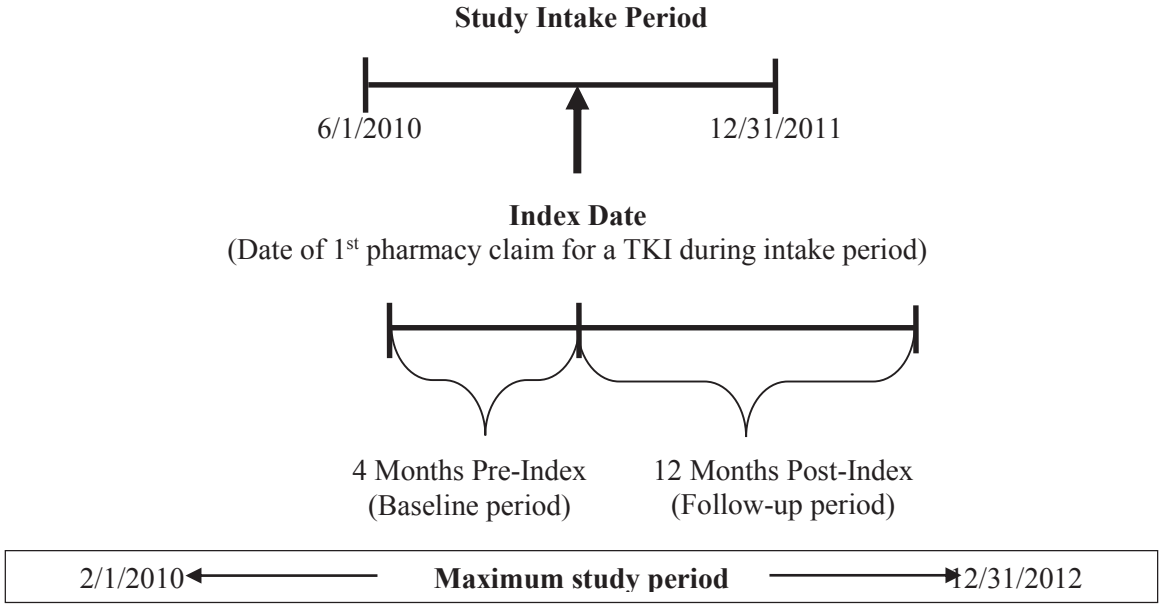

Figure 4.1 Study Time Period

4.3.2 Selection Criteria

Patients were included in the study sample if they (1) had at least one claim for a TKI therapy (i.e. imatinib, nilotinib, or dasatinib) during the intake period of June 1, 2010 to December 31, 2011; (2) were new users to TKI therapy defined as having no claim for a TKI therapy during the baseline period; (3) were continuously enrolled in a Humana commercial fully-insured or Medicare plan for 4 months during the baseline period; (4) were between the ages of 18 and 89 years old at the index date; and (5) had a diagnosis for CML at the time the TKI therapy was initiated. Patients who met the study criteria were categorized into two mutually exclusive medication cohorts using an 'as treated' design based on whether they received a first or second-generation TKI as their index medication: imatinib (first-generation TKI) and nilotinib or dasatinib (second-generation TKIs). An 'as treated' analysis classifies patients according to the treatment they took and may restrict analyses to adherent patients.

4.3.3 Subset of Patients Meeting Selection Criteria

To assess rates of health services utilization (i.e. number of outpatient physician visits, number of inpatient hospital admissions, length of inpatient hospital stays, and number of emergency room visits) and healthcare costs, it is necessary to access patients' medical data. Therefore, the subset of patients enrolled in a Humana plan that provides both pharmacy and medical coverage was further identified to compare differences in healthcare utilization and costs between patients initiating a second-generation versus first-generation TKI (Aim 4). Only those patients with at least 12 months of follow-up were evaluated for this aim. The purpose of Aim 5 is to perform exploratory analyses to determine if adherence, healthcare utilization, and healthcare costs differ between patients newly initiating a specific second-generation TKI (i.e. either nilotinib or dasatinib). Therefore, only patients in the second-generation TKI therapy cohort were included for the exploratory analyses (Aim 5).

4.4 Measures

4.4.1 Overview

This section describes how the patient demographic characteristics, patient clinical characteristics, and provider characteristics were measured. A detailed description of the independent variables, dependent variables, and the statistical analyses employed for each aim is described in Section 4.6.

4.4.2 Primary Study Measures

Type of TKI. A dichotomous variable was created to indicate whether the prescription filled at the index date was for a first-generation TKI (imatinib) or second-generation TKI (nilotinib or dasatinib). Use of a first-generation TKI was the referent.

Treatment interruption. Treatment interruption was defined as a gap in any TKI pharmacy claim that is longer than an allowable refill gap plus days' supply from the previous TKI medication claim. Baladi et al. evaluated treatment interruption on imatinib based on a 30 day refill gap.[84] For this

study, an allowable refill gap of 30 days was used. Time in days from the index date to date of treatment interruption was assessed.

TKI regimen change. Regimen change was defined as 1) a prescription claim for a different TKI therapy; or 2) an increase in dose for the same medication during the follow-up period.

Adherence. Adherence to TKI therapy was calculated as proportion of days covered (PDC). PDC is a newer measure for calculating adherence using administrative claims data than the medication possession ratio (MPR). Unlike MPR, PDC is not a simple summation of days' supply of medication over an interval.[100] PDC assesses days with or without medication, and has been described as the proportion of days a patient has a medication available in a study period.[101] The PDC relies on pharmacy data to determine the date of each TKI therapy prescription, the number of tablets dispensed, and days' supply for the prescription. It was assumed that a patient had the medication available for the day of the prescription and for the remaining days' supply of that prescription. The PDC method evaluates each day during the designated study time period to determine whether a patient has the TKI therapy they initiated for each day using a binary measure indicating presence or absence of a TKI therapy. For the primary analysis, patients were censored if they changed to a different TKI therapy, end of enrollment, or the end of the study period, whichever came first. The number of possession days for each patient was divided by the total days of follow-up for each patient to determine a continuous measure of PDC which ranges from 0 to 1. Each patient had a different denominator based on date of censoring. If a claim has a days' supply exceeding the end of the study period, days' supply was truncated to the end of the measurement period. PDC was dichotomized at 0.85.[79] Scores $\geq$0.85 were classified as adherent and scores <0.85 were classified as non-adherent.

Health services utilization. All-cause healthcare utilization was assessed during the follow-up period using the medical claims file. Four distinct utilization measures were assessed: (1) number of

outpatient physician visits; (2) number of inpatient hospitalization admissions; (3) number of inpatient hospital days; and (4) ER visits.

Healthcare costs. The total direct all-cause healthcare costs were calculated from medical and pharmacy claims data for each patient during the follow-up period. Covered services under the medical and pharmacy benefit are described in more detail under Section 4.2 Data Source. The cost calculation included both plan paid and member out-of-pocket costs (i.e. patient copayments and co-insurance). Three distinct variables were calculated: (1) medical costs; (2) pharmacy costs; and (3) total healthcare costs calculated as the sum of medical and pharmacy costs.

Table 4.2 Summary of primary study measures

Variable	Type	Source Data File	Definition
Type of TKI at index date	Dichotomous	Pharmacy claims file	Use of a second-generation TKI therapy (nilotinib or dasatinib) at index date with first-generation TKI therapy (imatinib) serving as referent
Treatment interruption	Continuous	Pharmacy claims file	Time in days from date of first TKI prescription claim to date of treatment interruption
TKI regimen change	Dichotomous	Pharmacy claims file	Regimen change, measured as a dichotomous variable indicating whether a patient changed to any different TKI therapy or increased dose for the same medication during the follow-up period
Adherence	Dichotomous	Pharmacy claims file	Adherence to TKI therapy during the follow-up period, measured by PDC. Patients with a PDC≥0.85 were classified as adherent and those with PDC <0.85 were classified as non-adherent.
Health services utilization	Count	Medical claims file	Four distinct variables were created and assessed during the follow-up period for 1) outpatient physician visits; 2) inpatient hospitalization stays; 3) inpatient hospital days; and 4) ER visits.
Healthcare costs	Continuous	Medical claims file	Three distinct variables were calculated for healthcare costs during the follow-up period for 1) pharmacy costs; 2) medical costs;

	and 3) total all-cause costs (pharmacy plus medical).

4.4.3 Covariates

The covariates included in this study are informed by Carpenter and colleagues' conceptual model for examining nonexperimental cancer comparative effectiveness research.[88] Covariates are divided into three categories: patient demographic characteristics, patient clinical characteristics, and provider characteristics. Operationalization of the covariates within each category is described below and summarized in Table 4.6.

Patient demographic characteristics

Age. Patient age was calculated in years as of the index date. Age was calculated as the number of days between the index date and the patient's date of birth divided by 12 months.

Gender. Patient gender was measured as a dichotomous variable.

Geographic region. Geographic region was based on the patient's state of residence on the index date. Refer to Table 4.3 for the regional assignment (Northeast, Midwest, South, West) which is based on the U.S. Census Bureau assignment of states to geographic region.

Table 4.3 Geographic Region Definitions

Region	States
Northeast	Connecticut, Maine, Massachusetts, New Hampshire, Vermont, Rhode Island, New Jersey, New York, and Pennsylvania
Midwest	Illinois, Indiana, Michigan, Ohio, Wisconsin, Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, and South Dakota
South	Delaware, District of Columbia, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, Alabama, Kentucky, Mississippi, Tennessee, West Virginia, Arkansas, Louisiana, Oklahoma, and Texas
West	Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming, Alaska, California, Hawaii, Oregon, and Washington

Source: *http://www.census.gov/geo/www/geo_defn.html#GeographicCode*

Plan. Patients were classified as having a commercial fully-insured or Medicare plan with Humana as of the index date. Differences between patient demographic characteristics, insurance benefits, and treatment patterns have been reported among Humana patients enrolled in a commercial versus a

Medicare plan. A study evaluating patterns of osteoporosis treatment demonstrated that commercial patients tended to be younger, with fewer comorbidities, and higher out-of-pocket expenses for medications.[89] Financial product indictor was used to determine whether a patient is enrolled in a fully-insured commercial or Medicare plan. A patient is enrolled in a fully-insured commercial plan when the financial product code is one of the following: IHM, IMV, HMOC, PPO, POS, or IND. A patient is enrolled in a Medicare plan when the financial code is one of the following: MEDR, MEDR-HMO, MEDR-PFFS, MEDR-POS, or MEDR-PPO.

Low Income Subsidy (LIS) nondual eligible status. Medicare beneficiaries with income below 150% of poverty and limited resources are eligible for additional premium and cost-share assistance for prescription drugs under the Medicare Part D program. These patients are flagged as LIS patients in Humana's claims database. This variable was measured at the index date for Medicare patients only. LIS nondual eligible patients are distinguished from dual eligible patients because LIS nonduals have higher incomes, proactively apply for LIS whereas duals are auto enrolled, and almost all duals had coverage under Medicaid before Part D.[91]

Dual eligibility. Dual eligibility indicates that Medicare patients are also covered under Medicaid which covers ancillary services not covered under the Medicare plan. Often these patients have increased disease burden and have different healthcare utilization patterns compared to other Medicare patients.[91] These patients are flagged as having Medicaid dual eligibility in Humana's claims database. Dual eligibility status was evaluated at the index date.

Patient clinical characteristics

TKI dose schedule. Treatment dose schedule for TKI therapy was assessed based on which TKI therapy was initiated at the index date. The treatment schedule of the index TKI therapy was classified as daily or twice daily based on the daily average consumption (DACON) for the index prescription. DACON is used to describe the average number of dosage units dispensed per day. A DACON of 1 represents once daily dosing and a DACON of 2 represents twice daily dosing.

Proxy for CML phase. Patients' starting dose of TKI therapy was assessed and used as a proxy for CML phase at the time of initiation. The dose was calculated as the strength of the TKI therapy dispensed, multiplied by the quantity filled, divided by the days' supply. Each TKI therapy has a dose that suggests suboptimal or accelerated phase (see Table 2.4). A dichotomous variable was created based on starting dose to distinguish 1) chronic phase initiation dosing; and 2) suboptimal or accelerated phase dosing.

Channel of drug distribution. The channel of drug distribution through which the index prescription was obtained was categorized as specialty, retail, managed care organization pharmacy, or long term care pharmacy.

Patient cost-share for TKI therapy. Patient cost-share was measured using cost per 30 day supply of TKI therapy for the index prescription. If the patient received a 30 day supply of medication for the index medication, the cost the patient paid for that prescription was reported. For patients receiving less than or greater than a 30 day supply for the index medication, the cost for the prescription was divided by the days' supply and then multiplied by 30.

Coverage gap. A dichotomous variable was created for Medicare beneficiaries to indicate whether a patient reached the coverage gap at any time during the follow-up period. The standard Medicare Part D prescription drug benefit has three phases of coverage during a plan year: initial, coverage gap, and catastrophic coverage. Until 2011, patients were responsible for the entire cost of medications during the coverage gap phase. Entry into the coverage gap was determined based upon the total amount spent on medications (that occurs through the Part D benefit) during each plan year. Each year, CMS establishes a new deductible, initial coverage period, coverage gap period, and catastrophic coverage period. The coverage gap period for each year and catastrophic phase are defined in Table 4.4. The standard Medicare Part D Prescription Drug Plan (PDP) varies by plan offering; however, the criterion for entry into the coverage gap does not vary.

Table 4.4 Standard Medicare Part D Prescription Drug Benefit

Plan Year	Initial Deductible	Total Drug Cost for Coverage Gap Entry	True Out of Pocket Cost (TrOOP) for Catastrophic Coverage Entry
2010	$310	$2,830	$4,550
2011	$310	$2,840	$4,550
2012	$320	$2,930	$4,700

RxRisk Score. The RxRisk-V is a prescription claims-based comorbidity index originally developed as an enhancement of the RxRisk risk assessment instrument for use in the Veterans Health Administration (VHA) population.[102-104] The RxRisk-V score is determined based on the identification of 45 distinct comorbid conditions via their associated medication treatments (Table 4.5). In order to calculate the RxRisk-V score, comorbid conditions are mapped to drug classes and individual drugs via Medi-Span generic product identifier (GPI) codes. The GPI is a therapeutic classification system that is useful for aggregating similar drug products at a drug class level. The GPI is a 14-digit code that contains 7 pairs of digits and uses a hierarchical therapeutic classification scheme. The first pair of digits represents the drug group and subsequent paired digits represent the drug class, drug subclass, drug name, drug name extension, dosage form, and strength. Three comorbid conditions that are defined based on claims for durable medical equipment (neurogenic bladder, ostomy, and urinary incontinence) were not included in the RxRisk-V score calculation since these claims are not captured in the pharmacy claims file.

Because the RxRisk-V score is derived from pharmacy claims data, it may provide a more complete and accurate comorbidity picture when data from a narrow window of claims are used, or in cases where diagnosis codes are not routinely recorded. The RxRisk-V has been rigorously tested and has demonstrated concordance with the Deyo-Charlson score. Although the RxRisk-V was originally developed for use in the Veterans Health Administration (VHA) population, the measure has been found to perform well in other populations. A recent evaluation of Rx Risk-V by Farley and

colleagues found that the RxRisk-V outperforms both the Deyo-Charlson and the Elixhauser comorbidity measures in predicting healthcare expenditures among managed care plan members.[105] In addition, Farley et al. found that the unweighted version of the RxRisk-V has better predictive validity for costs than does the weighted version. The unweighted RxRisk-V score was calculated for each patient during the baseline period.

Table 4.5 RxRisk-V comorbidity categories and associated drug classes/drugs*

RxRisk-V Categories	Drugs classes/drugs
Alcohol dependence	disulfiram, naltrexone
Allergies	antihistamines (except hydroxyzine and diphenhhydramine), nasal anti-inflammatories
Anticoagulation	anticoagulants
Antiplatelet agents	antiplatelet agents
Anxiety and tension	anxiolytics (benzodiazepine and barbiturate)
Arrhythmias	antiarrhythmics, digoxin
Benign prostatic hypertrophy	alpha blockers
Bipolar disorder	lithium
CHF/hypertension	loop diuretics, ACE, and angiotensin II inhibitors
Dementia	donepezil, tacrine
Depression	antidepressants
Diabetes	insulins, oral hypoglycemics
End stage renal disease	alpha erythopoetin, calcifediol, calcitriol, sevelamer
Epilepsy	anticonvulsants
Gastric acid disorder	H2 blockers, proton pump inhibitors
Glaucoma	topical (ophthalmic) antiglaucoma agents
Gout	antigout agents
Hepatitis C	interferon/ribavirin combinations
HIV	anti-HIV antivirals
Hyperkalemia	sodium polystyrene sulfonate
Hyperlipidemia	antilipemic agents
Hypertension	thiazides, potassium-sparing agents, combination antihypertensives, other antihypertensives (eg, clonidine, hydralazine)
Hypothyroidism	thyroid replacements
IHD/angina	nitrates
IHD/hypertension	beta blockers, calcium channel blockers
Inflammatory bowel syndrome	IBS-specific drugs, rectal anti-inflammatories
Liver failure	lactulose
Malignancies	antineoplastic agents (all oral and systemic agents but excluding topicals)
Malnutrition	enteral nutritional supplements
Migraine	antimigraine medications (ergots, triptans, methysergide)
Neurogenic bladder	urinary catheters (supplies)
Osteoporosis/Pagets	alendronate, etidronate
Ostomy	colostomy and urostomy supplies
Pain	opiate-containing pain medications
Pain/Inflammation	nonsteroidal anti-inflammatory drugs
Pancreatic insufficiency	pancreatic exocrine enzyme replacements
Parkinson disease	antiparkinsonian agents
Psoriasis	systemic and topical antipsoriatics
Psychotic illness	antipsychotics
Reactive airway disease	inhaled bronchodilators, leukotriene inhibitors
Smoking cessation	nicotine, Zyban

Steroid-responsive conditions	glucocorticoids (steroids)
Transplant	immune suppressants
Tuberculosis	anti-tubercular agents
Urinary incontinence	diapers and pad (supplies)

*Adapted from Sloan et al., 2003

Deyo Charlson Comorbidity Index. The Deyo Charlson Comorbidity Index (DCI) uses 17 categories of comorbidity to calculate a score that reflects cumulative increased likelihood of one-year mortality.[106] It is based on ICD-9 diagnoses and procedure codes, and their associated weights. Table 4.6 lists the comorbidities and their weightings used in the calculation of the DCI. The DCI score can range from 0 to 33. Claims with the specified codes are used in the calculation of the DCI if they meet the following criteria: (1) used on an inpatient hospitalization; or (2) used on two or more outpatient claims, separated by a period of 30 days or more.[107]

Table 4.6 Deyo Charlson Comorbidity Index

Comorbidity	Codes	Weight
Myocardial Infarction	410.xx, 412.xx	1
Congestive Heart Failure	428.xx	1
Peripheral Vascular Disease	441.xx, 443.9, 785.4, V43.4, 38.48*	1
Cerebrovascular Disease	430.xx-437.xx, 438.xx	1
Dementia	290.xx	1
Chronic Pulmonary Disease	490.xx-496.xx, 500.xx-505.xx, 506.4	1
Connective Tissue Disease	710.xx, 714.xx, 725.xx	1
Peptic Ulcer Disease	531.4x-531.7x, 532.4x-532.7x, 533.4x-533.7x, 534.4x-534.7x, 531.0x-531.3x, 532.0x-532.3x, 533.0x-533.3x, 534.0x-534.3x, 531.9x, 532.9x, 533.9x, 534.9x	1
Mild Liver Disease	571.2, 571.4, 571.5, 571.6	1
Diabetes without Complications	250.0x-250.3x, 250.7x	1
Diabetes with Complications	250.4x-250.6x	2
Paraplegia and Hemiplegia	342.x, 344.1	2
Renal Disease	582.x, 583.0-583.7, 585.xx, 586.xx, 588.xx	2
Cancer (Including Leukemia and Lymphoma)	140.xx-172.xx, 174.xx-195.xx, 200.xx-208.xx	2
Moderate or Severe Liver Disease	572.2-572.8	3
Metastatic Carcinoma	196.x-199.x	6
Acquired Immunodeficiency Syndrome (AIDS)	042.xx-044.x	6

*ICD-9-CM Procedural Code

Number of unique concurrent medications. Total number of unique concurrent medications was defined using pharmacy claims data where the service date occurred during the baseline period. The total number of unique concurrent medications was a count of all medications with the exception of TKI therapies based on the GPI. GPI-8 identifies a product at the chemical or drug name level and

was used to identify unique medications where the patient was required to receive 2 or more claims. Two or more claims were required to eliminate including medications for short term use.

Vaccine use. Flu or pneumonia vaccine use was assessed during the baseline period. This covariate was included because patients who are adherent may have a health-seeking tendency and may be more likely to use preventative services.[94]

Provider characteristics

Gender. Provider gender was available through the Humana provider file and measured as a dichotomous variable.

Age. Provider age was calculated in years as of the index date. Age was calculated as the number of days between the index date and the provider's date of birth, which was available in the Humana provider file, divided by 12 months.

Provider specialty. National Provider Identifier (NPI) was available in the Humana provider file. NPI was used to identify provider specialty through the Centers for Medicare and Medicaid Services NPI registry.[108] Provider specialty was categorized as oncologist or other.

Practice type. Provider practice type was investigator coded and categorized as academic, private, and other. Other practice setting was defined as community hospitals, clinics, or outpatient cancer care facilities neither owned by the practicing physicians nor considered academic or university-based.[95] Provider name, practice name, and address were available in the Humana provider file. First, providers practicing in an academic setting were identified based on practice name and address available in the Humana provider file. Next, additional research was conducted for the remaining providers to determine whether a provider practiced in a private setting or other. Practice name and address were used to locate the practice's website. The information needed to determine if a practice was private or other was available in the "About us" or "history" sections of the websites.

Table 4.7 Summary of Covariates

Variable	Type	Data Source	Time Assessed	Definition
Demographic characteristics				
Age	Categorical	Pharmacy claims file	Index date	1=<55; 2=55-64; 3=65-74; 4=>75
Gender	Dichotomous	Membership file	Index date	0=female; 1=male
Geographic region	Categorical	Membership file	Index date	1=South; 2=Northeast; 3=Midwest; 4=West
Plan	Categorical	Membership file	Index date	0=Commercial fully-insured; 1=Medicare
LIS	Dichotomous	Membership file	Index date	0=no; 1=yes
Dual eligibility	Dichotomous	Membership file	Index date	0=no; 1=yes
Clinical characteristics				
TKI dose schedule	Categorical	Pharmacy claims file	Index date	0=once daily dosing; 1=twice daily dosing
Proxy for CML phase	Dichotomous	Pharmacy claims file	Index date	0=chronic phase dosing; 1=suboptimal or accelerated phase dosing
Channel of drug distribution	Categorical	Pharmacy claims file	Index date	1=specialty; 2=retail; 3=managed care organization (MCO); 4=long term care pharmacy
Member out-of-pocket cost for month supply of index TKI	Continuous	Pharmacy claims file	Index date	1=$0-$1000; 2=$1,001-$2,000; 3=$2001-$3,000; 4=$3,001-$4,000; 5=>$4,000
Coverage gap calculated separately for 2010, 2011, 2012	Dichotomous	Pharmacy claims file	Follow-up	0=no; 1=yes
RxRisk-V Score	Categorical	Pharmacy claims file	Baseline period	0=RxRisk-V score between 0-2; 1=RxRisk-V score >2
Deyo Charlson Comorbidity Index	Categorical	Medical claims file	Baseline period	0=DCI 0,1 1=DCI greater than 1
Number of unique concurrent medications	Count	Pharmacy claims file	Baseline period	0=medication count between 0-2; 1=medication count >2
Vaccine use	Dichotomous	Pharmacy claims file	Baseline period	0=no; 1=yes

Provider Characteristics				
Gender	Dichotomous	Provider file	Index date	0=female; 1=male
Provider age	Categorical	Provider file	Index date	0=<35; 1=35-44; 2=45-54; 3=55-64; 4=≥65
Provider specialty	Categorical	Provider file/NPI registry	Index date	0=other; 1=oncologist
Practice type	Categorical	Provider file/Investigator coded	June, 2013	1=academic; 2=private; 3=other

4.5 Power Analyses

Based on the data available for this study, 239 patients initiated therapy with a first-generation TKI (imatinib) and 132 patients initiated therapy with a second-generation TKI (nilotinib or dasatinib). Adherence (Aim 3) drives the power calculation. Adherence rates for imatinib, nilotinib, and dasatinib have been similar in clinical trials. Wu et al. evaluated adherence to imatinib therapy using claims data where adherence was defined as a MPR ≥85%.[79] Approximately, 60% of patients were adherent over a 12-month period. To test the hypothesis that adherence to second-generation TKI therapies (i.e. nilotinib and dasatinib) is higher compared to imatinib, adherence must be substantially higher. Using Proc Power®, a 2x2 proportion test with unequal sample sizes estimated that 371 patients provide approximately 97.7% power to detect a 20% difference in the proportion of adherent patients (i.e. 60% versus 80%) between imatinib and a second-generation TKI therapy using a two-tailed alpha=0.05. There is 81.4% power to detect a 15% difference (i.e. 60% versus 75%), 44.5% power to detect a 10% difference (i.e. 60% versus 70%), and 13.4% power to detect a 5% difference (i.e. 60% versus 65%) in adherence.

To test the hypothesis for Aim 4 that patients initiating a second versus first-generation TKI have lower total all-cause healthcare costs over a 12-month period, a power calculation using a two sample t-test with unequal sample sizes assuming unequal variances was completed. Cost data from Hirji et al. was used for the assumptions for the power calculations.[82] The mean 6-month all-cause healthcare costs for imatinib and dasatinib patients were $46,342 and $54,808, respectively. These

costs were multiplied by two to predict 12-month all-cause costs. It is estimated using an unequal group weight of 1.5:1, 133 patients provide >99% power to detect a $45,000 difference in 12 month all-cause healthcare costs between patients initiating a second versus first-generation TKI, >99% power to detect a $35,000 difference, 99.7% power to detect a $25,000 difference, and 80% power to detect a $15,000 difference.

4.6 Methodological Issues

Because there are no available RCTs with direct comparisons of the effectiveness for all three TKI therapies and there is limited ability to generalize RCT evidence to clinical practice, it is critical to use observational data to evaluate the effectiveness of a first-generation TKI (imatinib) to second-generation TKIs (nilotinib and dasatinib) in patients newly initiating TKI therapy for the treatment of CML. Observational data are used to compare outcomes of different therapies to inform clinical guidelines and practice. Although observational data can be used to supplement RCT data, it is often biased due to unmeasured confounders. Confounding in pharmacoepidemiology studies is multifaceted as treatment exposure is not randomized. The most cause for concern when comparing outcomes between first versus second-generation TKI therapy is that treatment decisions can be influenced by severity of disease, frailty and other prognostic factors (confounding by indication).[109] Second-generation TKIs were originally only indicated for second-line use in imatinib resistant or intolerant patients. Although the NCCN guidelines recommend a prognostic assessment at baseline to help guide the choice of primary treatment,[46] there is no current evidence suggesting physicians are prescribing second-generation TKIs in patients with more severe disease. Furthermore, it is unlikely that treatment decisions are currently influenced by severity of disease but by efficacy, dose schedule, and provider preferences. Second-generation TKIs have shown to be more efficacious compared to imatinib in patients newly diagnosed with CML and provide a faster and deeper response.[9,11] Recently, Cortes et al. published a paper describing how they treat newly diagnosed CP-CML patients and recommend all new patients be treated with second-generation TKI therapy as they believe in the

long run patients will do better with this strategy.[42] Additionally, physician's preference likely influences initial TKI therapy which may be guided by clinical experience as well as the dose schedule. Both imatinib and dasatinib are available as once daily dosing which may improve adherence whereas nilotinib is taken twice daily.

Although confounding by disease severity may not pose a threat to internal validity of the two cohorts, cancer severity is a factor that may confound the relationship between patients' adherence and healthcare costs and utilization. It is likely that patients in more advanced stages of CML have higher healthcare costs and different rates of adherence than patients in less advanced stages. The dataset being used in this study does not provide information to identify and adjust for the phase of CML (chronic phase, accelerated phase, or blast crisis). However, TKI starting dose was used as a proxy for chronic phase versus a more advanced stage.

Survival analysis was used to evaluate time to treatment interruption and time to regimen change because patients in the study had different lengths of follow-up. Time to event was defined as time elapsed between first TKI therapy fill (i.e. index date) and treatment interruption or switch. Poisson regression models were used to compare health servicesutilization between patients initiating a second versus first-generation TKI. To estimate the association between initiating a second versus first-generation TKI and healthcare costs while controlling for baseline differences, multivariate regression analyses were conducted. Because healthcare costs data are known to have a highly skewed distribution with non-constant variances, generalized linear models (GLM) were fitted to estimate mean healthcare costs.[110] Risk adjustment methods were used to address confounding in the analyses described above. Risk adjustment methods result in unbiased estimates by adjusting for measured confounders with the assumption that all confounders are either measured or that unmeasured are "ignorable".[111] If unmeasured confounders cannot be ignored, the estimates from risk adjustment are biased.

4.7 Statistical analyses

All analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Baseline Characteristics

Descriptive statistics were used to summarize demographics, other baseline characteristics, and TKI use. Baseline characteristics were evaluated for the baseline time period or at the time of the index date. The following information was presented:

Baseline Characteristics	
Age (at index date)	Number of unique concurrent medications
Gender	Chanel of distribution
Plan (commercial vs. Medicare)	Patient cost-share of index TKI therapy
Geographic region	Coverage gap
Dual eligibility status*	RxRisk-V
LIS status*	Charlson Comorbidity Index
Index TKI (1st vs. 2nd generation TKI)	Provider age
TKI starting dose	Provider gender
TKI dose schedule	Provider specialty
Proxy for CML phase	Provider practice setting
Vaccine use	

*For Medicare members only

Information listed above was compared between the two cohorts (first-generation and second-generation TKI). In general, continuous variables were compared using t-tests or Wilcoxon rank sum test while categorical variable were summarized using chi-square or Fisher's exact tests.

Propensity Score (PS) Estimation

Propensity score estimation is a technique used to control for naturally occurring differences between treatment groups in observational studies.[112] Propensity score methods include matching, stratification on the propensity score, inverse probability weighting using the propensity score, and regression adjustment.[113] Because patients were not randomly assigned their TKI therapy, a propensity score quintile was used as a covariate in the regression adjustment.

The methodology used for the estimation of a propensity score requires two groups at a time. The steps for estimating the propensity score for each subject are as follows[114]:

1. Use a logistic regression model to estimate the propensity score. Treatment assignment is the binary response (dependent variable) and the covariates are the explanatory (independent) variables.
2. Stratify observations by quintiles of the distribution of the estimated propensity scores.[115]
3. Check the balance achieved by comparing the covariate values across treatment groups for each quintile and covariate. A significant test result implies that the covariate is not balanced for the two treatments within the subclass.
4. If balance is not achieved, the model used to estimate the propensity score needs to be refined.
5. A histogram should be used to evaluate the PS range. Analyses should first be conducted without any restriction of the PS range. Then, if needed additional analyses should be restricted to observations within a PS range that is common to patients initiating a first versus second-generation TKI, thereby excluding all patients in the nonoverlapping parts of the PS distribution.[116]

The propensity score approach requires two assumptions. First, the propensity score only controls for observed characteristics. If there is an unobserved variable that significantly affects the outcome, it will not be controlled. Second, treatment assignment must be strongly ignorable. The treatment assignment is considered strongly ignorable if the treatment assignment (whether or not the patient received a particular medication) and the response (the outcome) is conditionally independent given the observed characteristics (e.g. age, gender).

4.7.1 Aim 1: Identify factors associated with newly initiating therapy for CML with a second-generation versus a first-generation TKI

4.7.1.1 Logistic Regression

A multivariable logistic regression analysis was performed to assess factors associated with newly initiating a second-generation TKI therapy compared to a first-generation TKI for the treatment

of CML (Model 1). Statistical significance was assessed at alpha=0.05 for this purpose. Model fit and predictability statistics were reported (e.g. Hosmer and Lemeshow Goodness-of-Fit Test, c statistics).

Model 1:

$$\mathbf{Logit}(\boldsymbol{second-generation\ TKI\ use}) = \boldsymbol{\beta_0} + \boldsymbol{\beta_1}(\boldsymbol{age}) + \boldsymbol{\beta_2}(\boldsymbol{gender}) + \boldsymbol{\beta}\ \ (\boldsymbol{region}) + \boldsymbol{\beta_4}(\boldsymbol{plan}) + \boldsymbol{\beta_5}(\boldsymbol{LIS}) + \boldsymbol{\beta_6}(\boldsymbol{dual\ eligibility}) + \boldsymbol{\beta_7}(\boldsymbol{comorbidities}) + \boldsymbol{\beta_8}(\boldsymbol{vaccine\ use}) + \boldsymbol{\beta_9}(\boldsymbol{medication\ count}) + \boldsymbol{\beta_{10}}(\boldsymbol{provider\ characteristics}) + \boldsymbol{\varepsilon}$$

Age: a vector of age at index date
Gender: a vector of male and female gender
Geographic region: a vector of region indicators (NE, MW, S, W)
Plan: a vector of patients enrolled in a commercial or Medicare plan
LIS: a vector of LIS vs. non-LIS (Medicare patients only)
Dual eligibility: a vector of dual eligibility vs. non-dual eligibility (Medicare patients only)
Comorbidities: a vector of RxRisk score >2 compared to ≤2
Vaccine use: a vector of vaccine vs. non-vaccine use
Medication count: a vector of medication count >2 compared to ≤2
Provider characteristics: a vector of age, gender, provider type, and practice type

4.7.1.2 Sensitivity Analysis

Two sensitivity analyses were performed. The first sensitivity analysis was limited to patients enrolled in a MAPD plan or fully-insured commercial plan. These patients have medical data available. The logistic regression model used the Deyo Charlson Comorbidity Index as a measure of comorbidity instead of the RxRisk score. Patients may have comorbidities not treated by medication which are not captured using RxRisk score. The second sensitivity analysis included only patients who initiated on chronic phase dosing; therefore, patients with accelerated disease were removed and this covariate was not included in the model.

4.7.2 Aim 2: Examine differences in treatment interruption and regimen change comparing patients newly initiating a second-generation versus a first-generation TKI

4.7.2.1 Overview

The null-hypothesis for Aim #2 is that there are no significant differences in medication use patterns between patients who newly initiate a second-generation compared to a first-generation TKI therapy for the treatment of CML. The alternative hypothesis for Aim #2 is that patients initiating a second-generation TKI therapy stay on therapy longer and are less likely to have a regimen change.

The percentage of patients that had a treatment interruption and a TKI regimen change during the follow-up period was reported for each cohort. Additionally, risk adjustment analyses and multivariable logistic regression were used to evaluate differences in medication use patterns between patients initiating first versus second-generation TKI therapy. Cox proportional hazard models were used to evaluate the time to treatment interruption and regimen change which was interpreted as the duration of TKI therapy, for patients initiating first versus second-generation TKI therapy.

4.7.2.2 Treatment Interruption

4.7.2.2.1 Main Analyses

Risk Adjustment Analyses

Survival analysis was used to evaluate time to treatment interruption because patients in the study have different lengths of follow-up. Time to event was defined as time elapsed between first TKI therapy fill (i.e. index date) and date of treatment interruption, end of enrollment, or the end of the study period, whichever came first. Risk adjustment methods were used to address confounding. Risk adjustment methods result in unbiased estimates by adjusting for measured confounders with the assumption that all confounders are either measured or that unmeasured confounders are "ignorable".[111] If unmeasured confounders cannot be ignored, the estimates from risk adjustment will be biased.

Cox proportional hazard (CPH) regression models were used as the regression model for the risk adjustment analysis. CPH is a robust model and is preferred over other survival approaches when there are several explanatory variables.[117] An unadjusted CPH model was used to estimate the non-adjusted time to treatment interruption for the first-generation and second-generation TKI groups.

Additionally, a multivariable CPH model was used to control for differences in the distribution of covariates across the two cohorts and evaluate the potential confounding effects of the covariates (Model 2). Model 2 adjusts for all time-independent baseline demographic and clinical characteristics. The Cox model formula states that the hazard at time *t* is the product of two factors: (1) $h_0(t)$ is the baseline hazard function that is left unspecified, and is non-negative and (2) an exponentiated linear function of a set of X fixed variables. Finally, a CPH model that included PS quintile as a covariate in the regression adjustment was used (Model 3). There are three statistical objectives for the CPH model: (1) to test for the significance of the treatment status variable, adjusted for possible confounding; (2) to obtain a point estimate of the effects (ßs) of the explanatory variables; and (3) to obtain a confidence interval for this effect.[118] The measure of effect, the hazard ratio, can be calculated from these estimates.

Model 2:

$$\mathbf{h_i(t,x_i) = h_0(t) * \exp(\beta_t T_i + \beta_x X_i)}$$

t: the time (days) from the index prescription to event or censoring
T: treatment (1 second-generation TKI and 0 for first-generation TKI)
X: the vector for all baseline characteristics
β_t: coefficient of T, the difference in survival time
β_x: a vector of coefficients for the X
i: individual patient

Model 3:

$$\mathbf{h_i(t,x_i) = h_0(t) * \exp(\beta_t T_i + \beta_{ps} PS_i)}$$

t: the time (days) from the index prescription to event or censoring
T: treatment (1 second-generation TKI and 0 for first-generation TKI)
β_t: coefficient of T, the difference in survival time
β_{ps}: a vector of coefficients for the PS
PS: the propensity score quintile
i: individual patient

Post-hoc Treatment Patterns Analysis for Patients with a Treatment Interruption

For those patients identified as having a treatment interruption during the follow-up period, a post-hoc analysis was included to evaluate behavior change following treatment interruption. TKI

treatment patterns were then followed for patients with a treatment interruption from the date of interruption until there was another change. Patients were classified has having a medication change, reinitiating the index medication, discontinuing therapy, or disenrolling from a Humana plan.

4.7.2.2.2 Sensitivity analysis

Two sensitivity analyses were completed. The first sensitivity analysis was conducted and limited to patients who were initiated on a starting dose that indicated chronic phase disease. Three CPH models were included: unadjusted, multivariable, and PS quintile. The second sensitivity analysis was completed to censor for death. Therefore, in this sensitivity analysis, time to event was defined as time elapsed between first TKI therapy fill (i.e. index date) and date of treatment interruption, end of enrollment, date of death, or the end of the study period, whichever came first.

3.7.2.3 TKI Regimen Change

3.7.2.3.1 Main Analyses

Risk Adjustment Analyses

Similar risk adjustment analyses were conducted for time to regimen change as were used for treatment interruption. Time to event was defined as time elapsed between first TKI therapy fill (i.e. index date) and regimen change, end of enrollment, or the end of the study period, whichever came first.

4.7.2.2.2 Sensitivity Analyses

Two sensitivity analyses were completed. The first sensitivity analysis was conducted and limited to patients who were initiated on a starting dose that indicated chronic phase disease. Three CPH models were included: unadjusted, multivariable, and PS quintile. The second sensitivity analysis used logistic regression models to assess the association between initiating a first versus second-generation TKI therapy and regimen change.

4.7.3 Aim 3: Determine if adherence is higher among patients newly initiating a second-generation versus a first-generation TKI

4.7.3.1 Overview

The null-hypothesis for Aim 3 is that there is no significant difference in medication adherence among patients who newly initiate a second-generation compared to a first-generation TKI therapy for the treatment of CML. The alternative hypothesis for Aim 3 is that patients taking a second-generation TKI therapy are more adherent compared to patients taking a first-generation TKI therapy.

Unadjusted mean adherence, measured using PDC, was compared between the cohorts using a t test. Additionally, each patient was categorized into one of three adherence categories based on PDC values: high (PDC ≥0.85); intermediate (PDC 0.40-0.84); and low (PDC <0.4). The percentage of adherent patients was compared between the cohorts using chi-square test.

Differences in adherence between patients initiating first versus second-generation TKI therapy was assessed using logistic regression. Adherence, measured using PDC, was dichotomized at 0.85. Scores ≥0.85 were considered adherent and scores <0.85 were considered non-adherent.

4.7.3.2 Logistic Regression and Propensity Score Adjustment

Three logistic regression models were included (i.e. unadjusted, multivariable, and PS quintile) to examine differences in adherence between patients initiating a first compared to a second-generation TKI therapy. The dependent variable was adherence to TKI therapy, defined as PDC ≥0.85. The primary independent variable was initiation of therapy with a first-generation versus second-generation TKI therapy.

4.7.3.3 Sensitivity Analyses

Three different types of sensitivity analyses were performed. First, sensitivity analyses were conducted to include modifications of the logistic regression model. Dose schedule and duration of therapy (i.e. days on therapy) were included and added separately to the initial model. A sensitivity analysis was conducted and limited to patients who were initiated on a starting dose that indicated chronic phase disease.

Second, sensitivity analyses were conducted with adherence dichotomized at 0.80. Scores ≥0.80 were considered adherent and scores <0.80 were considered non-adherent. Although an *a priori* sensitivity analysis to evaluate high, intermediate, and low adherence was planned, the analysis was limited by a small sample size for the low adherence category (n=4).

Third, adherence was assessed using an ITT approach. For this analysis, patients were assigned to either the first-generation or second-generation TKI cohort, regardless of whether the patient subsequently had a treatment interruption or changed therapy. Patients were censored by the end of the study period or end of enrollment, whichever occurred first.

4.7.4 Aim 4: Determine if rates of health services utilization (i.e. outpatient physician visits, inpatient hospital admissions, inpatient hospital days, and ER visits) and healthcare costs differ between patients initiating a second-generation versus a first-generation TKI

Overview

The null-hypothesis for Aim 4 is that there are no significant differences in health services utilization or healthcare costs between patients who initiate a second-generation versus a first-generation TKI.

The association between TKI therapy and health services utilization and healthcare costs while controlling for other baseline confounders was assessed. Usual linear regression models are inappropriate in this context, primarily because healthcare costs and utilization are non-negative and their distributions right skewed. Ordinary least squares linear models assuming a normal distribution may yield badly biased and/or less precise estimates of means.[119,120] Therefore, generalized linear models (GLMs), a class of estimators that allow for a non-normal distribution as well as non-constant variance were used. The GLM framework is flexible enough to accommodate different types of dependent variables. For health services utilization, GLM with Poisson distribution and log link has been widely used in the literature.[110,121] For healthcare costs, GLM with gamma distribution and log

link function was utilized. Health services utilization and healthcare costs were evaluated over a fixed 12 month period following the index date.

4.7.4.2 Health Services Utilization

Separate models were estimated for each outcome, including number of outpatient physician office visits, number of inpatient hospital admissions, number of inpatient hospital days, and number of ER visits. If the majority of patients never used a particular service, a logistic regression model was used to compare healthcare resource utilization between the two cohorts. If the majority of patients had more than one type of visit during the follow-up period, Poisson regression models were used to compare healthcare utilization between the two cohorts (Model 4), where the *ßs* are the log relative risk parameters. Unadjusted and adjusted means were reported.

Model 4:

$$\log\left(\frac{\mathbf{n}}{\mathbf{t}}\right) = \boldsymbol{\beta_0} + \boldsymbol{\beta_1}(\boldsymbol{Type\ of\ TKI\ therapy}) + \boldsymbol{\beta_2}(\mathbf{PS}) + \boldsymbol{\varepsilon}$$

n: count of events for a given individual
t: is time for follow-up
Type of TKI therapy: an indicator of first or second-generation TKI therapy use
PS_i: the propensity score quintile

4.7.4.3 Healthcare costs

Medical, pharmacy, and total cost categories (i.e. pharmacy plus medical costs) were analyzed separately. To estimate the association between TKI therapy and healthcare costs, GLMs were fitted to estimate mean healthcare costs (Model 5). The usefulness of the GLM model for modeling healthcare costs is its ability to handle non-constant variance (heteroscedasticity) and avoids having to retransform log-transformed costs, which is a common strategy for handling highly skewed healthcare cost data.[110] The ßs are the regression coefficients, which are the log relative risk parameters. The fitted GLM was used to produce adjusted mean cost estimates for patients initiating therapy on first versus second-generation TKI therapy and tested whether the differences between adjusted means was statistically significant. Unadjusted and adjusted means were reported.

Model 5:

$$\mu_{it} = e^{\beta_0 + \beta_1 P_{i1} + \beta_2 Xij}$$

μ_{it}: represents mean costs for patient i at time t
P_i: indicates whether a patient initiated therapy with a second-generation versus a first-generation TKI
X_{i_i}: a vector of coefficients for control variables

4.7.5 Aim 5: Perform exploratory analyses to determine if adherence, healthcare utilization, and healthcare costs differ between patients newly initiating nilotinib versus dasatinib.

4.7.5.1 Overview

The null hypothesis for Aim #5 is that no significant differences exist between nilotinib and dasatinib for adherence, healthcare utilization, and healthcare costs.

To date, there have been no direct comparisons of nilotinib and dasatinab as first-line therapy for CML patients. Additionally, there are no observational studies available comparing adherence, healthcare utilization, and healthcare costs among patients newly initiating nilotinib and dasatinib. The analytical approaches for comparing nilotinib and dasatinib were the same as those comparing first and second-generation TKI therapies.

4.8 Missing Data

The pharmacy claims data were explored to determine the amount of missing data and patterns of missing data for claims for TKI therapy. There were no missing data for any of the claims for TKI therapy. Additionally, there were few missing data in the medical data. Multiple imputation would have been used for handling missing data for independent variables with missing data on less than 5% of a variable.[122] This approach was not used as there were no missing data for the independent variables.

CHAPTER V: RESULTS

5.1 Study Population

A flowchart of the sample selection process and construction of the study cohorts is illustrated in Figure 5.1. There were 2,369 patients with a pharmacy claim for a TKI therapy between June 1, 2010 and December 31, 2011. After applying the inclusion and exclusion criteria, 368 patients remained for analysis for Aims 1, 2, and 3. This included 237 patients who initiated therapy on a first generation TKI (i.e. imatinib) and 131 patients who initiated therapy on a second-generation TKI (i.e. 68 dasatinib, 63 nilotinib). A subset of 133 patients was identified who (1) were enrolled in a Humana plan that provides both pharmacy and medical coverage and (2) had at least 12 months of follow-up data available. Data from these patients were used to compare differences in healthcare utilization and costs between patients who initiated a first versus second-generation TKI therapy (Aim 4). Finally, within the subset of 133 patients, 23 were taking dasatinib and 19 were taking nilotinib. These two groups were used for the exploratory analyses that comprise Aim 5.

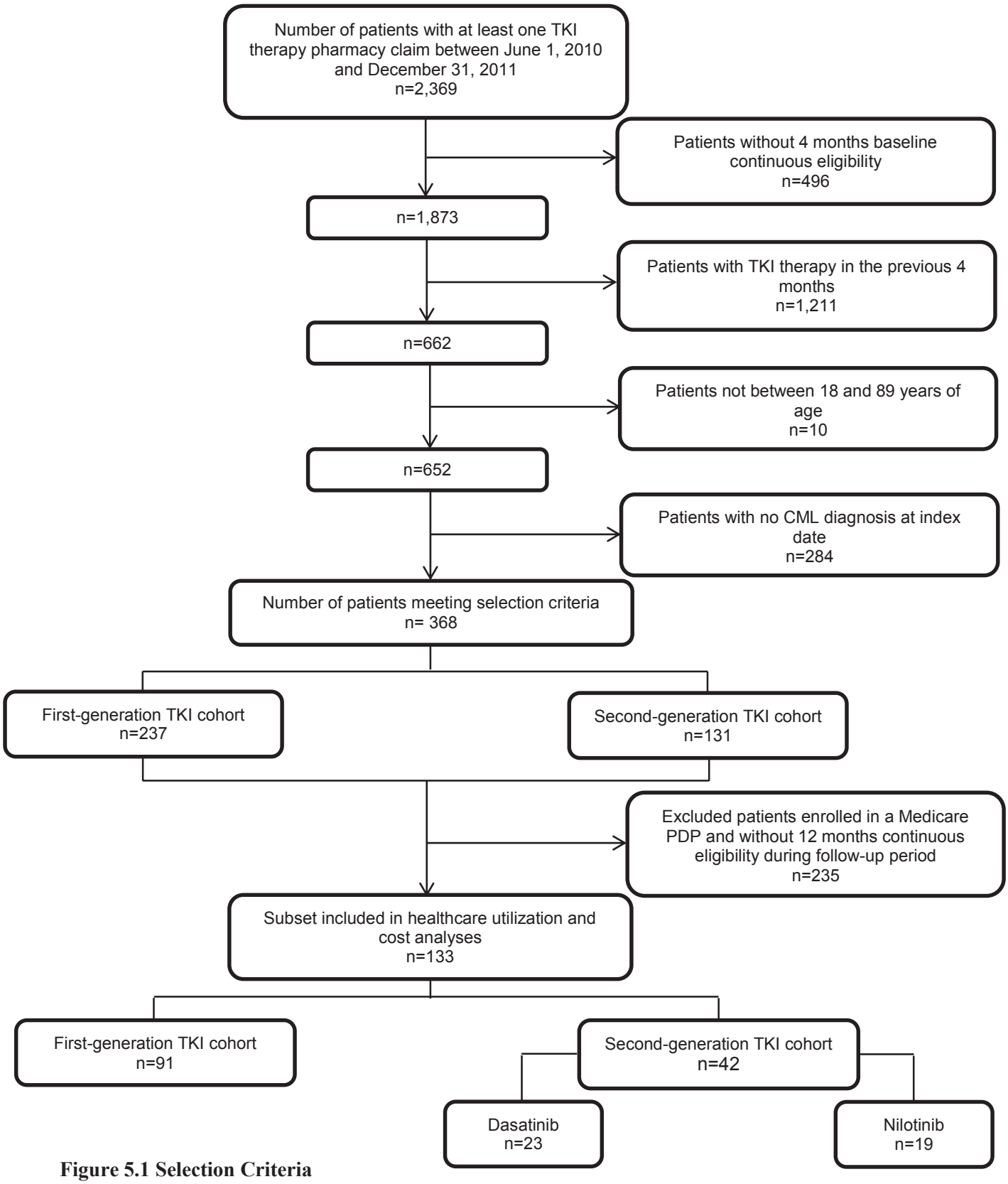

Figure 5.1 Selection Criteria

5.2 Baseline Characteristics

The characteristics of patients newly initiating a TKI therapy for the treatment of CML are presented in Table 5.1. Of the 368 patients included in the full sample, 64.4% (n=237) were started on a first-generation TKI. The two cohorts differed on the following five characteristics: age; plan type; dose schedule of the TKI therapy; CML phase, as measured by the starting dose proxy measure; and patient out-of-pocket costs for the index TKI prescription. Patients included in the second-generation TKI cohort were younger compared to those in the first-generation TKI cohort ($p=0.04$). Additionally, a higher proportion of patients in the second-generation TKI cohort were enrolled in a commercial plan compared to those in the first-generation TKI cohort ($p=0.04$). Although the RxRisk-V and Charlson Comorbidity scores were similar between cohorts, there was a difference on the proxy measure of CML phase, as measured by the starting dose proxy measure. Specifically, patients who were initiated on a second-generation TKI were more likely to start on a dose that indicates accelerated disease than patients initiated on a first-generation TKI ($p<0.0001$). As expected, patients included in the first-generation TKI cohort were more likely to initiate TKI therapy with once daily dosing rather than twice daily compared to the second-generation TKI cohort ($p<0.001$). Although there were no differences between patient out-of-pocket costs for the index TKI prescription when cost was tested as a continuous variable, differences emerged when it was categorized as an ordinal variable. Patients initiating therapy on a second-generation TKI compared to a first-generation TKI had higher out-of-pocket costs for the index TKI prescription ($p<0.001$). Finally, patients initiated on therapy with a first-generation TKI were on average enrolled in a Humana plan for 335 days compared to 325 days for patients initiated on a second-generation TKI.

Table 5.1 Baseline Characteristics

	First-Generation TKI Cohort n=237	Second-Generation TKI Cohort n=131	p value
Demographic Characteristics			
Age (years), mean (SD), [range]	69.9 (11.4) [32-89]	67.2 (13.5) [24-88]	0.04
Age (years), n (%)			
<55	26 (11.0)	22 (16.8)	0.28
55-64	24 (10.1)	17 (13.0)	
65-74	102 (43.0)	53 (40.4)	
≥75	85 (35.9)	39 (29.8)	
Female, n (%)	125 (52.7)	74 (56.5)	0.49
Plan, n (%)			
Commercial	14 (5.9)	17 (13.0)	0.04
MAPD	94 (39.7)	37 (28.2)	
PDP	129 (54.4)	77 (58.8)	
Geographic region, n (%)			
Northeast	15 (6.3)	13 (9.9)	0.56
Midwest	50 (21.1)	29 (22.1)	
South	134 (56.5)	72 (55.0)	
West	38 (16.1)	17 (13.0)	
LIS status, n (%)*	54 (22.8)	36 (27.5)	0.32
Dual eligibility, n (%)*	26 (11.0)	22 (16.8)	0.11
Clinical Characteristics			
Index medication starting dose in mg, mean (SD), [range]			
Imatinib	378 (97) [100-800]	N/A	
Dasatinib	N/A	100 (22) [40-150]	
Nilotinib	N/A	606 (157) [150-800]	
Dose schedule, n (%)			
Once daily	234 (98.7)	73 (55.7)	<0.001
Twice daily	3 (1.3)	58 (44.3)	
Proxy for CML phase, n (%)†			
Chronic	230 (97.0)	108 (82.4)	<0.0001
Accelerated or blast crisis	7 (3.0)	23 (17.6)	
Vaccine use, n (%)	30 (12.7)	19 (14.5)	0.62
Number of unique concurrent medication, n (%)			
0-2	104 (43.9)	59 (45.0)	0.83
>2	133 (56.1)	72 (55.0)	
Channel, n (%)			
Specialty	125 (52.7)	81 (61.8)	0.22
Retail	105 (44.3)	49 (37.4)	
MCO	3 (1.3)	0 (0)	
Long term care	4 (1.7)	1 (0.8)	
Member out-of-pocket cost for index medication, mean (SD), [range]	$1,566 ($1,204) [$0-$4,742]	$1,844 ($1,586) [$0-$7,685]	0.12

Member out-of-pocket cost for index TKI prescription, n (%)			
$0-$1,000	89 (37.6)	51 (38.9)	0.001
$1,001-$2,000	45 (19.0)	14 (10.7)	
$2,001-$3,000	75 (31.6)	43 (32.8)	
$3,001-$4,000	23 (9.7)	8 (6.1)	
>$4,000	5 (2.1)	15 (11.5)	
Coverage Gap, n (%)			
2010	141 (59.5)	66 (50.4)	0.09
2011	225 (94.9)	123 (93.9)	0.67
2012	188 (79.3)	93 (71.0)	0.07
RxRisk-V Score, mean (SD), [range]	5.1 (3.3) [0-16]	5.0 (3.1) [0-14]	0.69
Charlson Comorbidity Index, mean (SD), [range]‡	2.5 (2.7) [0-14]	2.3 (3.1) [0-13]	0.81
Provider Characteristics			
Male, n (%)	194 (81.9)	104 (80.6)	0.65
Age (years), mean (SD), range	50.6 (9.5) [27-73]	49.8 (10.3) [31-74]	0.42
Age (years), n (%)			
≤44	68 (28.7)	46 (35.1)	0.53
45-54	85 (35.9)	39 (29.8)	
55-64	65 (27.4)	37 (28.2)	
≥65	19 (8.0)	9 (6.9)	
Specialty, n (%)			
Oncologist	221 (93.3)	122 (93.1)	0.97
Non-oncologist	16 (6.7)	9 (6.9)	
Practice Setting, n (%)			
Academic	30 (12.7)	18 (13.7)	0.87
Private	108 (45.6)	56 (42.7)	
Other¶	99 (41.8)	57 (43.5)	

LIS=low income subsidy; MAPD=Medicare Advantage Prescription Drug plan; PDP=prescription drug plan; MCO=managed care organization

*LIS and dual eligibility are only assessed for Medicare patients

†Patients' starting dose of TKI therapy was assessed and used as a proxy for CML phase at the time of initiation

‡Calculated only for patients with medical data available; 76 patients started on imatinib and 46 patients started on a 2G-TKI had medical data available

¶Other practice setting was defined as community hospitals, clinics, or outpatient cancer care facilities neither owned by the practicing physicians nor considered academic or university-based

5.3 Propensity Score (PS) Estimation

5.3.1 PS Generation

Because patients were not randomly assigned their TKI therapy, a propensity score was estimated and used as a covariate in the models to control for differences between first and second-generation TKI cohorts. A propensity score is the predicted probability of treatment conditional on selected covariates. Logistic regression was used to estimate propensity scores. The following

covariates were used to estimate the probability of initiating a second-generation TKI: patient demographic (i.e., age, gender, plan type, region, LIS, dual eligibility status), clinical (i.e., proxy for CML phase, RxRisk-V score, medication count, flu or pneumonia vaccination), and provider characteristics (i.e., age, gender, specialty, practice setting). Dose schedule, member out-of-pocket costs, and channel of distribution were not included in the propensity score because they were assessed at the index date and are correlated with the type of TKI or how the patient may obtain the TKI (i.e. channel of distribution).

5.3.2 Fit

The c, or concordance, statistic is often cited as a measure of the fit of the propensity score. It can take on values between 0.5 (classification no better than flipping a coin) and 1.0 (perfect classification). The c-statistic measures the ability of a model to predict treatment status using the observed covariates. Several reviews have reported a c-statistic greater than 0.90 indicates very good ability of the propensity score model to predict treatment status.[123] The c-statistic for this study was 0.70. Although a c-statistic is often reported, it provides no certainty that all measured confounders have been balanced between treatment groups. Therefore rather than letting the c-statistic guide selection of covariates into the propensity score model selection was informed by the conceptual model used to identify potentially important predictors of treatment selection (Figure 3.2).[123]

After model fit was evaluated, the distribution of the propensity scores for patients initiating first versus second-generation TKI therapy was evaluated. A histogram is commonly used to compare the distributions of the propensity scores for treatment groups. Figure 5.2 shows that PS significantly overlapped between patients who initiated therapy on first versus second-generation TKI therapy. Therefore, PS trimming was not needed.

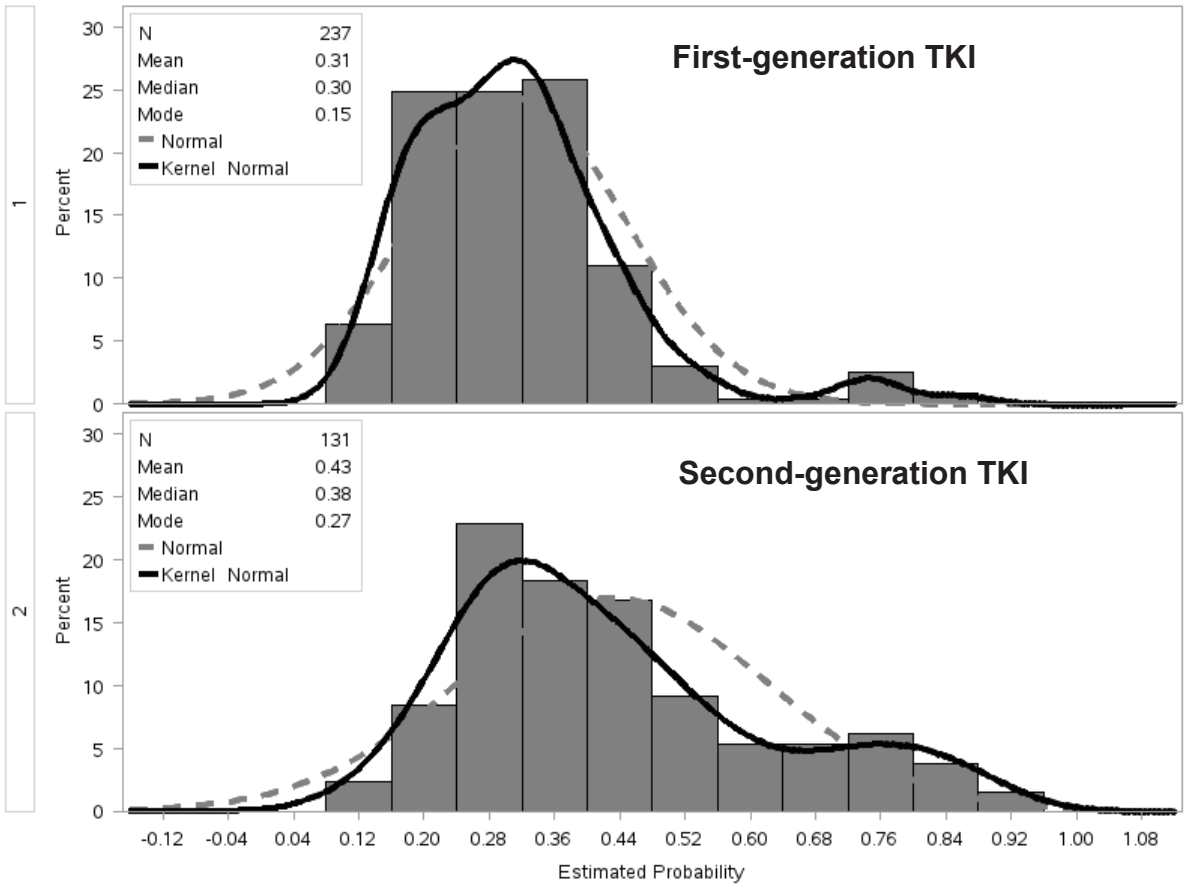

Figure 5.2 Distribution of propensity scores

5.3.3 Balance by quintiles

Table 5.2 shows the balance of covariates used to estimate the probability of initiating a second-generation TKI. Although in theory one must be able to achieve balance on all the covariates of interest to obtain an unbiased estimate, this did not occur. There are two covariates that were significantly different within the quintiles including patients with low income subsidy (quintile 1) and vaccine use (quintile 2) suggesting these covariates were not balanced for the two treatments within these subclasses. It was determined that these variables were not of clinical significance and therefore bias adjustment or adding interaction terms was not warranted.

Table 5.2 Balance of covariates by quintile

	Quintile 1 n=73 (61 1G; 12 2G)	**Quintile 2 n=74 (52 1G; 22 2G)**	**Quintile 3 n=74 (50 1G; 24 2G)**	**Quintile 4 n=73 (50 1G; 23 2G)**	**Quintile 5 n=73 (24 1G; 50 2G)**
Demographic characteristics	p-value	p-value	p-value	p-value	p-value
Age	0.25	0.80	0.13	0.60	0.21
Sex	0.48	0.52	0.24	0.89	0.42
Plan	0.20	0.11	0.78	0.18	0.34
Region	0.99	0.77	0.80	0.18	0.60
LIS	0.01	0.21	0.95	0.66	0.25
Duals	1.0	0.10	0.44	0.22	0.31
Clinical characteristics					
Proxy for CML phase	1.0	1.0	1.00	1.00	0.17
RxRisk-V score	0.30	0.57	0.51	0.60	0.77
Medication count	0.88	0.22	0.83	0.07	0.10
Vaccine use	0.19	0.05	0.50	0.41	0.95
Provider characteristics					
Age	0.55	0.71	0.82	0.91	0.99
Sex	0.34	0.94	0.48	0.61	0.20
Specialty	0.58	0.25	0.59	0.07	0.17
Practice type	0.36	0.95	0.93	0.90	0.95

1G=first-generation TKI; 2G=second-generation TKI

5.4 Aim 1: Identify factors associated with newly initiating therapy for CML with a second generation versus a first-generation TKI.

5.4.1 Main analyses

5.4.1.1 Summary of analyses

Logistic regression was used to identify factors associated with newly initiating a second-generation TKI therapy. Patient demographic (i.e., age, gender, plan type, region, LIS, dual eligibility status), clinical (i.e., RxRisk-V score, CML phase of disease, flu or pneumonia vaccination, medication count), and provider characteristics (i.e., age, gender, specialty, practice setting) were included as covariates for adjustment. Model fit was assessed through the Hosmer and Lemeshow goodness-of-fit test (p=0.61).

5.4.1.2 Results

CML disease phase and enrollment in a MAPD plan were the only factors associated with initiating a second-generation versus first-generation TKI. Patients with a starting dose that reflected accelerated disease (OR=8.06, 95% CI: 3.22-20.18) were more likely to initiate therapy with a second-generation TKI. Patients enrolled in a MAPD plan (commercial plan was referent) were less likely to initiate a second-generation TKI (OR: 0.27, 95% CI: 0.09-0.79).

Table 5.3 Factors associated with initiating a second-generation TKI

	Odds Ratio	95% CI	p-value
Demographic Characteristics			
Age (referent age<55)			
55-64	1.23	0.46-3.29	0.67
65-74	0.85	0.34-2.08	0.72
>75	0.90	0.36-2.27	0.82
Gender, male vs. female	0.71	0.44-1.14	0.16
Plan (referent commercial)			
MAPD	0.27	0.09-0.79	0.02
PDP	0.53	0.19-1.50	0.23
Region (referent south)			
Midwest	1.15	0.63-2.10	0.66
Northeast	1.38	0.57-3.35	0.48
West	0.82	0.42-1.65	0.58
LIS, yes vs. no	0.98	0.46-2.06	0.95
Duals, yes vs. no	1.78	0.72-4.38	0.21
Clinical Characteristics			
Proxy for CML phase, accelerated vs. chronic	8.06	3.22-20.18	<.0001
RxRisk-V score, >2 vs ≤2	1.13	0.57-2.24	0.74
Medication count, >2 vs ≤2	0.88	0.49-1.60	0.69
Vaccine, yes vs no	2.16	0.96-4.85	0.06
Provider Characteristics			
Age (referent <45)			
45-54	0.72	0.40-1.29	0.27
55-64	0.86	0.46-1.62	0.64
>65	0.81	0.31-2.10	0.67
Gender, female vs. male	1.01	0.52-1.93	0.99
Specialty, oncologist vs. non-oncologist	0.83	0.33-2.10	0.70
Practice setting (referent other)			
Academic	0.71	0.33-1.52	0.38
Private	0.93	0.56-1.54	0.78

5.4.2 Sensitivity Analyses

A sensitivity analysis was conducted for patients with medical data available (n=162). Model fit was assessed through the Hosmer and Lemeshow goodness-of-fit test (p=0.88). The Charlson comorbidity index replaced the RxRisk-V score as a measure of comorbidity in the sensitivity analysis. Similar to the main analyses, patient comorbidity was not a significant factor associated with initiating a second-generation versus a first-generation TKI therapy. In the sensitivity analysis, CML disease severity was associated with initiating a second-generation TKI which was consistent

with the main analyses. Additionally, increased patient age (reference age was <55 years) was associated with lower odds of initiating a second versus first-generation TKI therapy and vaccine use was associated with a higher odds of initiating a second-generation TKI therapy (Table 5.4).

Table 5.4 Factors associated with initiating a second versus first-generation TKI in sensitivity analysis limited to patients with medical data available (n=162)*

Covariates	Odds Ratio	95% CI
Accelerated phase vs. chronic phase†	22.50	4.36-116.07
Patient age (reference age<55)		
55-64	0.97	0.30-3.12
65-74	0.18	0.06-0.53
>75	0.19	0.06-0.62
Vaccine use (Yes vs. No)	3.01	1.23-7.35

*The following covariates were included in the full model: demographic characteristics (i.e. age, gender, plan type, region, LIS, dual eligibility status), clinical characteristics (i.e. Charlson comorbidity index, CML phase of disease, flu or pneumonia vaccination, medication count), and provider characteristics (i.e., age, gender, specialty, practice setting)

†Patients' starting dose of TKI therapy was assessed and used as a proxy for CML phase at the time of initiation

A second sensitivity analysis was conducted limited to patients who were initiated on a starting dose that indicated chronic phase disease (n=338). Therefore, patients' who initiated therapy on a dose that indicates accelerated disease were excluded. Patients with chronic phase disease who were enrolled in a Medicare plan (commercial plan was the referent) were less likely to initiate a second-generation TKI compared to a first-generation TKI. Vaccine use was associated with higher odds of initiating a second-generation TKI (Table 5.5).

Table 5.5 Factors associated with initiating a second versus first-generation TKI in sensitivity analysis limited to patients with chronic phase CML (n=338)*

Covariates	Odds Ratio	95% CI
Plan type (referent commercial)		
MAPD	0.21	0.08-0.53
PDP	0.52	0.23-1.18
Vaccine use (Yes vs. No)	2.34	1.04-5.28

*The following covariates were included in the full model: demographic characteristics (i.e. age, gender, plan type, region, LIS, dual eligibility status), clinical characteristics (i.e. Charlson comorbidity index, flu or pneumonia vaccination, medication count), and provider characteristics (i.e., age, gender, specialty, practice setting)

5.5 Aim 2: Examine differences in treatment interruption and regimen change comparing patients newly initiating a second-generation versus a first-generation TKI

5.5.1 Treatment interruption

5.5.1.1 Main analyses

5.5.1.1.1 Summary of analyses

Treatment interruption was defined as a gap in the index TKI therapy of greater than 30 days. Patients were followed from the first TKI therapy fill (i.e. index date) to the date of treatment interruption, end of enrollment or end of study period, whichever came first. Unadjusted outcomes are provided for treatment interruption. Additionally, three cox proportional-hazard (CPH) models were used to compare rates of treatment interruption between second-generation and first-generation TKI therapy. The three CPH models were an unadjusted, multivariable, and propensity score (PS) quintile. Finally, because half of the patients within the study had a treatment interruption, a post-hoc analysis was included to evaluate behavior change following treatment interruption.

5.5.1.1.2 Results

In the unadjusted analyses, patients in the first-generation TKI therapy cohort were less likely to have a treatment interruption compared to those in the second-generation TKI cohort (x^2=6.27, p=0.01) (Table 5.6). In addition, patients initiated on a first-generation TKI stayed on therapy longer compared to patients initiating a second-generation TKI therapy (233 days vs. 186 days, respectively, t=3.18, p=0.002).

Table 5.6 Unadjusted outcomes for treatment interruption by TKI therapy

	First-generation TKI cohort n=237	Second-generation TKI cohort n=131	p-value
Treatment interruption, n (%)	107 (45.1)	77 (58.8)	0.01
Time period treatment interruption occurred post index date, n (%)			
0-50 days	27 (90.0)	24 (92.3)	0.76
51-100 days	30 (76.9)	22 (73.3)	0.73
101-150 days	13 (68.4)	14 (93.3)	0.07
151-200 days	11 (100)	4 (66.7)	0.04
201-250 days	11 (84.6)	3 (100.0)	0.47
251-300 days	7 (87.5)	7 (100.0)	0.33
301-365 days	8 (6.8)	3 (6.8)	0.99
Number of days on therapy, mean (SD)	233.4 (138.1)	185.5 (139.4)	0.002

All three Cox proportional hazard models (i.e. unadjusted, multivariable, and PS quintile) demonstrated consistent results (Table 5.7). Patients initiating a second-generation TKI were at greater risk of experiencing a treatment interruption compared to those initiating therapy with a first-generation TKI (HR: 1.59 unadjusted, 95% CI: 1.18-2.12; HR: 1.48 multivariable, 95% CI: 1.08-2.02; HR: 1.50 PS quintiles, 95% CI: 1.10-2.04). Results from the unadjusted Cox proportional hazard model are shown in Figure 5.3. Table 5.8 shows the results from the multivariable CPH model. In addition to patients initiating a second versus a first-generation TKI being at increased risk for a treatment interruption, accelerated phase CML versus chronic phase CML was also associated with increased risk of treatment interruption (HR: 1.97, p<.01),

Table 5.7 Association between initiating a second-generation TKI and treatment interruption

Model	Hazard Ratio	95% CI
Unadjusted	1.59	1.18-2.12
Multivariable*	1.48	1.08-2.02
PS quintiles*†	1.50	1.10-2.04

*Multivariable and PS quintiles model included the following covariates for adjustment: primary independent variable was type of TKI, demographic characteristics (i.e. age, gender, plan type, region, LIS, dual eligibility status), clinical characteristics (i.e. RxRisk-V score, CML phase of disease, flu or pneumonia vaccination, medication count), and provider characteristics (i.e., age, gender, specialty, practice setting)
†PS quintiles was not associated with treatment interruption

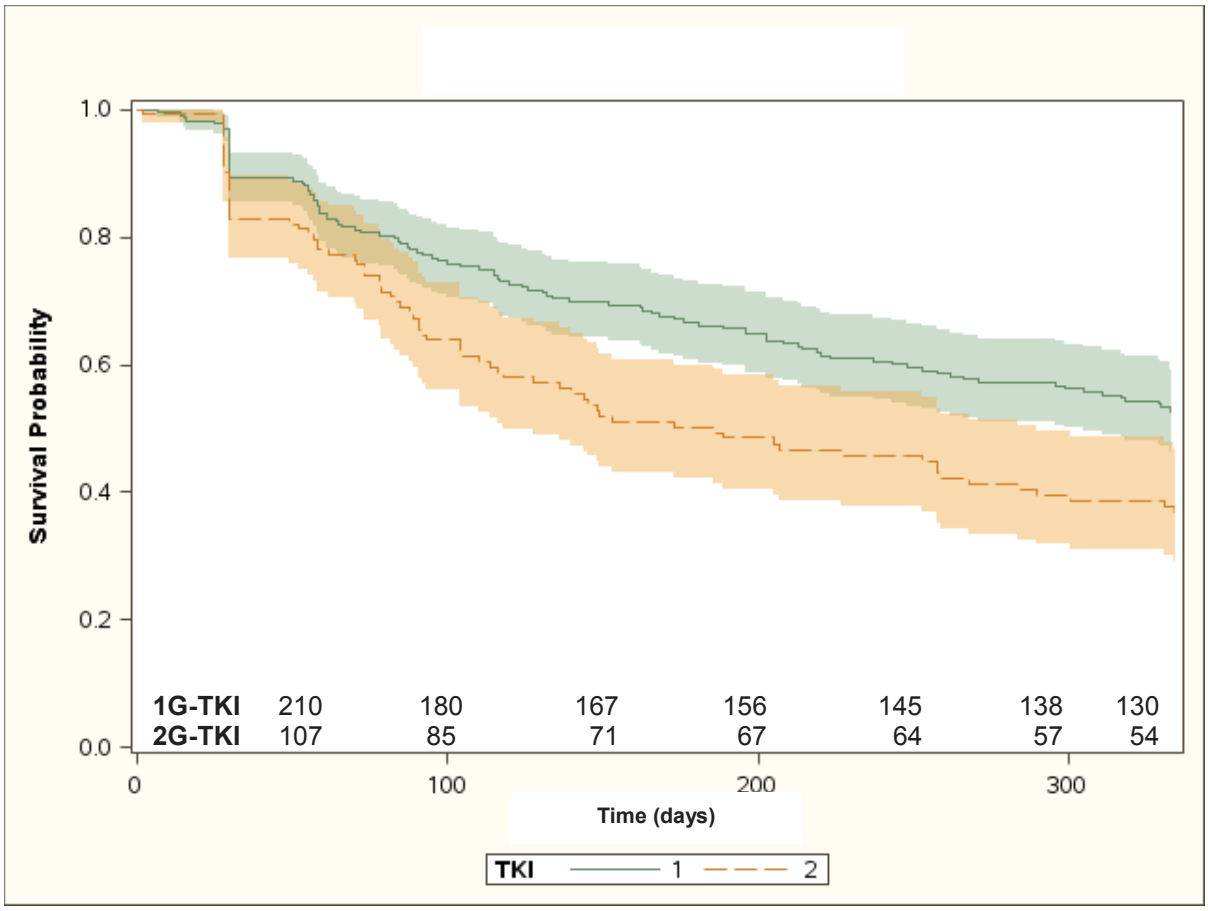

Figure 5.3 Time to treatment interruption, stratified by initiation with first versus second-generation TKI therapy

1G-TKI=first-generation TKI; 2G-TKI=second-generation TKI
Model fit: likelihood ratio p=0.0025.

Table 5.8 Multivariable analysis of initiation of TKI therapy with second versus first-generation TKI and treatment interruption

	Hazard Ratio	95% CI	p-value
Initiating a second-generation TKI versus first-generation TKI	1.48	1.08-2.02	0.01
Demographic Characteristics			
Age (referent age<55)			
55-64	0.95	0.52-1.76	0.87
65-74	0.72	0.42-1.31	0.27
>75	0.90	0.52-1.63	0.72
Gender, male vs. female	0.86	0.63-1.16	0.32
Plan (referent commercial)			
MAPD	0.97	0.48-2.02	0.93
PDP	0.94	0.48-1.93	0.86
Region (referent south)			
Midwest	0.87	0.58-1.27	0.48
Northeast	1.27	0.72, 2.3	0.39
West	1.28	0.81-1.95	0.27
LIS, yes vs. no	1.19	0.73-1.88	0.47
Duals, yes vs. no	0.77	0.43-1.38	0.38
Clinical Characteristics			
Proxy for CML phase, accelerated vs. chronic	1.97	1.16-3.20	<.01
RxRisk, >2 vs ≤2	1.12	0.71, 1.77	0.64
Medication count, >2 vs ≤2	1.15	0.79-1.70	0.49
Vaccine, yes vs no	0.76	0.44-1.27	0.31
Provider Characteristics			
Age (referent <45)			
45-54	1.64	1.10-2.46	0.02
55-64	1.48	0.96-2.29	0.08
>65	2.16	1.17-3.87	0.01
Gender, female vs. male	1.42	0.94-2.11	0.08
Specialty, oncologist vs. non-oncologist	1.01	0.55-2.05	0.98
Practice setting (referent other)			
Academic	1.17	0.71-1.85	0.53
Private	1.03	0.74-1.43	0.87

For those patients with a treatment interruption (n=184), medication change, re-initiation of the index medication, treatment discontinuation, or disenrollment from a Humana plan were evaluated. Approximately, 58% of patients who initiated therapy with a first-generation TKI re-initiated the index medication following a treatment interruption compared to 38% of patients who initiated therapy with a second-generation TKI (Figure 5.4). Medication change was the next most

common treatment pattern with almost one-fourth of patients changing medications in each cohort. A higher proportion of patients in the second-generation TKI cohort discontinued therapy compared to the first-generation TKI cohort by the end of the 1-year follow-up (30% vs. 15%, respectively). Few members with a treatment interruption disenrolled from a Humana plan.

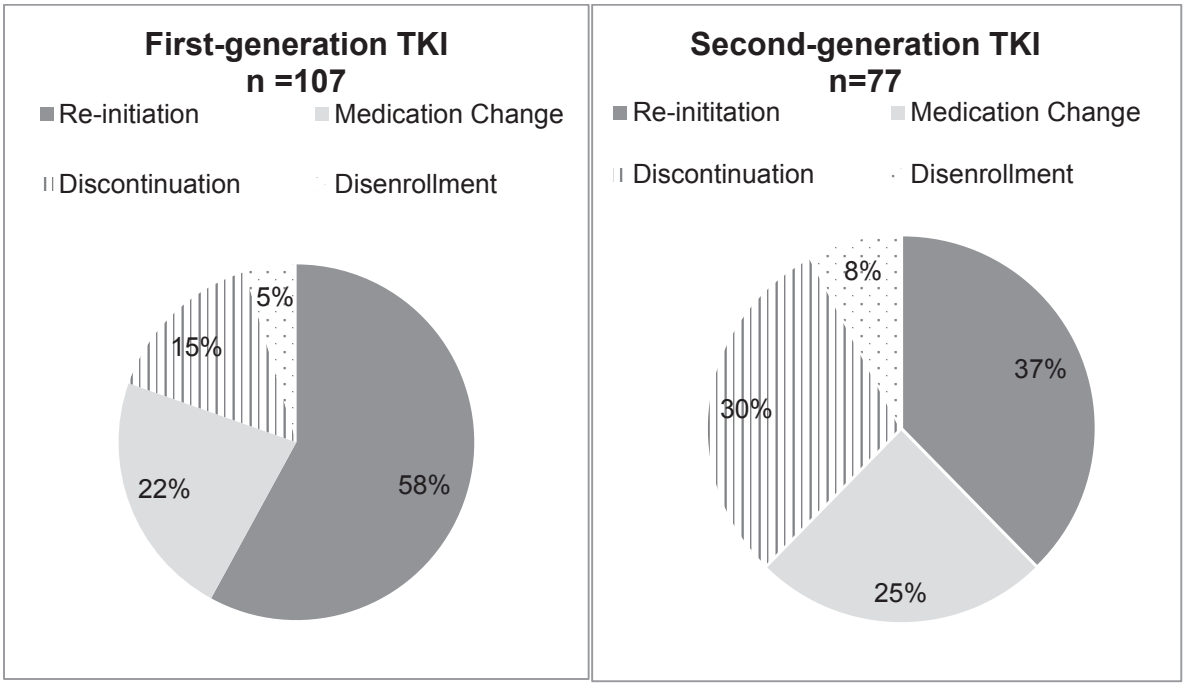

Figure 5.4 Treatment patterns following treatment interruption

Treatment patterns were followed for one change following treatment interruption. There were a total of 184 patients with a treatment interruption (107 from the first-generation TKI cohort and 77 from the second-generation TKI cohort)

5.5.1.2 Sensitivity Analyses

A sensitivity analysis was conducted and limited to patients who were initiated on a starting dose that indicated chronic phase disease (n=338). The results for the sensitivity analysis were consistent with those for the main analyses. Patients initiating a second-generation TKI were at greater risk of experiencing a treatment interruption compared to those initiating therapy with a first-generation TKI (Table 5.9).

A second sensitivity analysis was conducted to censor for death as a competing risk (Table 5.10). For this analysis patients were followed from the first TKI therapy fill (i.e. index date) to the date of treatment interruption, end of enrollment, date of death, or end of study period, whichever came first. The results were consistent with the main models. Patients initiating a second-generation TKI were at greater risk of experiencing a treatment interruption compared to those initiating therapy with a first-generation TKI.

Table 5.9 Association between initiating a second-generation TKI and treatment interruption in sensitivity analysis limited to patients with chronic phase CML (n=338)

Model	Hazard Ratio	95% CI
Unadjusted	1.44	1.05-1.98
Multivariable*	1.44	1.03-2.00
PS quintiles*	1.45	1.04-2.00

*Multivariable and PS quintiles model included the following covariates for adjustment: primary independent variable was type of TKI, demographic characteristics (i.e. age, gender, plan type, region, LIS, dual eligibility status), clinical characteristics (i.e. RxRisk-V score, CML phase of disease, flu or pneumonia vaccination, medication count), and provider characteristics (i.e., age, gender, specialty, practice setting)

Table 5.10 Association between initiating a second-generation TKI and treatment interruption in sensitivity analysis that includes censoring based on date of death (n=368)*

Model	Hazard Ratio	95% CI
Unadjusted	1.58	1.17-2.11
Multivariable†	1.46	1.07-1.99
PS quintiles†	1.50	1.10-2.04

*Patients were censored based on date of treatment interruption, death, disenrollment, or end of study period, whichever came first

†Multivariable and PS quintiles model included the following covariates for adjustment: primary independent variable was type of TKI, demographic characteristics (i.e. age, gender, plan type, region, LIS, dual eligibility status), clinical characteristics (i.e. RxRisk-V score, CML phase of disease, flu or pneumonia vaccination, medication count), and provider characteristics (i.e., age, gender, specialty, practice setting)

5.5.2 Regimen change

5.2.2.1 Main Analyses

5.2.2.1.1 Summary of analyses

Regimen change was defined as initiation of a different TKI therapy for CML (i.e. imatinib, dasatinib, nilotinib, and bosutinib) or a dose increase of the index TKI therapy during the follow-up period. Patients were followed from the first TKI therapy fill (i.e. index date) to the date of

medication change, end of enrollment or end of study period, whichever came first. Unadjusted outcomes were provided for regimen change. Additionally, three cox proportional-hazard models were used to compare regimen change rates between second-generation and first-generation TKI therapy.

5.2.2.1.2 Results

Approximately 19% of patients in each cohort had a regimen change during the follow-up period (Table 5.11). The majority of patients with a regimen change had a medication change (e.g. patients who initiated imatinib and changed to dasatinib) rather than a dose increase (e.g. patients who initiated imatinib 400 mg daily increasing their dose to 800 mg daily). There were no differences in regimen change between patients who initiated a first compared to a second-generation TKI based on bivariate results (x^2=0.06, p=0.88).

Results from the three Cox proportional hazard models (i.e. unadjusted, multivariable, and PS quintile) showed consistent results (Tables 5.12 and 5.13). There were no differences in TKI regimen change between patients initiating a first compared to a second-generation TKI. Table 5.13 shows the results from the multivariable CPH model. Older provider age (i.e. 45-64 years) versus younger provider age (i.e. <45 years) was associated with patients having a TKI regimen change.

Table 5.11 Unadjusted outcomes for regimen change by TKI therapy *

	First-generation TKI cohort	Second-generation TKI cohort	p-value
TKI regimen change, n (%)	45 (19.0)	24 (18.3)	0.79
Medication change, n (%)	32 (13.5)	19 (14.5)	0.88
Dose increase, n (%)	15 (6.3)	5 (3.8)	0.31
Time period regimen change occurred post index date, n (%)			
0-50 days	6 (60.0)	6 (75.0)	0.50
51-100 days	10 (50.0)	5 (35.7)	0.41
101-150 days	6 (46.1)	4 (80.0)	0.20
151-200 days	3 (60.0)	2 (40.0)	0.53
201-250 days	8 (72.7)	2 (50.0)	0.41
251-300 days	6 (75.0)	4 (66.7)	0.73
301-365 days	6 (3.5)	1 (1.1)	0.25

*Regimen change was defined as initiation of a different TKI therapy for CML (i.e. imatinib, dasatinib, nilotinib, and bosutinib) or a dose increase of the index TKI therapy during the follow-up period

Table 5.12 Association between initiating a second-generation TKI and regimen change

	Analysis	Hazard Ratio	95% CI
TKI regimen change	Unadjusted	1.01	0.60-1.63
	Multivariable*†	1.16	0.68-1.93
	PS quintiles*	1.13	0.66-1.87
Medication change	Unadjusted	1.13	0.63-1.97
	Multivariable*†	1.29	0.70-2.33
	PS quintiles*	1.23	0.67-2.20
Dose increase	Unadjusted	0.61	0.20-1.59
	Multivariable*†	0.70	0.21-2.00
	PS quintiles*	0.70	0.22-1.88

*Multivariable and PS quintiles model included the following covariates for adjustment: primary independent variable was type of TKI, demographic characteristics (i.e. age, gender, plan type, region, LIS, dual eligibility status), clinical characteristics (i.e. RxRisk-V score, CML phase of disease, flu or pneumonia vaccination, medication count), and provider characteristics (i.e., age, gender, specialty, practice setting)
† PS quintiles was not associated with TKI regimen change, medication change or dose increase

Table 5.13 Multivariable analysis of initiation of TKI therapy with second versus first-generation TKI and regimen change

	Hazard Ratio	95% CI	p-value
TKI (2nd versus 1st-generation)	1.16	0.68, 1.93	0.59
Demographic			
Age (referent age <55)			
55-64	1.33	0.50, 3.68	0.58
65-74	0.60	0.23, 1.70	0.31
>75	1.38	0.57, 3.74	0.50
Sex, male vs. female	0.78	0.78, 2.08	0.33
Plan (referent Commercial)			
MAPD	0.95	0.27, 3.92	0.94
PDP	1.40	0.43, 5.53	0.60
Region (referent south)			
Midwest	0.53	0.25, 1.05	0.08
Northeast	1.65	0.70, 3.61	0.23
West	0.72	0.32, 1.46	0.39
LIS*, yes vs. no	1.51	0.73, 2.89	0.24
Dual eligibility*, yes vs. no	0.61	0.25, 1.46	0.27
Clinical characteristics			
Proxy for CML phase†, accelerated vs. chronic	0.16	0.01, 0.73	0.07
RxRisk, >2 vs ≤2	0.94	0.44, 2.05	0.88
Medication count, >2 vs ≤2	1.14	0.62, 2.22	0.68
Vaccine	1.92	0.89, 4.49	0.14
Provider characteristics			
Age (referent <45)			
45-54	2.32	1.15, 4.95	0.03
55-64	2.74	1.35, 5.91	<0.01
>65	1.62	0.48, 4.78	0.40
Sex, female vs. male	0.90	0.40, 1.83	0.78
Specialty, oncologist vs. non-oncologist	0.85	0.34, 2.56	0.75
Practice type‡ (referent other)			
Academic	1.48	0.66, 3.06	0.31
Private	0.89	0.51, 1.53	0.66

*LIS and dual eligibility are only assessed for Medicare patients
†Patients' starting dose of TKI therapy was assessed and used as a proxy for CML disease severity at the time of initiation
‡Other practice setting was defined as community hospitals, clinics, or outpatient cancer care facilities neither owned by the practicing physicians nor considered academic or university-base

5.2.2.2 Sensitivity Analyses

A sensitivity analysis was conducted and limited to patients who were initiated on a starting dose that indicated chronic phase disease (n=338). The results for the sensitivity analysis were consistent with those for the main analyses. There was no difference in TKI regimen change for

patients initiating a second-generation TKI compared to those initiating therapy with a first-generation TKI (Table 5.14).

Table 5.14 Association between initiating a second-generation TKI and regimen change (n=338)*

Model	Hazard Ratio	95% CI
Unadjusted	1.13	0.67-1.85
Multivariable†	1.13	0.66-1.90
PS quintiles†	1.14	0.67-1.89

*Only patients with a starting dose indicating chronic phase disease were included
†Multivariable and PS quintiles model included the following covariates for adjustment: primary independent variable was type of TKI, demographic characteristics (i.e. age, gender, plan type, region, LIS, dual eligibility status), clinical characteristics (i.e. RxRisk-V score, CML phase of disease, flu or pneumonia vaccination, medication count), and provider characteristics (i.e., age, gender, specialty, practice setting)

A second sensitivity analysis used a logistic regression model to assess the association between initiating a first versus second-generation TKI therapy and changing TKI regimens (i.e. a dose increase or medication change) during the follow up period for those patients with 12 months continuous enrollment (n=311). The sensitivity analyses demonstrated consistent results with the main analyses. There was no association between initiating a first compared to a second-generation TKI and regimen change (Unadjusted: OR: 0.90, 95% CI 0.50-1.61; Multivariable: 0.95, 95% CI 0.52-1.87; PS quintile OR: 0.92, 95% CI 0.50-1.68).

5.6 Aim 3: Determine if adherence is higher among patients newly initiating a second-generation versus a first-generation TKI

5.6.1 Main Analyses

5.6.1.1 Summary of analyses

Adherence was calculated using proportion of days covered (PDC) for patients while they were on the initial TKI therapy only. Patients were censored if they changed to a different TKI therapy, end of enrollment, or the end of the study period, whichever came first. Three logistic regression models were used to evaluate the association between initiating a second-generation versus first-generation TKI therapy and adherence. The three logistic regression models were an unadjusted, multivariable, and PS quintile.

5.6.1.2 Results

Patients initiating a first-generation TKI had a higher mean adherence than patients initiating a second-generation TKI. The mean adherence was 0.77 and 0.68 for the first and second-generation TKI cohort, respectively (t=2.70, p=0.007) (Table 5.15). The proportion of adherent patients, defined as PDC ≥0.85, was similar between cohorts (x^2=0.84, p=0.36). Patients with high adherence (PDC ≥0.85) made up the largest group for both cohorts, followed by partial adherence (PDC, 0.4-0.85) and low adherence (PDC <0.4) (x^2=7.03, p=0.03).

Logistic regression was used to assess the association between initiating a second-generation versus first-generation TKI and adherence. Results from the logistic regression models shown in Tables 5.16 and 5.17 (i.e. unadjusted, multivariable, and PS quintile) were consistent with the unadjusted results (Table 5.15, x^2=0.84, p=0.36). There were no differences in adherence between patients initiating a second-generation compared to a first-generation TKI. Table 5.17 shows the results from the multivariable logistic regression model. Patients with accelerated phase CML versus chronic phase CML were less likely to be adherent (OR: 0.42, p=0.04)

Table 5.15 Unadjusted outcomes for adherence by TKI therapy

	First-generation TKI n=237	**Second-generation TKI n=131**	**p-value**
PDC, mean (SD), [range]	0.77 (0.24) [0.04-1.00]	0.68 (0.31) [0.06-1.00]	0.007
Adherent (PDC ≥0.85), n (%)	124 (52.3)	62 (47.3)	0.36
PDC, mean (SD), range by adherence category			
High, (PDC≥0.85)	0.94 (0.04) [0.85-1.0]	0.95 (0.04) [0.85-1.0]	0.32
Intermediate, (PDC, 0.4-0.85)	0.69 (0.11) [0.42-0.84]	0.63 (0.14) [0.41-0.84]	0.02
Low (PDC<0.4)	0.24 (0.10) [0.04-0.38]	0.19 (0.10) [0.01-0.36]	0.06
Adherence by category, n (%)			
High, (PDC≥0.85)	124 (52.3)	62 (47.3)	0.03
Intermediate, (PDC, 0.4-0.85)	85 (35.9)	40 (30.5)	
Low (PDC<0.4)	28 (11.8)	29 (22.0)	

Table 5.16 Association between initiating a first- versus second-generation TKI and adherence

	Model	Odds Ratio	95% CI
Adherence, defined as PDC ≥0.85	Unadjusted	0.82	0.53-1.26
	Multivariable*†	0.88	0.55-1.40
	PS quintiles*‡	0.88	0.56-1.38

* Multivariable and PS quintiles model included the following covariates for adjustment: primary independent variable was type of TKI, demographic characteristics (i.e. age, gender, plan type, region, LIS, dual eligibility status), clinical characteristics (i.e. RxRisk-V score, CML phase of disease, flu or pneumonia vaccination, medication count), and provider characteristics (i.e., age, gender, specialty, practice setting)
†See Table 5.17 for specific information related to covariates
‡PS quintiles was not associated with being adherent (OR: 0.93, 95% CI 0.80-1.08)

Table 5.17 Multivariable analysis evaluating the association between initiating a first versus second-generation TKI and adherence

	Odds Ratio	95% CI	p-value
Initiating a second-generation TKI versus first-generation TKI	0.88	0.55, 1.41	0.61
Demographic Characteristics			
Age (referent age<55)			
55-64	1.30	0.51, 3.29	0.58
65-74	1.88	0.56, 2.99	0.56
>75	0.93	0.42, 2.11	0.99
Gender, male vs. female	1.36	0.88, 2.11	0.17
Plan (referent commercial)			
MAPD	1.06	0.38, 2.97	0.91
PDP	1.26	0.48, 3.55	0.65
Region (referent south)			
Midwest	1.58	0.89, 2.81	0.12
Northeast	0.97	0.41, 2.27	0.94
West	0.87	0.47, 1.63	0.67
LIS, yes vs. no	0.87	0.44, 1.73	0.69
Duals, yes vs. no	1.20	0.51, 2.84	0.67
Clinical Characteristics			
Proxy for CML phase, accelerated vs. chronic	0.42	0.18, 0.99	0.04
RxRisk, >2 vs ≤2	1.02	0.54, 1.95	0.94
Medication count, >2 vs ≤2	0.66	0.38, 1.13	0.13
Vaccine, yes vs no	1.72	0.81, 3.62	0.15
Provider Characteristics			
Age (referent <45)			
45-54	0.82	0.47, 1.41	0.47
55-64	1.25	0.69, 2.25	0.47
>65	0.61	0.25, 1.49	0.28
Gender, female vs. male	0.60	0.33, 1.13	0.10
Specialty, oncologist vs. non-oncologist	0.85	0.34, 2.0	
Practice setting* (referent other)			
Academic	0.97	0.48, 1.96	0.93

Private	0.85	0.53, 1.36	0.49

*Other practice setting was defined as community hospitals, clinics, or outpatient cancer care facilities neither owned by the practicing physicians nor considered academic or university-based

5.6.2 Sensitivity Analyses

Additional covariates were added to the multivariable logistic regression model in the sensitivity analyses. First, twice daily dose schedule (referent once daily dosing) was added to the initial model. In this analysis, schedule was not associated with adherence (OR: 0.86, 95% CI: 0.42-1.85). Second, duration of therapy based on days on therapy days was added to the initial model as a categorical variable (i.e. 0-100 days, 101-200 days, 201-300 days, and 301-365 days). Longer duration of therapy was associated with higher odds of being adherent (OR: 54.20, 95% CI 21.08-139.68 for duration of therapy between 301-365 days compared to 0-100 days). An additional sensitivity analysis was completed to exclude patients with accelerated disease, leaving 338 for analysis. In this model, no covariates were associated with adherence.

It is generally agreed that a cut point of 0.8 provides meaningful information to distinguish between adherent and non-adherent patients. Therefore, a sensitivity analysis was conducted with adherence dichotomized at 0.80. Scores ≥0.80 were considered adherent and scores <0.80 were considered non-adherent. The logistic regression analyses are shown Table 5.18. Initiating a second versus a first-generation TKI was not associated with being more adherent when adherence was defined as ≥0.80. These results are consistent with the results from the primary analysis which defined adherence as a PDC ≥0.85.

Table 5.18 Association between initiating a second-generation TKI and medication adherence (defined as PDC ≥0.80)

	Analysis	Odds Ratio	95% CI
Adherence, defined as PDC ≥.80	Unadjusted	0.70	0.46-1.08
	Multivariable*†	0.76	0.47-1.23
	PS quintiles*‡	0.76	0.48-1.20

* Multivariable and PS quintiles model included the following covariates for adjustment: primary independent variable was type of TKI, demographic characteristics (i.e. age, gender, plan type, region, LIS, dual eligibility status), clinical characteristics (i.e. RxRisk-V score, CML phase of disease, flu or pneumonia vaccination, medication count), and provider characteristics (i.e., age, gender, specialty, practice setting)

†Vaccine use was associated with a higher odds of being adherent (OR: 2.22, 95% CI: 1.01, 4.84). Advanced phase CML was associated with lower odds of being adherent (OR: 0.37, 95% CI: 0.16, 0.87).
‡PS quintile was not associated with being adherent (OR: 0.91, 95% CI: 0.78-1.07).

Additionally, adherence was evaluated using an ITT approach. Patients were assigned to either the first-generation or second-generation TKI cohort, regardless of whether the patient subsequently had a treatment interruption or changed therapy. Patients were censored by the end of the study period or end of enrollment, whichever occurred first. Using this approach (data not shown), patients initiating a first-generation TKI therapy were more adherent compared to those initiating therapy with a second-generation TKI (PDC 0.77 and 0.68, respectively, t=2.94, p=0.003). Consistent with the main analysis, the proportion of adherent patients, defined as PDC ≥0.85, was similar between cohorts (54.8% vs. 45.0% for first-generation and second-generation TKI cohort, respectively; x^2=3.52, p=0.07).

5.7 Aim 4: Determine if rates of health services utilization (i.e. number of outpatient physician visits, number of inpatient hospital admissions, length of inpatient hospital stays, and number of emergency room visits) and healthcare costs differ between patients initiating a second-generation versus a first-generation TKI.

5.7.1 Health services utilization

5.7.1.1 Summary of analyses

Health services utilization were captured over the 12 months following initiation of therapy for a subset of patients with pharmacy and medical data available and compared between patients initiating a second-generation TKI versus a first-generation TKI. Unadjusted results were reported for each type of health service. Additionally, two generalized linear models (GLMs) were used to estimate outpatient visits and inpatient hospital days. Duration of the initial treatment, measured in days, was included in both adjusted models. Inpatient visits and ER visits were not widely used services. Therefore, a logistic regression model was used to compare inpatient visits between the two cohorts. Due to few patients having ER visits, only descriptive information is provided.

5.7.1.2 Results

Table 5.19 shows the unadjusted results for outpatient physician visits, inpatient hospitalization admissions, inpatient hospital days, and ER visits for patients initiating a first compared to a second-generation TKI therapy. Outpatient visits were the most used service. The mean number of outpatient visits during the 12-month period following initiation of TKI therapy was 37.8 and 42.4 for patients initiating a first compared to a second-generation TKI (p=0.33). Approximately, 20.4% (n=19) of patients initiating a first-generation TKI and 31.8% (n=14) of patients initiating a second-generation TKI had an inpatient visit during the follow-up period. There were only three patients with an inpatient visit who were classified as having accelerated phase disease. Patients initiating a first-generation TKI had, on average, lower inpatient admissions compared to those initiating therapy on a second-generation TKI (0.31 and 0.66 inpatient admissions, respectively, p=0.10). ER visits were the least used service for patients included in this study. Only 6 patients from each cohort had an ER visit during the follow-up period and all patients were classified as having chronic phase disease. Patients initiating a first-generation TKI had, on average a lower number of ER visits compared to those initiating therapy on a second-generation TKI (0.10 and 0.52 ER visits, respectively, p=0.10).

Results of the GLM examining the association between initiation of a second versus first-generation-TKI and (1) outpatient visits and (2) inpatient days are shown in Tables 5.20 and 5.21, respectively. Initiating a second-generation TKI was associated with increased outpatient visits and inpatient days. The estimates from the GLM were then exponentiated and can be interpreted as incidence rate ratios which are shown in Table 5.21.

A logistic regression model was used to evaluate the association between initiation of a second versus first-generation TKI and having an inpatient visit during the follow-up period (Table 5.22). As shown in Table 5.22, this association was not significant. However, patients with an increased baseline medication count (i.e. >2 medications versus ≤2) and those with LIS status had a

higher odds of having an inpatient visit. The following provider characteristics were associated with having a lower odds of having an inpatient visit: academic practice type versus other practice type and an oncologist versus non-oncologist.

Table 5.19 Health services utilization during the 12 month period post index date

	First-generation TKI Unadjusted mean (SD) range n=93	**Second-generation TKI Unadjusted mean (SD) range n=44**	**p-value**
Outpatient visits	37.83 (25.66) [0-149]	42.39 (25.42) [6-134]	0.33
Inpatient visits	0.31 (0.71) [0-4]	0.66 (1.29) [0-6]	0.10
Inpatient hospital days	1.30 (3.91) [0-28]	3.98 (8.54) [0-34]	0.05
ER visits	0.10 (0.39) [0-2]	0.52 (1.64) [0-7]	0.10

5.20 Association between initiating a second-generation versus first-generation TKI and outpatient visits and inpatient hospital days*

	Outpatient Visits			Inpatient Hospital Days		
Model	**Estimate**	**95% CI**	**p-value**	**Estimate**	**95% CI**	**p-value**
Multivariable†						
TKI (2nd versus 1st-generation)	0.12	0.06, 0.18	<.001	1.18	0.89-1.47	<.0001
Demographic						
Age	0.04	-0.0002, 0.07	0.05	0.10	-0.08, 0.29	0.28
Sex	-0.17	-0.23, -0.11	<.0001	0.63	0.37, 0.89	<.0001
Plan	0.09	0.05, 0.12	<.0001	0.26	0.09, 0.42	<.01
Region	-0.12	-0.15, -0.08	<.0001	0.06	-0.11, 0.24	0.48
LIS	0.13	0.05, 0.21	0.001	0.82	0.51, 1.13	<.0001
Dual	0.03	-0.07, 0.14	0.55	0.07	-0.35, 0.49	0.75
Clinical characteristics						
Duration of therapy	-0.0005	-0.0008, -0.0002	<.001	-0.0003	-0.0015, 0.0009	0.62
Proxy for CML phase	0.54	0.41, 0.66	<.0001	-0.19	0.58, 0.21	0.36
RxRisk	0.43	0.34, 0.52	<.0001	1.55	0.88, 2.18	<.0001
Medication count	0.07	-0.004, 0.14	0.06	0.95	0.59, 1.31	<.0001
Vaccine	0.25	0.19, 0.32	<.0001	0.32	0.01, 0.62	0.04
Provider characteristics						
Age	0.06	0.03, 0.09	<.001	0.13	-0.01, 0.28	0.07
Sex	-0.13	-0.23, -0.11	<.0001	-1.03	-1.35, 0.72	<.0001
Specialty	-0.18	-0.29, 0.07	<.01	0.42	0.24, 1.08	0.21
Practice type	-.011	-0.15, -0.07	<.0001	0.39	0.21, 0.58	<.0001
PS quintile†						
TKI (2^{nd} versus 1^{st}-generation)	0.12	0.05-0.19	<.0001	1.03	0.75, 1.30	<.0001
Quintile	-0.02	-0.04-0.00	0.06	0.09	0.008, 0.18	0.03
Duration of therapy	-0.0004	-0.0006—0.0001	<.01	0.0009	-0.0002, 0.002	0.11

* Mean health services utilization was evaluated using GLM with Poisson distribution and log link
NA, not applicable
†Multivariable and PS quintiles model included the following covariates for adjustment: primary independent variable was initiating a first versus second-generation TKI, demographic characteristics (i.e. age, gender, plan type, region, LIS, dual eligibility status), clinical characteristics (i.e. duration of treatment (days), RxRisk-V score, CML phase of disease, flu or pneumonia vaccination, medication count), and provider characteristics (i.e., age, gender, specialty, practice setting)

Table 5.21 Incidence rate ratio for outpatient visits and inpatient hospital days comparing initiation of a second versus first-generation TKI

TKI (2nd versus 1st-generation)	IRR	95% CI
Outpatient visits		
Multivariable analysis*	1.12	1.06, 1.20
PS quintile analysis	1.12	1.01, 1.21
Inpatient hospital days		
Multivariable analysis*	3.25	2.43, 4.35
PS quintile analysis	2.80	2.12, 3.67

IRR=incidence rate ratio

*Multivariable and PS quintiles model included the following covariates for adjustment: primary independent variable was initiating a first versus second-generation TKI, demographic characteristics (i.e. age, gender, plan type, region, LIS, dual eligibility status), clinical characteristics (i.e. duration of treatment (days), RxRisk-V score, CML phase of disease, flu or pneumonia vaccination, medication count), and provider characteristics (i.e., age, gender, specialty, practice setting)

5.22 Association between initiating a second-generation versus first-generation TKI and inpatient visits*

	Odds Ratio	95% CI	p-value
Inpatient visits			
Multivariable*†	3.91	0.91, 16.76	0.07
PS quintiles*‡	1.68	0.62, 4.60	0.31

* Multivariable and PS quintiles model included the following covariates for adjustment: primary independent variable was type of TKI, demographic characteristics (i.e. age, gender, plan type, region, LIS, dual eligibility status), clinical characteristics (i.e. duration of treatment (days), RxRisk-V score, CML phase of disease, flu or pneumonia vaccination, medication count), and provider characteristics (i.e., age, gender, specialty, practice setting)

†Covariates associated with increased risk of inpatient visits: increased medication count, low income subsidy; Covariates associated with decreased risk of inpatient visits: academic practice, oncologist

‡Quintile and duration of therapy were not significant in the model

5.7.2 Healthcare costs

5.7.2.1 Main Analyses

5.7.2.1.1 Summary of analyses

Medical, TKI-related pharmacy, non TKI-related pharmacy, and total costs (i.e. pharmacy plus medical costs) during the 12 months following TKI initiation were compared between patients who initiated therapy with a second versus first-generation TKI therapy. Unadjusted and adjusted healthcare costs are presented. For healthcare costs, GLM with gamma distribution and log link function was utilized. The two adjusted models were multivariable and PS quintile. Duration of the initial treatment, measured in days, was included in both adjusted models.

5.7.2.1.2 Results

The unadjusted mean total costs 12 months following initiation of a second-generation TKI ($88,804) were significantly higher compared to those patients who initiated a first-generation TKI therapy ($68,068, p<.01) (Table 5.23). The total costs for both cohorts were driven by TKI related costs ($54,284 and $66,954 for the first and second-generation TKI cohorts, respectively, p<.01).

Results of the GLM examining the association between initiation of a first versus second-generation-TKI and healthcare costs are shown in Tables 5.24 and 5.25. The βs presented in Table 5.24 are regression coefficients, which are the log relative risk parameters. Positive estimates are associated with higher costs and negative estimates are associated with lower costs. The results indicate that initiating a second-generation TKI compared to a first-generation TKI was associated with higher total healthcare costs (multivariable: estimate=0.26, p=0.01; PS quintile: estimate=0.30, p=<.001). Therefore, total healthcare costs for patients initiating a second-generation were 1.30 [exp(0.26)] times the total healthcare costs for patients initiating therapy on a first-generation TKI. This was also the case for TKI-related costs (multivariable: estimate=0.24, p<.01; PS quintile estimate=0.29, p<.01). However, the estimate was not significant for non TKI-related costs and medical costs. Finally, the predicted, adjusted total and TKI-related costs were greater among the second-generation TKI cohort compared to the first-generation TKI cohort, $86,509 versus $66,443 (p<.001) and $64,991 versus $55,838 (p<.01), respectively.

Table 5.23 Healthcare costs incurred during the 12 month period following initiation of first versus second-generation TKI therapy (n=133)*

	First-generation TKI Unadjusted mean costs (SD) [range] n=91	Second-generation TKI Unadjusted mean costs (SD) [range] n=42	p-value
Total costs (pharmacy + medical)	$68,068 ($29,207) [$7,459-$266,172]	$88,804 ($44,217) [$15,536-$193,950]	<.01
Pharmacy costs	$56,753 ($18,041) [$5368-$116,253]	$68,955 ($35,472) [$8,924-$134,040]	0.03
TKI-related	$54,284 ($18,691) [$3,920-$116,065]	$66,594 ($35,488) [$6,782-$128,791]	0.03
Non TKI-related	$2,469 ($4,458) [$0-$28,564]	$2,361 ($2,096) [$0-$7,360]	0.10
Medical costs	$11,315 ($22,119) [$0-$177,961]	$19,850 ($33,400) [$634-$183,237]	0.05

* Cost calculation included both plan paid and member out-of-pocket costs (i.e. patient copayments and co-insurance).

Table 5.24 Multivariable analysis of initiation of TKI therapy with second versus first-generation TKI and total, TKI-related costs, non TKI-related costs, and medical costs (n=133)*

Model	Total Costs			TKI-Related Costs			Non TKI-Related Costs			Medical Costs		
	Estimate	95% CI	p-value	Estimate	95% CI	p-value	Estimate	95% CI	p-value	Estimate	95% CI	p-value
Multivariable†												
TKI (2nd versus 1st-generation)	0.26	0.11-0.42	.001	0.24	0.07, 0.40	<.01	0.50	-0.07, 1.08	0.09	0.30	-0.18, 0.78	0.22
Demographic												
Age	-0.08	-0.17, 0.02	0.10	-0.11	-0.22, -0.004	0.04	0.09	-0.20, 0.39	0.53	0.05	-0.20, 0.29	0.71
Sex	0.08	-0.07, 0.22	0.28	0.06	-0.09, 0.21	0.46	-0.35	-0.78, 0.09	0.12	0.006	-0.40, 0.41	0.98
Plan	0.05	-0.04, 0.13	0.29	-0.08	-0.17, 0.01	0.09	0.16	-0.09, 0.41	0.22	0.55	0.31, 0.80	<.0001
Region	0.07	-0.03, 0.16	0.17	0.008	-0.10, 0.11	0.88	0.10	-0.19, 0.38	0.51	0.21	-0.08, 0.50	0.15
LIS	0.14	-0.05, 0.34	0.16	-0.01	-0.22, 0.20	0.91	0.36	-0.26, 0.99	0.26	0.95	0.37, 1.54	<.01
Dual	-0.21	0.49, 0.07	0.14	0.13	-0.3, 0.17	0.40	-0.23	-1.13, 0.68	0.63	-0.69	-1.51, 0.13	0.10
Clinical characteristics												
Duration of therapy	0.002	0.0009, 0.002	<.0001	0.003	0.002, 0.004	<.0001	-0.0003	-0.002, 0.002	0.81	-0.002	-0.004, -0.0005	0.02
Proxy for CML phase	-0.02	-0.29, 0.25	0.90	0.08	-0.21, 0.37	0.58	-0.72	-1.64, 0.21	0.13	0.10	-0.77, 0.98	0.82
RxRisk	0.11	-0.09, 0.31	0.29	0.02	-0.20, 0.23	0.87				0.99	0.40, 1.60	0.001
Medication count	0.10	-0.07, -0.28	0.25	0.07	-0.11, 0.26	0.44	0.92	0.40, 1.43	<.001	0.34	-0.16, 0.83	0.19
Vaccine	0.07	-0.10, 0.23	0.43	0.08	-0.10, 0.25	0.37	0.27	-0.24, 0.78	0.29	0.15	-0.33, 0.64	0.53
Provider characteristics												
Age	-0.08	-0.16, -0.004	0.04	-0.03	-0.11, 0.05	0.47				-0.13	-0.35, 0.09	0.25
Sex	0.09	-0.10, 0.27	0.38	0.08	-0.12, 0.28	0.43	0.17	-0.42, 0.76	0.57	-0.09	-0.61, 0.45	0.76
Specialty	-0.008	-0.29, 0.27	0.96	-0.007	-0.31, 0.30	0.96	0.13	-0.77, 1.03	0.78	--1.10	-1.91, -0.29	<.01
Practice type	-0.02	-0.10, 0.06	0.61	0.002	-0.08, 0.08	0.96	-0.14	-0.38, 0.11	0.28	-0.06	-0.28, 0.17	0.62
PS quintile‡												
TKI (2nd versus 1st-generation)	0.30	0.13, 0.47	<.001	0.29	0.11, 0.46	<.01	-0.17	-0.72, 0.39	0.55	0.38	-0.06, -0.83	0.09
Quintile	0.003	-0.05, 0.05	0.93	-0.02	-0.07, 0.04	0.60	0.12	-0.07, 0.31	0.22	0.07	-0.08, 0.22	0.35
Duration of therapy	0.001	0.006, 0.002	<.001	0.003	0.002, 0.004	<.0001	-0.0001	-0.003, 0.002	0.91	-0.004	-0.006, -0.002	<.001

* GLM with gamma distribution and log link; Cost calculation included both plan paid and member out-of-pocket costs (i.e. patient copayments and co-insurance).
†Multivariable model included the following covariates for adjustment: primary independent variable was initiating a first versus second-generation TKI; demographic characteristics (i.e. age, gender, plan type, region, LIS, dual eligibility status), clinical characteristics (i.e. duration of treatment (days) on index medication, RxRisk-V score, CML phase of disease, flu or pneumonia vaccination, medication count), and provider characteristics (i.e., age, gender, specialty, practice setting)
‡PS quintile model included the following covariates for adjustment: primary independent variable was initiating a first versus second-generation TKI, covariates (i.e. PS quintile, duration of treatment (days) on index medication)

Table 5.25 Predicted, adjusted healthcare costs during the 12 month period following initiation of first versus second-generation TKI therapy (n=133)*

	First-generation TKI mean costs (95% CI) n=91	Second-generation TKI mean costs (95% CI) n=42	p-value
Total costs (pharmacy + medical)	$66,443 ($61,194, $72,143)	$86,509 ($76,275, $98,125)	0.001
Pharmacy costs			
TKI-related	$51,344 ($47,014, $56,072)	$64,991 ($56,818, $74,340)	<.01
Non TKI-related	$1,387 ($1,064, $1,807)	$2,294 ($1,480, $3,556)	0.09
Medical costs	$9,331 ($7,389, $11,783)	$12,633 ($8,691, $18,365)	0.22

***** GLM with gamma distribution and log link; Cost calculation included both plan paid and member out-of-pocket costs (i.e. patient copayments and co-insurance).
Multivariable model included the following covariates for adjustment: primary independent variable was initiating a first versus second-generation TKI; demographic characteristics (i.e. age, gender, plan type, region, LIS, dual eligibility status), clinical characteristics (i.e. duration of treatment (days) on index medication, RxRisk-V score, CML phase of disease, flu or pneumonia vaccination, medication count), and provider characteristics (i.e., age, gender, specialty, practice setting)

5.7.2.2 Sensitivity Analyses

A sensitivity analysis limited to patients who were initiated on a starting dose that indicated chronic phase disease (n=123) was completed. The results were consistent with the main analyses, the unadjusted mean total healthcare, pharmacy and medical costs incurred during the 12 months following initiation of a second-generation TKI were significantly higher than those incurred by patients who initiated a first-generation TKI therapy (Table 5.26).

Table 5.26 Unadjusted healthcare costs incurred during the 12 month period following initiation of first versus second-generation TKI therapy (n=123)*

	First-generation TKI Unadjusted mean costs (SD) [range] n=89	Second-generation TKI Unadjusted mean costs (SD) [range] n=34	p-value
Total costs (pharmacy + medical)	$67,370 ($29,000) [$7,460-$266,172]	$93,079 ($43,908) [$15,536-$193,950]	<.001
Pharmacy costs	$55,838 ($16,921) [$5,368-$88,450]	$71,386 ($36,063) [$8,924-$134,040]	<.01
TKI-related	$53,315 ($17,499) [$3,919-$88,219]	$68,779 ($36,221) [$6,782-$128,791]	0.01
Non-TKI related	$2,522 ($4,494) [$0-$28,564]	$2,607 ($2,205) [$41-$7,360]	0.06
Medical costs	$11,532 ($22,320) [$0-$177,722]	$21,693 ($35,628) [$634-$183,237]	0.04

5.8 Aim 5: Perform exploratory analyses to determine if adherence, healthcare utilization, and healthcare costs differ between patients newly initiating dasatinib versus nilotinib.

Exploratory analyses were conducted to compare adherence, healthcare utilization, and healthcare costs between patients newly initiating dasatinib versus nilotinib.

5.8.1 Adherence

The results for adherence are shown in Table 5.27. There was no difference in mean adherence among patients initiating nilotinib compared to dasatinib. The mean adherence was 0.68 and 0.69 for patients initiating nilotinib and dasatinib, respectively (t=-0.10, p=0.92). Additionally, the proportion of adherent patients, defined as PDC ≥0.85, was similar between cohorts (x^2=0.40, p=0.52). Logistic regression was used to assess the association between initiating dasatinib versus nilotinib and adherence (Table 5.28) while controlling for potential confounders. As in the unadjusted analyses, there were no differences in adherence between patients initiating nilotinib compared to dasatinib. Further, none of the covariates in the model were significant.

Table 5.27 Unadjusted adherence outcomes for patients initiating nilotinib versus dasatnib

	Nilotinib n=63	**Dasatinib n=68**	**p-value**
PDC, mean (SD), [range]	0.68 (0.31) [0.08-1.0]	0.69 (0.31) [0.01-1.0]	0.92
Adherent (PDC ≥0.85), n (%)	28 (44.4)	34 (50.0)	0.52
Adherence by category, n (%)			
High (PDC, ≥0.85)	28 (44.4)	34 (50.0)	0.99
Intermediate (PDC, 0.4-0.85)	21 (33.3)	19 (27.9)	
Low (PDC, <0.4)	14 (22.2)	15 (22.1)	

Table 5.28 Multivariable analysis evaluating the association between initiating a second-generation TKI and adherence

	Odds Ratio	95% CI	p-value
Initiating nilotinib versus dasatinib	0.98	0.42, 2.32	0.97
Demographic Characteristics			
Age (referent age<55)			
55-64	1.72	0.32, 9.22	0.53
65-74	1.43	0.30, 6.94	0.66
>75	1.52	0.29, 7.96	0.62
Gender, male vs. female	1.93	0.84, 4.41	0.12
Plan (referent commercial)			
MAPD	1.32	0.22, 7.61	0.76
PDP	1.14	0.19, 6.87	0.89
Region (referent south)			
Midwest	1.47	0.49, 4.41	0.49
Northeast	1.59	0.39, 6.47	0.52
West	2.23	0.63, 7.86	0.21
LIS, yes vs. no	1.49	0.41, 5.45	0.55
Duals, yes vs. no	0.46	0.11, 2.02	0.30
Clinical Characteristics			
Proxy for CML phase, accelerated vs. chronic	0.36	0.11, 1.14	0.08
RxRisk, >2 vs ≤2	1.67	0.50, 5.53	0.40
Medication count, >2 vs ≤2	0.55	0.19, 1.57	0.26
Vaccine, yes vs no	2.03	0.44, 9.36	0.36
Provider Characteristics			
Age (referent <45)			
45-54	1.54	0.55, 4.35	0.41
55-64	1.11	0.38, 3.28	0.85
>65	1.48	0.27, 7.81	0.67
Gender, female vs. male	0.22	0.06, 0.80	0.02
Specialty, oncologist vs. non-oncologist	0.80	0.13, 4.79	
Practice setting* (referent other)			
Academic	1.03	0.27, 3.93	0.97
Private	0.77	0.32, 1.86	0.57

5.8.2 Health services utilization

Table 5.29 shows the results for outpatient physician visits, inpatient hospitalization admissions, inpatient hospital days, and ER visits during the12 month follow-up period for patients initiating nilotinib and dasatinib. Outpatient visits were the most used service with mean number of visits of 39 and 45 for patients initiating nilotinib and dasatinib, respectively (p=0.43). Inpatient visits and ER visits were not widely used services. Six patients had at least one inpatient visit during the follow-up period; whereas, 14 patients had at least one ER visit during this time period.

Results of the GLM examining the association between initiating dasatinib versus nilotinib and (1) outpatient visits and (2) inpatient days are shown in Tables 5.30 and 5.31. Unlike the bivariate analyses, initiating dasatinib compared to nilotinib was associated with increased outpatient visits and inpatient days. The estimates from the GLM were then exponentiated and can be interpreted as incidence rate ratios which are shown in Table 5.31. The number of outpatient visits for patients initiated on dasatinib was 1.14 [exp(0.13)] times the number of outpatient visits for patients initiated on nilotinib (Table 5.31).

A logistic regression model was used to evaluate the association between initiating dasatinib versus nilotinib and inpatient visits (data not shown). This model indicated no association between initiating dasatinib compared to nilotinib and having an inpatient visit. Further, no other covariates included in the model were statistically significant.

Table 5.29 Health services utilization during the 12 month period following initiation of nilotinib versus dasatinib

	Nilotinib Unadjusted mean (SD) [range] n=20	**Dasatinib Unadjusted mean (SD) [range] n=24**	**p-value**
Outpatient visits	39.05 (23.19) [9-91]	45.17 (27.32) [6-134]	0.43
Inpatient visits	0.50 (1.10) [0-4]	0.79 (1.44) [0-6]	0.46
Inpatient hospital days	2.70 (6.78) [0-29]	5.4 (9.78) [0-34]	0.37
ER visits	0.35 (1.35) [0-6]	0.67 (1.86) [0-7]	0.53

Table 5.30 Association between initiating dasatinib versus nilotinib and outpatient visits and inpatient days*

	Outpatient Visits			Inpatient Hospital Days		
Model	**Estimate**	**95% CI**	**p-value**	**Estimate**	**95% CI**	**p-value**
Multivariable†						
TKI (dasatinib versus nilotinib)	0.13	0.01, 0.25	0.03	1.17	0.55, 1.79	.0002
Demographic						
Age	0.12	0.05, 0.19	0.001	0.08	-0.20, 0.36	0.59
Sex	0.006	-0.12, 0.12	0.92	-1.09	-1.79, -0.40	<.01
Plan	0.006	0.06, 0.17	<.001	0.33	0.07, 0.60	0.01
Region	-0.06	-0.15, 0.02	0.14	0.95	0.49, 1.42	<.0001
LIS	0.40	0.25, 0.54	<.0001	3.08	2.24, 3.92	<.0001
Dual	-0.45	-0.66, -0.24	<.0001	-0.48	-1.89, 0.92	0.50
Clinical characteristics						
Duration of therapy	-0.0002	-0.0006, 0.002	0.34	0.005	0.003, 0.008	<.0001
Proxy for CML phase	0.58	0.42, 0.74	<.0001	1.45	0.55, 2.35	<.01
RxRisk	0.17	0.06, 0.33	0.03	0.88	-0.52, 2.28	0.22
Medication count	0.11	-0.05, 0.26	0.16	3.63	2.71, 4.55	<.0001
Vaccine	0.05	-0.12, 0.23	0.55	-2.51	-3.46, -1.56	<.0001
Provider characteristics						
Age	0.009	-0.05, 0.07	0.77	-0.08	-0.39, 0.25	0.65
Sex	0.04	-0.14, 0.21	0.67	-0.39	-1.60, 0.81	0.52
Specialty	-0.27	-057, 0.03	0.08	-3.99	-6.29, -1.70	<.001
Practice type	0.08	-0.02, 0.17	0.10	1.28	0.95, 1.62	<.0001
PS quintile†						
TKI (datastinib versus nilotinib)	0.05	-0.03, 0.16	0.20	0.69	0.36, 1.01	<.0001
Quintile	-0.12	-0.15, -0.09	<.0001	0.07	-0.03, 0.17	0.16
Duration of therapy	-0.0001	-0.0005, 0.0003	0.63	0.004	0.002, 0.005	<.0001

* Mean health services utilization was evaluated using GLM with Poisson distribution and log link
†Multivariable and PS quintiles model included the following covariates for adjustment: primary independent variable was initiating dasatinib versus nilotinib, demographic characteristics (i.e. age, gender, plan type, region, LIS, dual eligibility status), clinical characteristics (i.e. duration of treatment (days), RxRisk-V score, CML phase of disease, flu or pneumonia vaccination, medication count), and provider characteristics (i.e., age, gender, specialty, practice setting)

Table 5.31 Incidence rate ratios for outpatient visits and inpatient hospital days comparing initiation of dasatinib versus nilotinib

TKI (dasatinib vs. nilotinib)	IRR	95% CI
Outpatient visits		
Multivariable analysis*	1.14	1.01, 1.28
PS quintile analysis*	1.05	0.97, 1.17
Inpatient hospital days		
Multivariable analysis*	3.22	1.73, 5.99
PS quintile analysis*	1.99	1.43, 2.75

IRR=incidence rate ratio
*Multivariable and PS quintiles model included the following covariates for adjustment: primary independent variable was initiating dasatinib versus nilotinib, demographic characteristics (i.e. age, gender, plan type,

region, LIS, dual eligibility status), clinical characteristics (i.e. duration of treatment (days), RxRisk-V score, CML phase of disease, flu or pneumonia vaccination, medication count), and provider characteristics (i.e., age, gender, specialty, practice setting)

5.8.3 Healthcare costs

5.8.3.1 Main Analyses

The results for unadjusted and adjusted healthcare costs are presented in Tables 5.32 and 5.34. Total costs, TKI-related pharmacy costs, non TKI-related pharmacy costs, and medical costs incurred during the 12 month period following the initiation of TKI therapy were not significantly different for patients initiating dasatinib versus nilotinib. The total unadjusted costs for patients initiating dasatinib and nilotinib were driven by TKI-related pharmacy costs ($62,140 and $70,273, respectively, p=0.44) (Table 5.32).

Results of the GLM examining the association between initiating nilotinib versus dasatinib and healthcare costs are shown in Tables 5.33 and 5.34. The results are consistent with the unadjusted results showing no difference in total, TKI-related costs, non TKI-related costs or medical costs during the 12 month period following initiation of therapy. Increased number of days on therapy was associated with higher total healthcare and TKI-related costs; however, there was no association between duration of therapy and non TKI-related or medical costs.

Table 5.32 Healthcare costs incurred during the 12 month period following initiation of nilotinib versus dasatinib (n=44)*

	Nilotinib Unadjusted mean costs (SD) [range] n=20	**Dasatinib Unadjusted mean costs (SD) [range] n=24**	**p-value**
Total Costs (pharmacy + medical)	$80,617 ($41,124) [$15,536-$168,179]	$95,568 ($46,415) [$25986-$193,950]	0.32
Pharmacy Costs	$64,533 ($34,158) [$8,924-$110,178]	$72,607 ($36,871) [$9132-$134,040]	0.45
TKI-related	$62,140 ($34,308) [$7,445-109,290]	$70,273 ($36,781) [$6,782-$128,791]	0.44
Non-TKI related	$2,394 ($2,049) [$236-$7,052)	$2,335 ($2,179) [$0-$7,360]	0.82
Medical Costs	$16,084 ($22,990) [$2,069-$88,085]	$22,961 ($40,302) [$634-$183,237]	0.32

*Cost calculation included both plan paid and member out-of-pocket costs (i.e. patient copayments and co-insurance).

Table 5.33 Association between initiating nilotinib versus dasatinib and total, TKI-related costs, non TKI-related costs, and medical costs*

Model	Total Costs			TKI-Related Costs			Non TKI-Related Costs			Medical Costs		
	Estimate	95% CI	p-value	Estimate	95% CI	p-value	Estimate	95% CI	p-value	Estimate	95% CI	p-value
Multivariable†												
TKI (nilotinib vs. dasatinib)	0.19	-0.07, 0.45	0.16	0.08	-0.22, 0.39	0.58	-0.10	-0.61, 0.40	0.69	0.17	-0.52, 0.86	0.63
Demographic												
Age	-0.06	.023, 0.11	0.50	-0.11	-0.30, 0.08	0.25	0.34	-0.08, 0.75	0.11	0.18	-0.28, 0.64	0.45
Sex	0.04	-0.26, 0.34	0.80	0.18	-0.16, 0.52	0.31	-0.16	-0.78, 0.46	0.62	-0.86	-1.57, -0.15	0.02
Plan	-0.01	-0.15, 0.13	0.89	-0.11	-0.26, 0.04	0.15	0.21	-0.07, 0.50	0.14	0.44	0.08, 0.79	0.02
Region	0.20	0.02, 0.39	0.03	-0.12	-0.35, 0.11	0.31	0.50	0.15, 0.86	<.01	0.54	0.09, 0.99	0.02
LIS	0.13	-0.22, 0.48	0.47	-0.004	-0.40, 0.40	0.99	1.19	0.43, 1.96	<.01	2.12	1.16, 3.09	<.0001
Dual	-0.22	-0.73, 0.29	0.40	0.24	-0.35, 0.82	0.42	-0.19	-1.32, 0.93	0.74	-1.29	-2.45, -0.14	0.03
Clinical characteristics												
Duration of therapy	0.002	0.001, 0.003	<.0001	0.005	0.003, 0.006	<.0001	-0.003	-0.005, 0.0005	0.02	-0.002	-0.004, 0.001	0.29
Proxy for CML phase	-0.13	-0.51, 0.24	0.49	0.02	-0.45, 0.48	0.94	-0.34	-1.11, 0.43	0.39	-0.25	-1.11, 0.61	0.56
RxRisk	-0.13	-0.49, 0.23	0.49	0.21	-0.19, 0.60	0.31	1.51	0.83, 2.19	<.0001	0.31	-1.24, 0.62	0.51
Medication count	0.30	-0.03, 0.63	0.07	-0.06	-0.44, 0.31	0.74	0.45	-0.22, 1.11	0.19	1.55	0.67, 2.4	<.001
Vaccine	-0.20	-0.60, 0.20	0.33	0.08	-0.41, 0.57	0.75	-0.017	-0.81, 0.77	0.97	-0.81	-1.79, 0.18	0.11
Provider characteristics												
Age	-0.06	-0.21, 0.08	0.39	0.12	-0.04, 0.29	0.14	-0.06	-0.33, 0.21	0.65	-0.11	-0.49, 0.27	0.58
Sex	0.54	0.17, 0.91	<.01	0.06	-0.38, 0.49	0.80	1.15	0.36, 1.95	<.01	0.27	-0.72, 1.26	0.60
Specialty	-0.82	-1.51, 0.13	0.02	-0.09	-0.87, 0.69	0.82	-1.86	-3.28, 0.45	0.01	-2.73	-4.42, -1.05	<.01
Practice type	0.03	-0.13, 0.19	0.70	0.05	-0.13, 0.24	0.57	0.19	0.50, 0.13	0.25	0.24	-0.16, 0.65	0.23
PS quintile‡												
TKI (nilotinib versus dasatinib)	0.20	-0.09, 0.48	0.18	0.19	-0.09, 0.47	0.19	-0.03	-0.65, 0.60	0.93	0.26	-0.46, 0.98	0.48
Quintile	-0.05	-0.16, 0.06	0.38	-0.006	-0.11, 0.10	0.91	-0.005	-0.24, 0.23	0.96	-0.11	-0.39, 0.18	0.46
Duration of therapy	0.003	0.001, 0.004	<.0001	0.005	0.004, 0.006	<.0001	-0.0001	0.003, 0.002	0.93	-0.002	-0.005, 0.001	0.21

* GLM with gamma distribution and log link; Cost calculation included both plan paid and member out-of-pocket costs (i.e. patient copayments and co-insurance).
†Multivariable included the following covariates for adjustment: primary independent variable was initiating nilotinib vs. dasatinib, demographic characteristics (i.e. age, gender, plan type, region, LIS, dual eligibility status), clinical characteristics (i.e. duration of treatment (days) on index medication, RxRisk-V score, CML phase of disease, flu or pneumonia vaccination, medication count), and provider characteristics (i.e., age, gender, specialty, practice setting)
‡PS quintile included the following covariates for adjustment: primary independent variable was initiating nilotinib vs. dasatinib, covariates (i.e. PS quintile, duration of treatment (days) on index medication

Table 5.34 Predicted, adjusted healthcare costs during the 12 month period following initiation of nilotinib versus dasatinib (n=44)*

	Nilotinib mean costs (95% CI) n=20	Dasatinib mean costs (95% CI) n=24	p-value
Total Costs (pharmacy + medical)	$72,817 ($61,010, $86,916)	$87,807 ($74,997, $102,816)	0.16
Pharmacy Costs			
TKI-related	$53,874 ($43,958, $66,026)	$58,618 ($48,913, $70,242)	0.58
Non-TKI related	$1,781 ($1,256, $2,528)	$1,606 ($1,175, $2,196)	0.69
Medical Costs	$10,773 ($6,871, $16,892)	$12,776 ($8,602, $18,974)	0.63

***** GLM with gamma distribution and log link; Cost calculation included both plan paid and member out-of-pocket costs (i.e. patient copayments and co-insurance).
Multivariable model included the following covariates for adjustment: primary independent variable was initiating nilotinib vs. dasatinib; demographic characteristics (i.e. age, gender, plan type, region, LIS, dual eligibility status), clinical characteristics (i.e. duration of treatment (days) on index medication, RxRisk-V score, CML phase of disease, flu or pneumonia vaccination, medication count), and provider characteristics (i.e., age, gender, specialty, practice setting)

5.8.3.2 Sensitivity Analysis

A sensitivity analysis of the unadjusted costs was conducted and limited to patients who were initiated on a starting dose that indicated chronic phase disease (n=34) (Table 5.35). Similar to the main analysis, total healthcare, TKI-related pharmacy, non TKI-related pharmacy, and medical costs during the 12 month period following the initiation of TKI therapy were not significantly different for patients initiating dasatinib versus nilotinib.

Table 5.35 Healthcare costs incurred during the 12 month period following initiation of nilotinib versus dasatinib (n=34)*

	Nilotinib Unadjusted mean costs (SD) [range] n=14	Dasatinib Unadjusted mean costs (SD) [range] n=20	p-value
Total Costs (pharmacy + medical)	$84,772 ($42,135) [$15,536, $168,179)	$98,894 ($45,247) [$25,986, $193,950]	0.40
Pharmacy Costs	$64,683 ($34,085) [$8,924-$110,178)	$76,078 ($37,518) [$9,132-$134,040]	0.34
TKI-related	$61,934 ($34,377) [$7,445, $109,290]	$73,570 ($37,569) [$6,782, $128,791]	0.33
Non-TKI related	$2,749 ($2,228) [$236-$7,052]	$2,507 ($2,242) [$41, $7,360]	0.74
Medical Costs	$20,089 ($25,737) [$2,069-$88,085]	$22,817 ($41,811) [$634, 183,237]	0.36

*Only patients with a starting dose indicating chronic phase disease were included

CHAPTER VI: DISCUSSION

6.1 Overview

This study describes factors associated with initiating a second-generation compared to a first-generation TKI for the treatment of CML and patterns of TKI treatment interruption and regimen change in a large national health plan that included both commercial and Medicare members after second-generation TKI therapies were FDA approved as first-line therapy. In addition, adherence, health services utilization and healthcare costs were compared between patients newly initiating a second versus first-generation TKI. During the study period, approximately 64% of patients received a first-generation TKI (i.e. imatinib) as the initial therapy. Patients' starting dose of TKI therapy was used as a proxy for disease phase at the time of initiation. Of the patients included in the study, 92% of patients were initiated on a dose indicating chronic phase disease. The study results support four main findings.

First, within the entire population, 50% of patients had a treatment interruption, defined as a gap in therapy of at least 30 days, during the follow-up period. In this study, patients in the first-generation TKI cohort were less likely to have treatment interruption compared to those in the second-generation TKI cohort. Additionally, patients initiated on a first-generation TKI stayed on therapy longer compared to patients initiating a second-generation TKI therapy. These findings were opposite of what was hypothesized. Of the patients with treatment interruption, 58% of patients who initiated therapy with a first-generation TKI re-initiated the index medication following an interruption compared to 38% of patients who initiated therapy with a second-generation TKI. In both cohorts, medication change was the next most common treatment pattern with almost one-fourth of patients changing medications in each cohort. A larger proportion of patients in the second-

generation TKI cohort discontinued therapy compared to the first-generation TKI cohort by the end of a year follow-up (30% vs. 15%, respectively).

Second, there is evidence that adherence to first-line TKI therapy, regardless of whether patients initiated a second versus first-generation TKI, is suboptimal in patients with CML. Approximately, half of patients had a PDC lower than 85% during the follow-up period. Although there was no association between initiating a second versus first-generation TKI and adherence when PDC was dichotomized at 0.85 when PDC was used as a continuous measure mean adherence was higher for patients initiating first compared to second-generation TKI therapy (PDC 0.77 and 0.68, respectively, p=0.007). This finding was opposite of what was hypothesized (i.e. patients taking a second-generation TKI therapy are more adherent compared to patients taking a first-generation TKI therapy).

Third, outpatient visits were the most used health service for both cohorts. Patients initiating a first-generation TKI had fewer outpatient visits and hospital days compared to patients initiating a second-generation TKI which was opposite of the study hypotheses for these outcomes. No differences were noted between inpatient hospitalizations or ER visits during the 12 month follow-up period between the two cohorts which is consistent with the study hypotheses. Patients initiating a first-generation TKI had lower overall healthcare, pharmacy and medical costs during the follow-up period. It is important to note that this analysis used an ITT approach and patients were assigned to the first or second-generation TKI cohort based on the initial treatment. Total healthcare costs for both cohorts were driven by TKI-related costs.

Fourth, the exploratory analysis comparing patients initiating dasatinib and nilotinib showed similar results between the two agents for the outcomes studied which was consistent with the study hypotheses. There were no differences in mean adherence for patients initiating dasatinib versus nilotinib or health services utilization. The average total costs for patients initiating nilotinib over the

12 month follow-up period were higher compared to patient initiating dasatinib but these results were not statistically significant.

6.2 Interpretation

The rationale for initiating a second-generation TKI as frontline therapy for patients with chronic phase disease is remarkable rates of early responses with almost 90% of patients achieving a complete cytogenetic response (CCyR) by 3 months of therapy and excellent event-free survival, transformation-free survival, and survival.[14-16] The counterargument is that approximately two-thirds of patients have an acceptable response to imatinib based on the results of the IRIS study[17] and other reports.[18,19] Although second-generation TKIs achieve quicker and deeper clinical responses, the results of this study show that imatinib was more widely prescribed as frontline therapy compared to second-generation TKIs in this population between 2010 and 2011.

This study showed that patients enrolled in a commercial plan and patients with a starting dose that reflected accelerated disease were more likely to initiate therapy with a second-generation TKI. Patients enrolled in a commercial plan are on average younger than patients enrolled in a Medicare plan. Providers may prescribe second-generation TKIs to younger patients because they perceived these patients were most likely to benefit.[109] Better prognosticators are needed to determine which patients do better on first versus second-generation TKI therapy frontline. Other analyses have shown that patients with CML who present with features of accelerated disease at the time of diagnosis have an excellent outcome with TKIs, particularly second-generation TKI.[124] Consistent with studies showing improved clinical endpoints, patients in this study with accelerated phase disease were more likely to initiate a second-generation TKI.

Although there is not a consensus on whether to initiate patients with chronic phase CML on a first versus second-generation TKI, the goal of therapy is to achieve optimal adherence which is a critical factor for achieving molecular responses. Marin and colleagues found a correlation between low adherence, defined as ≤90%, and 6-year probability to achieve a major molecular response and

complete molecular response.[20] The current study found that adherence to TKI therapy was suboptimal in patients with CML, regardless of whether patients initiate on a first versus second-generation TKI. Approximately half of patients had optimal adherence, defined as ≥85%, during the follow-up period. This rate is slightly lower than what others have shown for patients initiating therapy on imatinib with approximately 60% being classified as having optimal adherence.[79,125]

When PDC was used as a continuous variable, mean adherence was higher for patients initiating first compared to second-generation TKI therapy (PDC 0.77 and 0.68, respectively, p=0.007). The mean adherence rate for patients initiating imatinib was similar to other reports.[79,84] Darkow and colleagues, reported mean adherence of 77.7% over a 12 month follow-up, with 31% of patients having a treatment interruption. All patients restarted imatinib within the study period.

In the current study, the proportion of patients with a treatment interruption was similar to what has been reported within clinical trials. Specifically, 58.8% of patients initiating therapy on a second-generation TKI had a treatment interruption during the 12-month follow-up period compared to 45.1% of patients initiating a first-generation TKI. Within the Phase III study, DASISION, comparing dasatinib versus imatinib, 59% and 43% had a treatment interruption, respectively.[10] Similar results have been reported in the Phase III study, ENESTnd, comparing nilotinib 600 mg and 800 mg versus imatinib. The proportion of patients with an adverse event leading to a dose reduction or interruption was 55%, 63%, and 46%, respectively.[62] Treatment interruptions and dose reductions were allowed to manage adverse events in the clinical trials. In the current study, the difference between treatment interruptions among patients initiating a first versus second-generation TKI is likely due to the differences in toxicity profiles of the specific agents resulting in adverse events. The second-generation TKI therapies have unique toxicities which could contribute to extended treatment interruptions compared to imatinib. Specifically, pleural effusion is a unique adverse event related to dasatinib treatment and QT prolongation has been reported among patients taking nilotinib.

Additionally, the second-generation TKI therapies have deeper cytogenetic and molecular responses, which mean longer time to hematologic recovery.

Of the patients with a treatment interruption in the current study, the majority re-initiated the starting therapy or changed medications. However, 15% of patients in the first-generation TKI cohort and 30% of patients in the second-generation TKI cohort who had a treatment interruption discontinued therapy for the remainder of the study period. Within the clinical trials, there were no differences in discontinuation between patients randomized to a second-generation TKI versus imatinib. The two-year follow-up DASISION study reported 23% of patients taking dasatinib and 25% of patients taking imatinib discontinued treatment.[10] The ENESTnd study only reported discontinuation due to adverse events. Adverse events leading to discontinuation occurred in 13% of patients taking the higher dose of nilotinib versus 11% of patients taking imatinib.[62] Other reasons for permanent discontinuation reported in real world reports include: progression, intolerance, failure, elective allogeneic transplantation, and death from non-CML-related causes.[19]

In practice, a therapy change is indicative of treatment failure or intolerance. For example, a patient who has lost a CCyR or a complete hematologic response (i.e. secondary resistance), therapy should be changed immediately.[42] A delayed treatment change in a patient who has lost cytogenetic response can cause a decreased probability of event-free survival.[71] Approximately 19% of patients in each cohort had a regimen change during the follow-up period which most often involved changing to a different TKI.

CML is a chronic disease requiring routine follow-up. As expected, outpatient visits were the most used service with an average of 37.8 and 42.4 visits for patients initiating a first compared to a second-generation TKI over a 12 month period. This is consistent with what others have reported.[79] The average number of inpatient and ER visits for both cohorts was low. However, patients initiating a first-generation TKI had fewer hospitalizations, hospital days, and ER visits during the 12 month follow-up period compared to patients initiating a second-generation TKI.

Both the overall pharmacy costs and total healthcare costs for both cohorts were driven by TKI-related costs. Although we found that patients initiating a first-generation TKI had lower overall healthcare, pharmacy and medical costs during the follow-up period, these results need to be interpreted with caution. This analysis used an ITT approach and patients were assigned to the first or second-generation TKI cohort based on the initial treatment. Duration of initial therapy was controlled for in the GLM models and was associated with greater total healthcare, pharmacy and medical costs.

An exploratory analysis was conducted and limited to patients taking either dasatinib or nilotinib. Similar to indirect comparisons of these agents to each other in the clinical trials (i.e. DASISION and ENESTnd), there were no differences in any of the endpoints studied between patients initiating dasatinib versus nilotinib.

6.3 Strengths

This study contributes to the literature by being the first to compare second versus first-generation TKI therapy as frontline treatment for CML using real world data. Because there is no consensus on whether to start patients on a first compared to a second-generation TKI therapy as first-line therapy, this study helps to fill knowledge gaps using observational data since the second-generation TKIs received a first-line indication. Prior studies have evaluated adherence, health services utilization, and healthcare costs for patients who initiated imatinib as first-line and second-generation TKIs in the second-line setting.[79,80,84]

The main strengths of this analysis include a robust database for evaluating outcomes for a rare cancer affecting older adults. This study identified 368 newly treated CML patients over a year and a half period which is more than expected based on the incidence rate reported in the literature. The literature reports an incidence rate of 1.6 per 100,000 and Humana had approximately 5.8 million enrollees during plan years 2010 and 2011. In addition to the large sample size for CML, this study also included both commercial and Medicare plan types. The diversity of plan type enrollees

increases the external validity of the results to a larger cross section of both commercial and Medicare populations in the United States.

6.4 Limitations

Limitations common to studies using administrative claims data apply in this study. These include lack of certain information in the database (e.g., health behavior and health belief information), error in claims coding, and the potential influence of unidentified confounding variables. Administrative claims data include paid claims only. If a patient were given sample medications, these would not be reflected in the claims data. On the other hand, a claim for a TKI therapy does not necessarily mean the patient actually took the medication.

Although having a robust sample of newly treated CML patients is a strength of this study, it is important to note a higher incidence of CML in the Humana plan may be due adverse selection. The median age at diagnosis is 64. Humana is second largest Medicare Part D provider, and TKI therapy to treat CML is expensive. Because the current study utilized claims data from a single health plan, specifically a large Medicare Part D provider, the results might not be generalized to the general population.

Information regarding the phase of CML and other factors that could lead physicians and patients to select a particular TKI therapy was not readily available through medical chart review. Although patients' starting dose of TKI therapy was assessed and used as a proxy for CML phase at the time of initiation, this method has not been validated. Appropriate CML staging is determined during the work-up through bone marrow aspiration and cytogenetic analysis. The nature of this study prevents us from making definitive causal association between type of TKI therapy and adherence, health services utilization and healthcare costs. Additionally, TKI utilization is being measured over the same time period outcomes are being assessed and therefore no clear temporal relationship between exposure and outcome can be established. We attempted to reduce selection bias and strengthen the causal inference by using a new user design with multivariate regression

modeling, however, these methods can only reduce bias caused by measured covariates; neither can reduce bias caused by unmeasured covariates. Achieving a complete cytogenetic response is considered the gold standard for good response to therapy. The laboratory results for cytogenetic and molecular responses were not available for this study and therefore stage of disease at diagnosis and disease progression was not assessed.

All cost data were based on the actual cost during the plan year they were incurred. Costs were not converted to $US (2013) using the medical component of the Consumer Price Index. Total healthcare costs were driven by the TKI-related costs. The price of TKI therapy has increased year over year. For example, imatinib and dasatinib have taken a 9.9% and 3.8% price increase, respectively during 2012. This trend is likely to increase as brand name imatinib is ending its life cycle. Therefore, the healthcare cost data presented in this study is likely lower than what would be expected in 2013.

Since this study was initiated, the landscape of available TKIs for treating CML has rapidly evolved. Bosutinib was FDA approved in September 2012 for adult patients with chronic, accelerated, or blast crisis CML with resistance or intolerance to prior therapy. Ponatinib was also approved in the second-line setting in December 2012 and is the most potent TKI for the treatment of CML. Ponatinib has subsequently been removed from the market because of the risk of life-threatening blood clots and severe narrowing of blood vessels. Although having several treatment options available for the treatment of CML is beneficial, there is concern that this may increase temptation of rapid succession of treatment changes because of perceived suboptimal response or adverse events.[42] This practice should be avoided. The expected long-term outcome with the current treatment needs to be compared with the expectations of a newer agent before changing therapy.[42]

New treatment options have become available after the study period for second-line use. Therefore, the results of this study may not reflect practice today. Although there is clinical rationale to support starting patients on either a first or second-generation TKI as frontline therapy, the

availability of additional second-line therapies may influence treatment decisions for frontline treatment. Further, physicians may be more willing to start patients on a second-generation TKI now that three year follow-up data are available for both dasatinib and nilotinb (i.e. DASISION and ENESTnd) and additional second-line agents are available for patients who have suboptimal response to nilotinib and dasatinib when used as first-line therapy.

6.5 Policy implications

This study was a first step in evaluating treatment patterns and economic outcomes among patients newly initiating first and second-generation TKI therapies for the treatment of CML. With the availability of several treatment options and imatinib becoming generically available in 2015, payers and providers are faced with more considerations when managing patients with CML. Although oncology is a CMS protected class and these therapies must be covered by Part D sponsors, payers will consider more restrictive preferred therapies and will drive generic utilization with imatinib. Recent guidance issued by the National Institute for Health and Clinical Excellence (NICE) recommends imatinib and nilotinib, both made by Novartis, for first-line treatment of CML.[24] Dasatinib, made by Bristol-Myers Squibb, is not recommended. NICE concluded from indirect comparisons that dasatinib and nilotinib could be considered equally effective in treatment of CML and accepted an undisclosed patient access scheme reducing the cost to approve nilotinib on the formulary in the United Kingdom. U.S. payers may consider a similar approach and have a preferred second-generation TKI (i.e. nilotinib or dasatinib).

Physicians will not only consider efficacy but adherence as well as cost when recommending frontline therapy for the treatment of CML. This will become increasingly important when imatinib becomes generically available in 2015. Furthermore, the argument of initiating older patients on imatinib is further strengthened by the results of this study. Patients who initiated therapy with imatinib had lower rates of treatment interruption, higher mean adherence, fewer inpatient and ER

visits, and overall healthcare costs during the follow-up period compared to patients who were initiated on second-generation TKIs.

6.6 Future Research

The first-line treatments available today have been studied in isolation and only address the issue of what drug is better.[9,11,57] These studies do not address how to adequately treat patients with a suboptimal response on first-line therapy. Future research is needed to determine which strategy is better: use of second-generation TKIs as initial therapy or after failure of imatinib.[42] Additionally, comparative effectiveness analyses with larger sample sizes are needed to determine whether initiating a first versus second-generation TKI is preferred and for those patients who switch, the best sequencing for second-line and third-line agents. Comparative effectiveness research using real world data should continue to be used to inform formulary decision making and help physicians identify which patients may benefit from a particular therapy.

6.7 Conclusion

Using a large dataset of privately insured and Medicare patients, this study demonstrated that the majority of patients were initiated on a first-generation TKI compared to a second-generation TKI as first-line treatment. Initiating therapy on a first-generation TKI was associated with lower risk of treatment interruption. Although mean adherence was higher for patients initiating imatinib compared to a second-generation TKI, adherence to therapy is suboptimal. Initiating therapy on a first compared to a second-generation TKI was associated with fewer inpatient hospital stays, emergency room visits, and overall lower healthcare costs during the follow-up period.

For analyses assessing intended drug effects, it is often the case that many important confounders are unmeasured. Although we attempted to reduce selection bias and strengthen causal inference by using a new user design with multivariate regression modeling, the results from this study should be interpreted with caution due to the potential of unmeasured confounding. Specifically, this study found statistically significant differences for some study outcomes for patients

initiating first versus second-generation TKI therapy. Although this study adjusted for CML phase, patients with accelerated CML were more likely to initiate therapy on a second-generation TKI therapy. Therefore, the possibility of residual confounding by disease severity cannot be excluded. Instrumental variable methods have been proposed as a potential approach to control for confounding by disease severity in non-experimental studies and should be considered for future research comparing CML therapies.

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