OBSERVATIONAL STATISTICAL ANALYSIS PLAN

DETERMINING CHANGE IN CARDIOVASCULAR AND METABOLIC RISKS IN PATIENTS WITH CHRONIC PHASE CHRONIC MYELOID LEUKEMIA RECEIVING BCR-ABL TYROSINE KINASE INHIBITOR FIRST-LINE THERAPY IN THE UNITED STATES

SAP for Protocol CA180653

VERSION Final 1.0

This SAP contains information that is confidential and proprietary to Bristol-Myers Squibb (BMS)

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List of Abbreviations and Definitions of Terms

Term	Definition
AE	adverse events
ATC	anatomical therapeutic chemical
BCR-ABL	Abelson (Abl) tyrosine kinase gene at chromosome 9 and the break point cluster (Bcr) gene at chromosome 22
BMI	body mass index
BMS	Bristol-Myers Squibb
CAC	coronary artery calcium
CCyR	cytogenetic response
CHR	complete hematologic response
CI	confidence interval(s)
CML	chronic myeloid leukemia
COPD	chronic obstructive pulmonary disease
CP	chronic phase
CP-CML	chronic phase chronic myeloid leukemia
CRO	contract research organization
CRP	c-reactive protein
CSR	clinical study report
CT	computed tomography
CTC	common terminology criteria
CV	cardiovascular
CVD	cardiovascular disease
CVE	cardiovascular event
DM	diabetes mellitus
EKG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
HDL	high-density lipoprotein
HTN	hypertension
ICH	International Conference on Harmonization
IRB	institutional review board

iVH	inVentiv Health
KM	Kaplan-Meier
LDL	low-density lipoprotein
MMR	major molecular response
MMRM	mixed models for repeated measures
NCCN	National Comprehensive Cancer Network
NHLBI	National Heart, Lung, and Blood Institute
OS	overall survival
PAH	pulmonary arterial hypertension
qPCR	quantitative polymerase chain reaction
RTF	rich text format
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	standard of care
TKI	tyrosine kinase inhibitor
US	United States
VOE	vascular occlusive event
WHO	World Health Organization

1. INTRODUCTION

1.1. Background and rationale

This Statistical Analysis Plan (SAP) has been developed after review of Sponsor Protocol CA180653 (version 2.0 dated October 25, 2016) and the corresponding electronic case report form (eCRF). This SAP describes the statistical methods to be used for the analysis and reporting of all effectiveness and safety data collected during the conduct of the study. This SAP provides the detailed procedures of the statistical considerations identified in the protocol and where considerations are substantially different, they will be identified as such in this document. Additional analyses that emerge at a later point to meet the changing landscape requirements will be considered on an ad hoc basis and not necessarily obligated to make it part of the CSR (case by case reviews are permitted).

This SAP is being written with consideration of the recommendations outlined in the International Conference on Harmonization (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

BCR-ABL1 targeted tyrosine kinase inhibitor (TKIs) have changed the treatment landscape in chronic myeloid leukemia (CML) with age-adjusted life expectancy approaching that for similar patients without CML. Before TKI therapy approval, survival for patients with CML was poor. Only 40% of patients 20 to 44 years of age remained alive at 5 years after diagnosis. Older patients (> 65 years) had worse outcomes, with a 5-year overall survival (OS) rate of approximately 20%.[1] The FDA approval of imatinib mesylate in 2001 changed both the care of patients with CML and raised the prospect of a targeted approach to cancer therapies.[2] Although imatinib has dramatically altered the inevitable disease progression of CML, > 30% of patients with CML will either be unable to tolerate or will develop resistance to imatinib. As a result, newer generations of BCR-ABL kinase inhibitors including dasatinib, nilotinib, bosutinib, and ponatinib have been developed. Three BCR-ABL1 TKIs (dasatinib, imatinib, and nilotinib) are indicated for the treatment of chronic phase CML in previously untreated patients and have a Category 1 recommendation in the National Comprehensive Cancer Network (NCCN) guidelines for newly diagnosed CP-CML patients.[3] Imatinib and these second-generation TKIs (dasatinib and nilotinib) now constitute the backbone of CML treatment and clinical outcomes for patients with CML have dramatically improved over the past decade.[4,5]

With the advent of BCR-ABL targeted TKIs for CML, a novel paradigm of indefinite, continuous, uninterrupted therapy has become the standard. This regimen is different from historical regimens for other primary therapies aimed at remission induction and/or cure. While treatment-free remission is an active area of research and defined duration of treatment and ‘functional cure’ is developing as a goal of therapy, patients require several years of therapy and the current standard regimen is uninterrupted, indefinite treatment. The 4-year overall survival rate for CML patients is

as high as 95%,[6] and survival rates of CML patients who experience a complete cytogenetic response is comparable to their age-matched control subjects.[7] With this prolonged survival, patients have the risk to develop unwanted comorbidities such as cardiovascular or metabolic complications, which have the potential to be exacerbated by targeted TKI treatment. Clinical outcomes do not solely rely on treatment efficacy but also on how well therapy is tolerated and on the development of comorbidities. Therefore, it is essential that physicians prevent or manage these complications associated with the use of these agents. Overall, TKIs have demonstrated a favorable safety profile in both the clinical trial and real world setting. Although many patients may experience adverse events, they are more often mild to moderate and usually resolve with adequate treatment management or are resolved shortly upon treatment dose reduction/discontinuation. Whenever a treatment interruption is required due to intolerance, re-treatment with the same TKI or a switch to an alternative TKI is able to control disease in the majority of the cases.[8]

The potential of long-term toxicities for individual patients on chronic therapy should be considered when a first line TKI is selected. The decision of which TKI to use must take into account disease-related, TKI-related, and patient-related variables.[9] Disparate clinical trial inclusion and exclusion criteria, differing patient populations, and treatment options make it difficult to perform cross trial comparisons and to evaluate the optimal treatment option in this setting.

Cardiovascular and metabolic risk

Cardiovascular and metabolic complications associated with first and second generation BCR-ABL TKI treatment of chronic phase CML have been seen in registration studies. In clinical practice, evidence of elevation of risk factors for both cardiovascular and metabolic events has been shown with TKI treatment. A correlation between predictive risk factors and an increase of cardiovascular or metabolic disease will allow a vehicle to assess the safety of first and second generation BCR-TKIs and anticipate elevations of the risk for these adverse events. Due to differential off-target effects of these agents, adverse event profiles vary between BCR-ABL TKIs. Nilotinib treatment appears to have the most off-target toxicity leading to cardiovascular and metabolic adverse events, while imatinib and dasatinib have lower number of adverse events than nilotinib, but with similar incidence. Overall, the onset of these risk factors will be measurable within the first 2 years of treatment.

The Framingham Heart Study defines cardiovascular disease as a composite of coronary heart disease (coronary death, myocardial infarction, coronary insufficiency, and angina), cerebrovascular events (including ischemic stroke, hemorrhagic stroke, and transient ischemic attack), peripheral artery disease (intermittent claudication), and heart failure.[10] The impact of preexisting cardiovascular risk on the development of CVEs during TKI therapy has been investigated. Hochhaus et al used baseline Framingham general cardiovascular risk scores and analyzed downstream events for all evaluable patients treated with either nilotinib or imatinib in the ENESTed trial. Using the Framingham Heart Study definition,[11] the majority of patients had scores in the low-risk category (i.e., 10% predicted risk of experiencing a first cardiovascular disease event

over 10 years with a smaller proportions of patients had scores in the intermediate- risk (i.e., ≥ 10% to 20% predicted risk of experiencing a first cardiovascular disease event over 10 years) or high-risk (i.e., ≥ 20% predicted risk of experiencing a first cardiovascular disease event over 10 years. During study treatment, CVEs occurred most frequently among patients in the high-risk and intermediate-risk categories, whereas patients in the low-risk category experienced fewer CVEs. Framingham general cardiovascular risk scores were evaluable for two of the three patients with deaths temporally associated with CVEs during study treatment both of these patients had scores in the intermediate-risk range.

Cardiovascular events

Atherosclerosis, the underlying cause of cardiovascular disease, results when you have a buildup of cholesterol plaque in your arteries for which LDL cholesterol is a major culprit. For this reason, the guidelines recommend therapy aimed at lowering LDL cholesterol in patients at metabolic risk to reduce risk for cardiovascular (CV) disease. In a head to head study of nilotinib versus imatinib, newly diagnosed patients with CML demonstrated higher levels of elevated total cholesterol (28% vs 4% patients) and elevated triglycerides (12% vs 8% patients) after receiving nilotinib or imatinib, respectively. Correlation of these risk factors to cardiovascular events is seen as more patients experienced a CV event, as defined by ischemic heart disease, ischemic cerebrovascular events, peripheral artery disease and other cardiovascular events at 5 years.[12]

When the incidence of these CV events were analyzed by year of nilotinib and imatinib treatment, events occurred within the first two years of treatment and were distributed across treatment years up to 7 years.[13]
Regarding the incidence of dasatinib-associated cardiovascular events, the DASISION study (CA180056) showed that the majority of CV events occurred within the first year of treatment with few events at later treatments.[14] This contrasts to what was seen with nilotinib and imatinib which had consistent incidences out to 6 years.

Comparing the incidence across all BCR-ABL TKIs, nilotinib has a higher rate of cardiovascular events as compared to imatinib, while dasatinib has similar CVEs as imatinib (Figure 1.1-1).[15]

Metabolic Disease

Several risk factors are predictive of the development of metabolic disease and include:

- body mass index (BMI)
- high triglycerides (≥ 150 mg/dL) or currently taking medication to lower triglycerides
- low levels of high-density lipoprotein cholesterol (< 40 mg/dL in men or < 50 mg/dL in women), or currently taking medication to increase HDL
- high blood pressure (≥ 130 mm Hg systolic or ≥85 mm Hg diastolic) or taking blood pressure medication
- high blood glucose (fasting glucose ≥100 mg/dL) or currently taking medication to lower glucose levels.

The impact of first and second generation BCR-ABL TKIs and these risk factors have been directly assessed in a number of studies. In the ENESTnd study, hyperglycemia (all grades) occurred in 50% and 31% of patients in the nilotinib and imatinib arms, respectively. In a separate analysis of 168 consecutive patients with CML, Iurlo et al specifically investigated these parameters in patients currently being treated with BCR-ABL TKIs.

Iurlo et al identified that the group treated with nilotinib had significantly higher levels of fasting plasma glucose, insulin, C-peptide, insulin resistance, and total and LDL cholesterol than the imatinib (n=92) and dasatinib (n=40) groups.[16] These changes are evident within the first 16 months of treatment.

Selecting a First line Therapy: Focus on Cardiovascular (CV) and Metabolic Considerations: The NCCN recommends the choice of TKI therapy in a given patient be based on the risk score, physician experience, age, ability to tolerate therapy, and the presence of comorbid conditions. A comprehensive work-up that includes multiple considerations (i.e. toxicity and comorbidities) to better define which patients would be ideal candidates for certain TKIs is limited to the discussion section of the NCCN guidelines and expert opinion publications.

Long-Term Considerations: CV and Metabolic Considerations: As experience with TKIs continues to evolve beyond initial clinical trials, long-term outcomes continue to be reported. Markers of long-term outcomes can include progression to accelerated or blast phase; however, more patients are dying from comorbidities rather than CML. The importance of comorbidities has been linked with an increased Charlson Comorbidities Index associated with decreased overall survival. The role of TKIs exacerbating these comorbidities or precipitating new conditions has been documented for CV and metabolic events. Further understanding to inform guideline development to increase awareness and education is needed.

The study is being conducted in an effort to better understand incidence rates of comorbidities, risk factors, and outcomes associated with adverse events in the real world setting in the United States (US).

1.2. Research Questions

In TKI- naïve, chronic-phase (CP)-CML patients who are initiating first line TKIs (dasatinib, imatinib, or nilotinib) in routine clinical practice in the US:

- What are the increased risks for cardiovascular or metabolic disease?
- What are safety and effectiveness outcomes?
- What are the treatment and management patterns of cardiovascular and metabolic disease?
- What parameters are associated with increased risk of cardiovascular or metabolic disease?

No research hypothesis is to be tested by this study.

2. Objectives

2.1. Primary Objective

The primary objectives for this study are:

- To evaluate the changes in cardiovascular risk from baseline using the Framingham Coronary Heart Disease Score
- To evaluate the changes in metabolic risk from baseline using metabolic laboratory values.

2.2. Secondary Objectives

The secondary objectives for this study are:

- To evaluate the incidence of cardiovascular or metabolic disease and/or exacerbation of comorbity(ies)
- To assess the safety and tolerability of first-line BCR-ABL TKIs in adults with CP-CML
- To describe clinical outcomes (including survival, major molecular response [MMR], complete cytogenetic response [CCyR], complete hematologic response [CHR])
- To identify time to clinical outcomes
- To assess treatment patterns and management of adverse events and comorbid disease
- To determine factors associated with initial treatment choice and change of treatment.

2.3. Exploratory Objectives

Exploratory objectives include the following:

- To identify biomarkers that are predictive of an increased risk for cardiovascular or metabolic disease
- To identify safety imaging parameters that are predictive of increased risk for cardiovascular disease.

3. Study Design

This version of the SAP corresponds to Protocol V2.0 dated 25 OCT 2016.

3.1. Overview of Study Design

This prospective, cohort study is intended to characterize the impact of three approved first and second generation BCR-ABL1 tyrosine kinase inhibitors (i.e., dasatinib, imatinib, nilotinib) on cardiovascular and metabolic risk factors in CP-CML treated patients who are TKI- naïve and initiating first line TKIs in routine clinical practice in the US.

The Framingham 10-year general CVD risk prediction equations will be used as a basis for assessing risks and is shown in the Study Protocol Appendix 1. The National Heart, Lung, and Blood Institute (NHLBI) provide a Risk Score calculator and an interactive Risk Assessment Tool. The development of these CVD risk prediction equations were the outcome of extensive data from

several large, racially and geographically diverse, modern NHLBI-sponsored cohort studies,[17,18,19] and from the Framingham Original and Offspring Study cohorts.[20,21]

Standard of care effectiveness assessments will be collected, as available. All testing for cytogenetic analysis (FISH, karyotype), molecular analysis (qPCR), and any mutational analysis performed at local sites will be collected. Current National Comprehensive Cancer Network (NCCN) Guidelines (version 1.2016) note that monitoring response to TKI therapy and mutational analysis should occur every 3 months after initiating treatment. After CCyR has been achieved, NCCN Guidelines notes that monitoring should occur every 3 months for 2 years and every 3 to 6 months, thereafter. CA180653 study data will be collected at all SOC routine office visits.

A 24 month data collection period will include extraction of medical records via case report forms and the additional collection of fasting blood samples (collected following 8 hours of fasting) for metabolic panels during routine office visits. All treatment decisions will be determined by treating physician(s) and no additional patient visits outside of standard of care will be required. As the study is collecting data on cardiovascular and metabolic risk factors in parallel with the management of CML, this study will not influence prescribing or management practices at participating sites.

Fasting blood samples will be collected as part of routine office visits for blood collection as per standard of care treatment timelines. Additional blood and urine samples for biomarker analyses will be collected for metabolic panels. Results from biomarker analyses will be analyzed and presented in the final study report. Safety imaging will be conducted as part of routine office visits as per standard of care treatment timelines. Results from diagnostic imaging will be analyzed and presented in the final study report.

Approximately 25 sites in the US will be recruited to enroll an estimated 200 patients. In order to best capture representative treatment patterns for follow-up as well as maximize the chances of capturing quality data on cardiovascular and metabolic risk, site recruitment will include a majority of sites for this study from the academic-based sites, including the Cure CML Consortium (novel CML research consortium) sites. Enrollment will be competitive across all sites.

3.2. Study Population

Newly-diagnosed, treatment- naïve CP-CML patients (n = 200) who are ≥ 18 years at the time of CP-CML diagnosis who are scheduled to initiate treatment with dasatinib, imatinib, or nilotinib are eligible for enrollment at 25 participating sites.

No enrollment caps are planned for the three TKIs of interest (dasatinib, imatinib, or nilotinib) and these cohorts will be fitted according to natural distribution among eligible participants for this study. However, at the sponsor's discretion, enrollment into a specific cohort may be suspended to ensure representative cohorts are available for analysis.

3.2.1. Inclusion Criteria

- ≥ 18 years at the time of Ph+ CP-CML diagnosis
- Newly diagnoses chronic phase of Ph+ CP-CML, confirmed with cytogenetic and/or molecular testing at baseline
- Treatment-naïve and initiating treatment with dasatinib, imatinib, or nilotinib
- Willingness and ability to comply with routine office visits.

3.2.2. Exclusion Criteria

- Any other prior or active non-CML active malignancy for which the patient is receiving treatment
- Participant in a therapeutic clinical trial for CML disease.

3.3. Data Source/Data Collection Process

This study will employ prospective data collection based local sites entering data in electronic Case Report Forms (eCRFs). The investigator-accessed eCRF will be password-protected to ensure security and confidentiality. Investigators will assign a unique identifier for each patient, alive or deceased, enrolled in the study. This identifier will be used to facilitate follow-up on data queries and validation.

3.3.1. Study Assessments

Clinical assessments or laboratory data, as part of routine clinical care, will be collected, which normally includes visits every three months. All cardiovascular assessments (e.g., EKG, vital signs, ankle brachial index, etc.) will be collected. Additional fasting blood sample and urine collection for biomarker analyses will be collected to assess cardiovascular and metabolic risks. Additional diagnostic imaging (i.e., echocardiogram, coronary calcium scoring) will be collected.

3.3.1.1. Blood Sample Collection for Biomarker Assessments

Fasting blood samples (collected following 8 hours of fasting) will be collected during routine office visits as per SOC blood testing. Additional volumes of blood will be drawn for metabolic profiling and biomarker analysis and will be required for all participants receiving treatment. These fasting blood samples will be used to test the biochemical composition and changes that evolve during treatment. Measuring these biochemical changes in the metabolome will help identify cardiovascular and metabolic risks in this treatment population. No additional visits for blood sample collection will be required.

The timing of blood collection for biomarker assessment will correspond with standard practice blood draw schedules at each institution with the exception that 8h fasting is required. Blood collection should occur prior to administration of therapy when feasible and at intervals coinciding with study enrollment and routine office visits. All evaluations of blood samples will be conducted within the scope of the informed consent. The contract research organization (CRO) will provide the sites with shipping kits for shipment of biomarker blood samples to the CRO. The CRO will be responsible for mailing the biomarker samples to a BMS-designated laboratory for storage until further testing and analyses.

3.3.1.2. Additional Research Collection

This study will include residual sample storage for additional research. Additional research is required for all study participants, except where prohibited by IRBs/ethics committees, or academic/institutional requirements. Where one or more of these exceptions occurs, participation in the additional research should be encouraged but will not be a condition of overall study participation.

- If the IRB/ethics committees and site agree to the mandatory additional research retention and/or collection, then the study participant must agree to the mandatory additional research as a requirement for inclusion in the study.
- If optional participation is permitted and approved, then the study participants may opt out of the additional research retention and/or collection.

Samples kept for future research will be stored at the BMS Biorepository in Hopewell, NJ, USA or an independent, BMS-approved storage vendor.

- The manager of these samples will ensure they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than fifteen (15) years after the end of the study or the maximum allowed by applicable law.
- Transfers of samples by research sponsor to third parties will be subject to the recipient's agreement to establish similar storage procedures.

Samples will be stored in a coded fashion, and no researcher will have access to the key. The key is securely held by the Investigator at the clinical site, so there is no direct ability for a researcher to connect a sample to a specific individual.

Further details of sample collection and processing will be provided to the site in the procedure manual.

3.3.1.3. Urine Sample Collection

Urine tests will be administered along the same schedule as blood sample collection. Increased urinary protein excretion may be an early clinical manifestations of cardiovascular and metabolic disease, such as diabetic nephropathy or underlying cardiovascular disease.[22,23,24,25,26.] Moderately increased albuminuria tests will be used to assess early changes in vascular endothelial function. In conjunction with the creatinine test results from SOC blood work, the albumin-to-creatinine ratio may be calculated. As the waste product, creatinine is removed and secreted, albumin levels may increase due to hypertension of metabolic disease (e.g., diabetes).

The timing of urine collection for biomarker assessment will correspond with standard practice blood draw schedules at each institution. Urine collection should occur prior to administration of therapy when feasible and at intervals coinciding with study enrollment and routine office visits. All evaluations of urine samples will be conducted within the scope of the informed consent. The contract research organization (CRO) will provide the sites with shipping kits for shipment of biomarker urine samples to the CRO. The CRO will be responsible for mailing the biomarker samples to a BMS-designated laboratory for storage until further testing and analyses.

Further details of sample collection and processing will be provided to the site in the procedure manual.

3.3.1.4. Diagnostic Imaging

All radiologic imaging from this study will be transmitted to a centralized imaging core lab and will be reviewed by a central review committee as determined by the Sponsor. Sites will be trained in image acquisition parameters and submission process, prior to scanning the first study subject. If required, imaging results may be unblinded to local site if a patient has a cardiac event after imaging data acquisition. Analysis of study imaging will be performed periodically during study conduct and results will be released in the final study report. These guidelines will be outlined in a separate CA1803653 Site Imaging Manual and Imaging Charter.

Coronary calcium scoring is a non-invasive imaging test that allows high-resolution, three-dimensional visualization of the heart coronary arteries and other adjacent structures and does not require administration of iodinated contrast. Coronary calcium scoring is the simplest application of cardiac CT and does not require administration of iodinated contrast. The presence of coronary artery calcification has been associated with increased burden of atherosclerosis and cardiovascular mortality. Coronary calcium is then quantified (e.g., Agatston score) and categorized as minimal (0 to 10), mild (10 to 100), moderate (100 to 400), or severe (> 400). Coronary artery calcium (CAC) scores are then normalized by age and gender and reported as percentile scores. Population-based studies in asymptomatic cohorts have reported high cardiac prognostic value of CT calcium score. With appropriate techniques, the radiation dose associated with CAC scanning is very low (~1–2 mSv). [27]

Echocardiography uses high-frequency sound waves (ultrasound) to penetrate the body, reflect from relevant structures, and generate an image. The basic physical principles of echocardiography are identical to other types of ultrasound imaging, although the hardware and software are optimized for evaluation of cardiac structure and function. Three-dimensional echocardiography is being increasingly used for assessment of congenital heart disease and valves, although current image quality lags behind two-dimensional ultrasound.

In addition to the generation of two-dimensional images that provide information about cardiac structure and function, echocardiography can be used to interrogate blood flow within the heart and blood vessels by using the Doppler principle to ascertain the velocity of blood flow. The velocity of blood flow between two chambers will be directly related to the pressure gradient between those chambers.[27]

3.3.1.5. Treatment Patterns and TKI Selection

Treating physicians select TKIs based on different criteria, such as disease characteristics, adverse event profiles, comorbidities, and patient preference.[28] To determine factors associated with initial treatment choice and change of treatment, treating physicians will complete questions within the eCRF after enrollment and TKI treatment choice has been decided.

Table 3.3.1.5-1: Screening Procedural Outline (CA180653)		
Procedure	**Screening**	**Notes**
Eligibility Assessments		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	
Medical History	X	Including Sokal score, Framingham Coronary Heart Disease Score smoking status, history of HTN, hyperlipidemia, hyperglycemia (prediabetes)
Concomitant medications	X	
Safety Assessments		
Physical Examination	X	Includes height, weight, and BMI.
Vital Signs	X	Includes blood pressure and heart rate.
Adverse Events Assessment	X	
Efficacy Assessments		
Collection of clinical assessments	X	Disease status and mutational analysis
Laboratory Tests		
Collection of hematology and biochemistry panel results	X	All SOC laboratory assessments

Table 3.3.1.5-2: On Treatment Procedural Outline at Routine Office Visits (CA180653)

Procedure	Baseline 0 M	Every 3 M	6 M only	24M only	Notes
Safety Assessments					
Physical Examination	X				Includes height, weight, and BMI.
Targeted Physical Examination		X			Includes height, weight, and BMI.
EKG	X	X			
Medical History	X	X			Including Sokal score, Framingham Coronary Heart Disease Score smoking status, history of HTN, hyperlipidemia, hyperglycemia (prediabetes)
Vital Signs	X	X			Includes blood pressure and heart rate.
Ankle-brachial index	X	X			
Adverse Events Assessment	----------continuously----------				
Efficacy Assessments					
Collection of clinical assessments	X	X			Disease status and mutational analysis
Diagnostic Imaging					
Echocardiogram	X		X	X	Evaluation for functional change, elevation in pulmonary arterial pressures / pulmonary hypertension
Coronary calcium scoring	X		X	X	Evaluation for presence of coronary artery calcification
Laboratory Tests					

Collection of hematology and chemistry panel results	X	X			Including fasting blood glucose, Hg A1C, fasting lipid panel (total cholesterol, HDL, LDL, triglycerides) and all SOC laboratory assessments. (8 hours of fasting is required)

Table 3.3.1.5-2: On Treatment Procedural Outline at Routine Office Visits (CA180653)

Procedure	Baseline 0 M	Every 3 M	6 M only	24M only	Notes
Investigational biomarker blood collection	X	X			Including different metabolites, cytokines, chemokines, and other biomarkers (e.g., high-sensitivity CRP, GDF-15, homocysteine, insulin, C-Peptide, NT-proBNP, hsTNT, sST2, and Lox-1 DNA sequencing. [A] (8 hours of fasting is required)
Urine collection	X	X			Moderately increased albuminuria test to assess early changes in vascular endothelial function (8 hours of fasting is required)

[A] Lox-1 sequencing will be performed at a single time point when disease burden is at a minimum.

3.4. Definitions of Study Variables

3.4.1. Outcomes/Endpoint Variables

Summary of outcomes/endpoint variables to be collected in accordance with study objectives are listed in Table 3.4.1-1 and will be collected as reported in patient medical records.

Table 3.4.1-1: Summary of Outcomes/Endpoint Variables

Variables	Data Collected
Treatment-related variables	Procedures and therapies received prior to study enrollment (e.g., transplant) Start/end date of treatment (duration of therapy) Documented adverse events possibly caused by systemic treatment Details on adverse event management (e.g., concomitant medications, treatments, and procedures) Dosing regimen, duration of treatment, discontinuation, treatment change Reason for treatment discontinuation, if documented
Practice pattern-related variables	Diagnostic tests, pathological diagnosis Laboratory /diagnostic tests
Clinical Outcomes	Overall survival (OS) Clinical response to TKI treatment (MMR, CCyR, cCHR) Time to clinical response and duration Results of mutational analyses

3.4.2. Cardiovascular and metabolic risk variables

Summary of cardiovascular and metabolic risk variables to be collected in accordance with study objectives are listed in Table 3.4.2-1 and will be collected as reported in patient medical records.

Table 3.4.2-1: Summary of Cardiovascular and Metabolic Risk Variables

Variables	Data Collected
Targeted cardiac events	Development of arrhythmia, cardiac dysfunction, cerebrovascular ischemic disease, coronary death, coronary insufficiency, heart failure, left ventricular systolic function, myocardial infarction, peripheral artery occlusive disease, pulmonary arterial hypertension (PAH), QT prolongation, ischemic or hemorrhagic stroke, transient ischemic attack, venous thromboembolism, other vascular occlusive events (VOEs) and the Framingham Coronary Heart Disease Score Subclinical changes that lead to development of new risk factors or exacerbation of known risk factors (newly diagnosed diabetes, newly diagnosed hypertension, progressive symptoms of disease [e.g., claudication, angina, etc.])
Targeted metabolic events	Diagnosis of diabetes mellitus (DM), impaired fasting glucose, elevated HbA1c, metabolic syndrome, abnormal laboratory values for events of special interest (e.g., out of range)

Hematologic variables	Collection of fasting blood glucose, HbA1, fasting lipid panel [total cholesterol, HDL, LDL, triglycerides]). Changes from baseline will be calculated.
Metabolic variables	Collection of BMI, metabolites, cytokines and chemokines from biomarker panel (e.g., insulin, glucose, high-sensitivity CRP, GDF-15, homocysteine, insulin, C-Peptide, NT-proBNP, hsTNT, sST2, LOX-1 polymorphism), and moderately increased albuminuria levels. Changes from baseline will be calculated.
Diagnostic variables	Collection of echocardiogram, ankle-brachial index, and coronary calcium scoring assessments. Changes from baseline will be calculated.

3.4.3. Exposure/Independent Variables of Interest

TKIs (i.e., dasatinib, imatinib, and nilotinib) for first line treatment of CP-CML are the exposure variables and will be the basis of three main study cohorts of interest.

Pre-defined treatment/ exposure groups will be defined and summarized as follows:

- Treatment Group No. 1: **dasatinib TKI patients who remain on dasatinib.** Defined as dasatinib TKI patients who either remained exclusively on their initial (index) dasatinib TKI during the study period or added another agent to their index TKI for a combination therapy for second line. Patients in this group remained on dasatinib TKI and did not switch to a different TKI or another CML treatment anytime during the study period.
- Treatment Group No. 2: **dasatinib TKI patients who switched to a different TKI or another CML treatment.** Defined as patients who switched from their index **dasatinib TKI** to a different TKI or another CML treatment anytime during the study period.
- Treatment Group No. 3: **imatinib TKI patients who remain on imatinib.** Defined as imatinib TKI patients who either remained exclusively on their initial (index) imatinib TKI during the study period or added another agent to their index TKI for a combination therapy for second line. Patients in this group remained on imatinib TKI and did not switch to a different TKI or another CML treatment anytime during the study period.
- Treatment Group No. 4: **imatinib TKI patients who switched to a different TKI or another CML treatment.** Defined as patients who switched from their index **imatinib TKI** to a different TKI or another CML treatment anytime during the study period.
- Treatment Group No. 5: **nilotinib TKI patients who remain on nilotinib.** Defined as nilotinib TKI patients who either remained exclusively on their initial (index) nilotinib TKI during the study period or added another agent to their index TKI for a combination therapy for second line. Patients in this group remained on nilotinib TKI and did not switch to a different TKI or another CML treatment anytime during the study period.

- Treatment Group No. 6: **nilotinib TKI patients who switched to a different TKI or another CML treatment.** Defined as patients who switched from their index **nilotinib TKI** to a different TKI or another CML treatment anytime during the study period.

The treatment groups may be specified more on exploration of the data.

3.4.4. Other Co-variates/Control Variables

Summary of demographic and clinical variables to be collected in accordance with study objectives are listed in Table 3.4.4-1 and will be collected as reported in patient medical records.

Table 3.4.4-1: Summary of Demographic and Clinical Variables

Variables	Data Collected
Patient Characteristics	Gender Race/Ethnicity Age at advanced/metastatic lung cancer diagnosis Performance status (ECOG status) Previous systemic treatment, transplant Past and present smoking status Medical history (e.g., obesity, pre- diabetes) Comorbidities at enrollment Geographic location by state in the US Rural/urban residence
Disease Characteristics	CML disease characteristics (date of diagnosis, treatment change, treatment management Clinical status, baseline values, and method of diagnostic (Ph+ determination) Risk scores (Sokal score, Framingham Coronary Heart Disease Score) Spleen size (if available) Concomitant medications for non-CML related diagnoses Concomitant medications for management of adverse events

3.5. Conventions

3.5.1. Calculation of Study Day

Study Day will be calculated relative to the index therapy start date.
For purpose of calculating study day, time on study (days), etc., the start date of index therapy will be designated as Study Day 1. Study Day will be calculated as [date of event – start date of index therapy + 1]. For example, if the start date for index therapy is May 4, 2012 and the date of event is May 10, 2012, then the study day for this event would be 7 (May 10 – May 4 = 6 + 1 = 7). For the purpose of converting days to years or months, one year = 365.25 days, and one month = 30.44 days.

3.5.2. Handling Missing Data

Imputation for partial or missing death dates:

- If only the day is missing, the later of the date last known to be alive and the 1st of the month will be used to replace the missing day.
- If both the day and the month are missing, the later of the date last known to be alive and Jan 1st will be used to replace the missing information.

Imputation for partial or missing AE dates:
AEs with missing start dates that cannot be clearly determined to have fallen before treatment started will be classified as having occurred after treatment initiation. Incomplete dates of AEs will be replaced using the following conventions:

- If partial AE onset date where month and year match those of the treatment period start, the day will be set to match treatment start day (considered "on study")
- If the day is missing, but the month and year are present, the day will be set to the first of the month for start dates
- If both the month and day are missing, and year is missing or does not distinguish before or after treatment start, it will be classified as after treatment initiation and the start date will be set to the index date.

Imputation for partial or missing disease assessment or response dates:

- If only the day is missing, the 1st of the month will be used to replace the missing day.
- If the day and month are missing, the date of assessment/response will be the last assessment/response date +1 month.

For other variables, whether to impute for partial or missing date will be determined after an evaluation of the proportion of the partial or missing date is performed based on enough data collected.

3.5.3. Visit Windows

As this is a non-interventional study, there are no pre-specified visit windows for sites or patients. For the primary study objective, risk variables for assessment of assessments for cardiovascular and metabolic disease, however, are supposed to be complete at selected timepoints, which are: baseline, 3, 6, 9, 12, 15 18, 21, and 24 months.

3.5.4. Multiplicity

No multiplicity adjustment for endpoints will be used for testing.

4. Sample Size and Power

The target enrollment for this descriptive CML study is approximately 200 patients receiving first-line TKI therapy. The primary objectives of this study is to evaluate risk for specific CV and metabolic conditions (e.g., development of cardiovascular risk variables such as peripheral edema, hypercholesterolemia (event rate range from lowest to highest of 15% to 28%), and change in Framingham coronary heart disease score (approximately 15% with change over time), in the patient sample. Summary statistics will be provided around the proportion of patients who develop specified clinical and disease characteristics. With 200 CML patients receiving first line TKI therapy, the maximum width (precision estimate) of an exact 95% confidence interval around a proportion is ± 5.5%. This is based upon the maximum variance obtained when the event proportion (based on lower event rate of cardiovascular events and similar change in Framingham score) is 15% with corresponding 95% CI: 9.5% - 20.5%.

The sample size of 200 patients should provide sufficient information to describe the primary objectives, as well as explore the secondary and additional study objectives. No formal hypothesis testing or statistical significance testing is planned. Post-hoc power calculations will be performed to determine if additional analysis and comparisons are warranted. The study is not powered for treatment comparisons or for CV events that occur at low rates, as confidence intervals (CI) could become larger and often invalid.

5. Study Limitations and Strengths

Limitations: One of the limitations of the study includes 24-months timeframe between baseline and end-of-study data collection. This time period is suitable in evaluating short term clinical outcomes but may not be sufficiently long period of time to assess longer term clinical outcomes.

A potential limitation is the sample size, which may not be sufficiently large to analyze some of the stratifying variables with sufficient statistical power. Therefore, the study will have to focus on select common adverse events.

Requesting additional fasting blood draw from patients may inhibit participation in the study, therefore create selection bias. As all blood draws will occur during routine office visits and routine blood draws, minimal inconvenience to the patient should negate any bias.

Finally, all non-interventional data are potentially subject to unmeasured confounding limiting causal interpretation.

Strengths: This prospective study will include patient populations who suffer from the disease that physicians encounter in clinical practice and in the real world, therefore enhancing the generalizability of study results.

The collection of blood and urine samples for central laboratory biomarker analysis and diagnostic imaging for core imaging laboratory evaluation will allow additional data generation on cardiac and metabolic risks without potential impact of altering treatment during study.

6. STATISTICAL ANALYSES

6.1. General Methods

All statistical analyses are performed with the understanding that this is a non-interventional wherein treatment assignment is based on the investigator's judgment and there is no treatment randomization. Any exploratory statistical comparisons will be two-sided and done at the 5% Type I error rate.

Continuous data will be summarized using descriptive statistics: count (n), mean, standard deviation, median, 25th and 75th percentiles, minimum, maximum and count missing (n miss). If applicable, 95% confidence intervals (CI) of mean will be provided.

Categorical data will be described using frequencies and percentages. The number and percentage of missing data will also be reported as "missing" category for each categorical variable if one or more patients had missing data. In addition, a percentage will not be presented against zero counts in the tables.

Patients will be followed continuously during and after treatment until withdrawal of consent, death, loss to follow-up, or to the end of the study, whichever comes first. For patients that discontinue the study or are lost to follow-up, every effort will be made to collect vital status at 6 month intervals.

Patients who switch from their index TKI therapy to a different TKI or other CML treatment will be summarized by initial index treatment and then broken out into subgroups for additional analyses. Subgroups will be determined after descriptive analyses are available. Time to switch and reason for switch will be evaluated and summarized.

Patients who are either lost to follow-up, discontinued or remained on study will be summarized For clinical outcome assessments, patients lost to follow-up or who remained on study will be censored at the date they were last known to be alive as provided by study documentation.

P-values from the statistical tests will be rounded to four decimal places. P-values less than 0.0001 will be reported as '< 0.0001' in tables. Adjusted mean and standard error (SE) from the statistical tests will be rounded to two and three decimal points, respectively.

All statistical analyses will be performed using SAS® v9.3 or above. All final data collected from eCRFs or from external sources will be presented in listings. All outputs will be produced in Rich Text Format (RTF).

All tables and analyses for the prospective patient cohorts will be provided by overall and by treatment cohorts as well as other specified co-variates of interest as the population size permits except for the AE/SAE tables that will be provided by CTC grade. Patient disposition and demographic tables will be provided by line of therapy and other specified covariates of interest as sample size permits.

6.1.1. Analysis by Treatment Group

Variables will be summarized by the following treatments groups:

- Treatment Group No. 1: dasatinib TKI patients who remain on dasatinib.
- Treatment Group No. 2: dasatinib TKI patients who switched to a different TKI or another CML treatment.
- Treatment Group No. 3: imatinib TKI patients who remain on imatinib.
- Treatment Group No. 4: imatinib TKI patients who switched to a different TKI or another CML treatment.
- Treatment Group No. 5: nilotinib TKI patients who remain on nilotinib.
- Treatment Group No. 6: nilotinib TKI patients who switched to a different TKI or another CML treatment.

The columns 'All dasatinib TKI Patients', 'All imatinib TKI Patients', 'All nilotinib TKI Patients' and 'All Patients' will also be displayed in the tables.

Based on the number of patient's receiving other CML treatment, BMS and iVH will determine if the count warrants further breakouts of the therapy groups, separating out other CML treatment for extra detail.

6.1.2. Patient Disposition

Characterization of the study sample is a necessary step in properly understanding the analysis population and informs the interpretation of the final study results. It will also address primary objectives.

Summary statistics will be tabulated for each of the following categories and broken out by analysis treatment group (as stated in section 6.1.1 Analysis by Treatment Group):

- Number and percentage of prospectively followed patients enrolled, total, by treatment group, and by regional district /site.
- Number and percentage of patients to be followed prospectively who signed informed consent form for each regional district, total, and by treatment group.
- Number and percentage of prospectively followed patients who completed, lost to follow-up, and discontinued the study, total, by treatment group, and by regional district /site. The reasons for discontinuation and death will be tabulated as well.
- Number and percentage of prospectively followed patients that received dasatinib TKI throughout the study (i.e., those patients who did not switch to a different TKI or another CML treatment), and overall.
- Number and percentage of prospectively followed patients that received imatinib TKI throughout the study (i.e., those patients who did not switch to a different TKI or another CML treatment), and overall.
- Number and percentage of prospectively followed patients that received nilotinib TKI throughout the study (i.e., those patients who did not switch to a different TKI or another CML treatment), and overall.
- Number and percentage of prospectively followed patients initiated with dasatinib TKI and switched to a different TKI or another CML treatment during the study and the reasons for switching. Descriptive statistics and Kaplan-Meier estimation (mean and standard deviation (SD); median, 25th and 75th quartiles and 95% CI) on the time to switching from the first dasatinib TKI to the first non-dasatinib therapy during the study period will also be reported.
- Number and percentage of prospectively followed patients initiated with imatinib TKI and switched to a different TKI or another CML treatment during the study and the reasons for switching. Descriptive statistics and Kaplan-Meier estimation (mean and SD; median, 25th and 75th quartiles and 95% CI) on the time to switching from the first imatinib TKI to the first non-imatinib therapy during the study period will also be reported.
- Number and percentage of prospectively followed patients initiated with nilotinib TKI and switched to a different TKI or another CML treatment during the study and the reasons for switching. Descriptive statistics and Kaplan-Meier estimation (mean and SD; median, 25th and 75th quartiles and 95% CI) on the time to switching from the first nilotinib TKI to the first non-nilotinib therapy during the study period will also be reported.
- Number and percentage of prospectively followed patients that received any dasatinib TKI throughout the study (i.e., those patients who had dasatinib TKI anytime during the study period, independent of switching), and overall.
- Number and percentage of prospectively followed patients that received any imatinib TKI throughout the study (i.e., those patients who had imatinib TKI anytime during the study period, independent of switching), and overall.
- Number and percentage of prospectively followed patients that received any nilotinib TKI throughout the study (i.e., those patients who had nilotinib TKI anytime during the study period, independent of switching), and overall.

6.2. Primary Objectives

- To evaluate the changes in cardiovascular risk from baseline using the Framingham Coronary Heart Disease Score
- To evaluate the changes in metabolic risk from baseline using metabolic laboratory values

6.2.1. Analysis Plan of Primary Objectives

For the primary study objective, the following risk variables for assessments of cardiovascular and metabolic disease (Table 3.4.2-1) will be described for each cohort at specified time points and stated every 3 months (baseline, 3, 6, 9, 12, 15 18, 21, and 24 months):

- Framingham Coronary Heart Disease Score (first primary objective) [See Appendix 1 for Scoring Details]
- Metabolic lab values (second primary objective)
  - BMI
  - Metabolites
  - Cytokines and chemokines from biometric panel (e.g. insulin, glucose, high-sensitivity CRP, GDF-15, homocysteine, insulin, C-Peptide, NT-proBNP, hsTNT, sST2, LOX-1 polymorphism)
  - Moderately increased albuminuria levels
- Other CV and metabolic parameters of interest (second primary objective)
  - Fasting blood glucose
  - HbA1c
  - Fasting lipid panel (total cholesterol, HDL, LDL, triglycerides).

Descriptive statistics will be presented for each timepoint (baseline, 3, 6, 9, 12, 15 18, 21, and 24 months) in addition to the change from baseline to 3, 6, 12, 15, 18, 21, and 24 months and change between time periods (3 to 6 months, 6 to 12 months, 12 to 15 months, 15 to 18 months, 18 to 21 months and 21 to 24 months). These descriptions will be based on the observed values of patients at each time point (i.e., no last observation carried forward [LOCF]).

In addition, changes in risk assessments over time will be explored for each cohort using appropriate analyses for longitudinal data, e.g., Mixed Models for Repeated Measures (MMRM) (as sample size permits). Within treatment group changes from baseline to 3, 6, 12, 15, 18, 21 and 24 months will be tested and p-values <=0.05 will be considered significant. In addition, descriptive p-values comparing change from baseline (to 3, 6, 12, 15, 18, 21 and 24 months) between the index versus the switch treatment groups for each TKI will be presented.

6.3. Secondary Objectives

- To evaluate the incidence of cardiovascular or metabolic disease and/or exacerbation of comorbidity(ies) [1st]

- To assess the safety and tolerability of first-line BCR-ABL TKIs in adults with CP-CML [2nd]
- To describe clinical outcomes (including survival, major molecular response [MMR], complete cytogenetic response (CCyR], complete hematologic response [CHR]) {3rd}
- To identify time to clinical outcomes [4th]
- To assess treatment patterns and management of adverse events and comorbid disease [5th]
- To determine factors associated with initial treatment choice and change of treatment [6th]

6.3.1. Analysis Plan for Secondary Objectives

6.3.1.1. Cardiovascular and Metabolic Events of Interest

For the first secondary objective, the incidence rates for each cardiovascular and metabolic event of interest:

- Arrhythmia
- Cardiac dysfunction
- Cerebrovascular ischemic disease
- COPD
- Coronary death
- Coronary insufficiency
- Diabetes mellitus (DM)
- Heart failure
- Hypertension
- Hyperlipidemia
- Hyperglycemia
- Ischemic or hemorrhagic stroke
- Impaired fasting glucose
- Left ventricular systolic function
- Myocardial infarction
- Peripheral artery occlusive disease
- Pulmonary arterial hypertension (PAH)
- QT prolongation
- Transient ischemic attack
- Venous thromboembolism
- Other events (will be broken out into individual conditions if there are >=10% of events)

will be calculated as (N/100 patient years) and a 95% confidence interval provided by treatment cohort. Incidence rates will be reported both cumulatively and by year since initiation of treatment. Exacerbations of comorbidities will be assessed with same method. The incidence for each condition will be compared with descriptive t-tests comparing the following treatment groups:

- TKI patients who remain on dasatinib vs. dasatinib TKI patients who switched
- TKI patients who remain on imatinib vs. imatinib TKI patients who switched
- TKI patients who remain on nilotinib vs. nilotinib TKI patients who switched.

6.3.1.2. Treatment-related AEs and SAEs

The second secondary objective is to characterize the treatment-related AEs and to ascertain how they were treated or managed. Reported adverse events will be coded using MedDRA and tabulated by treatment cohort. Descriptive data will be provided for treatment-related adverse events that occur in the treatment cohorts. Frequency data for treatment -related adverse events (AEs) and serious adverse events (SAEs) will be reported in aggregate for the cohorts. No comparisons between the treatment cohorts will be made with regard to the frequency of adverse reactions (ARs).

- Patients with any treatment-related AE, patients with any treatment-related AE with the severe grade 3/4, patients with any serious treatment-related AE, patients with any AE leading to drug discontinuation / resulted in death.
- Treatment-related AE's by system organ class, preferred term and worst CTC grade. A similar table will be produced for SAE. As a general rule for AE reporting by system organ class and preferred term, a patient with more than one AE with the same preferred term is counted only once for that preferred term (using worst CTC grade) and a patient with more than one AE under a system organ class is counted only once for that class (using worst CTC grade).
- Treatment-related AE's leading to drug discontinuation by system organ class, preferred term and worst CTC grade Treatment-related AE's that resulted in death by system organ class, preferred term and worst CTC grade

The Frequency of concomitant medications and procedures, tests, and other drivers of treatment choice will be described. Drivers will be identified after review of descriptive analyses. Evaluation of management of CML and CML treatment related AE's and their impact to changes in disease management will be investigated and summarized.

All Concomitant medications will be coded using World Health Organization Drug Dictionary (WHO-DRUG), version December 2010 or higher and the Anatomical Therapeutic Chemical (ATC) classification system. Coding will include the drug class and drug name.

Concomitant medications will be summarized using numbers and percentages by ATC class (Level 2), ATC class (Level 3) and preferred term, by reason for treatment (management of CML or treatment of adverse event) and by treatment group.

Similarly, procedures will be summarized using numbers and percentages by type, reason for procedure (management of CML, treatment of adverse event or diagnosis) and by treatment group.

6.3.1.3. Clinical Effectiveness

The third and fourth secondary objectives are clinical effectiveness outcomes:

- Overall survival (OS)

- Major molecular response (MMR)
- Complete cytogenetic response (CCyR)
- Complete hematologic response (CHR)

and will be summarized by treatment group in descriptive tables and estimated using Kaplan-Meier product limit method and medians with corresponding two-sided 95% confidence intervals. Kaplan-Meier curves will also be plotted for each of treatment group and additional co-variates as sample size permits. These Kaplan-Meier curves will be used in to evaluate time to event (clinical outcomes) as well. For survival analysis, death is the event, for MMR, a major molecular response is the event, for CCyR, the event is a complete cytogenetic response and for CHR, the event is a complete hematologic response. Further specifics of these analyses are described below in the following sections.

6.3.1.3.1. Overall Survival

Overall survival probabilities will be estimated using Kaplan-Meier product limit method, medians with corresponding two-sided 95% confidence intervals will be reported. Overall survival is defined as the duration from the therapy first dose date to the date of death and will be calculated as (the date of death – the therapy first dose date + 1), expressed as days. For patients who complete the study, the date last known to be alive will be the "completed date". For patients who discontinued the study, the date last known to be alive will be the discontinued date. For patients who are lost to follow-up, the date last known to be alive will be the last alive date. Patients without a death date will be censored at the date last known to be alive.

The hazard ratio and its associated two-sided 95% confidence interval will be estimated using a Cox model with treatment as the only covariate. The event-free probabilities for each treatment will be estimated and plotted using the Kaplan- Meier (KM) product-limit method. The estimates of the median and corresponding two-sided 95% confidence intervals will be calculated using the log-log transformation method. Median, 25th percentile and 75th percentile and their associated 95% CI will be estimated using the method of Brookmeyer and Crowley. Yearly survival rates will be provided based upon the KM estimate along with its corresponding log-log transformed two-sided 95% confidence intervals. For each TKI group, log-rank p-values will be calculated and displayed in the KM curves for patients who remain on index versus those who switched. The timeframe for these rates being produced will be driven by the extent of follow-up, i.e., the maturity of the survival data relative to that time-point. Because patient follow-up will begin with treatment initiation, rather than time of consent, immortal time bias will be minimized. However, the potential for immortal time bias remains due to patient treatment exposure status prior to on-study therapy exposure (for pre-treated patients).

The descriptive statistics will be reviewed by the study clinical personnel and the appropriate covariates selected based on clinical relevance such as age, gender, line of therapy, disease status, biomarkers, etc. Cox model will be conducted, overall and for each treatment group. The second

stage will apply a Cox proportional hazards univariable model to the data separately using each of the covariates selected in the first stage. The third stage will apply the Cox proportional hazards multivariable model to the data using the covariates selected in the first stage. A stepwise selection method for Cox model will be used to select covariates for the final model and both the full and final models will be presented in the tables. Statistical significance for inclusion in the model will be defined at the 5% level.

The final model will include all statistically significant factors and treatment group. Model fit will be tested using the -2 Log L statistic. Hazard ratio (HR) and the associated 95% CI and P value for treatment group and each covariate will be calculated from the model. Given the possibility for missing data for baseline variables of interest, Cox models that include variables of baseline characteristics could yield estimates that lack precision (e.g., have wide confidence intervals).

6.3.1.3.2. Time to Major Molecular Response (MMR) and MMR Response Rate (MMR-RR)

Time to major molecular response is defined as the duration from the therapy first dose date to the date of first recorded date of a major molecular response (MMR) for an individual patient. Time to MMR will be calculated as (the date of first MMR – the therapy first dose date + 1), expressed as days. For patients who complete the study, discontinued the study, or died without a recorded date of MMR will be censored at the date of last MMR assessment. Since the response is only for the Index Treatment for MMR, for patients who switch off their index treatment, the summaries will only include the data up to the switch and patients who have not responded will be censored at the last assessment time prior to the switch.

The MMR event-free probabilities for each treatment will be estimated and plotted using the Kaplan- Meier (KM) product-limit method and will be analyzed in the same manner described for overall survival.

In addition MMR response rate (MMR-RR) will be calculated as number of patients who reported a response of MMR to a particular treatment divided by the total number of patients who received that treatment.

6.3.1.3.3. Time to Complete Cytogenetic Response (CCyR) and CCyR Response Rate (CCyR-RR)

Time to complete cytogenetic response is defined as the duration from the therapy first dose date to the date of first recorded date of a complete cytogenetic response (CCyR) for an individual patient. Time to CCyR will be calculated as (the date of first CCyR – the therapy first dose date + 1), expressed as days. For patients who complete the study, discontinued the study, or died without a recorded date of CCyR will be censored at the date of last CCyR assessment. Since the

response is only for the Index Treatment for CCyR, for patients who switch off their index treatment, the summaries will only include the data up to the switch and patients who have not responded will be censored at the last assessment time prior to the switch.

The CCyR event-free probabilities for each treatment will be estimated and plotted using the Kaplan- Meier (KM) product-limit method and will be analyzed in the same manner described for overall survival.

In addition CCyR response rate (CCyR-RR) will be calculated as number of patients who reported a response of CCyR to a particular treatment divided by the total number of patients who received that treatment.

6.3.1.3.4. Time to Complete Hematologic Response (CHR) and CHR Response Rate (CHR-RR)

Time to complete hematologic response is defined as the duration from the therapy first dose date to the date of first recorded date of a complete hematologic response (CHR) for an individual patient. Time to CHR will be calculated as (the date of first CHR – the therapy first dose date + 1), expressed as days. For patients who complete the study, discontinued the study, or died without a recorded date of CHR will be censored at the date of last CHR assessment. Since the response is only for the Index Treatment for CHR, for patients who switch off their index treatment, the summaries will only include the data up to the switch and patients who have not responded will be censored at the last assessment time prior to the switch.

The CHR event-free probabilities for each treatment will be estimated and plotted using the Kaplan- Meier (KM) product-limit method and will be analyzed in the same manner described for overall survival.

In addition CHR response rate (CHR-RR) will be calculated as number of patients who reported a response of CHR to a particular treatment divided by the total number of patients who received that treatment.

6.3.1.4. Treatment patterns and management of treatment-related AEs and comorbidities

To assess treatments patterns and management of treatment related AE's and comorbidities per the fifth secondary objective, descriptive summary tables will be provided. For each treatment cohort, the description will include: initial treatment regimen, treatment rationale, dosing frequency, change in dosing (including reasons for dose change and, if applicable, physician classification criteria and grade of intolerance) treatment interruptions (and reasons), change in treatment (including switch [yes or no]; switched therapy [to and from] as defined by TKI treatment to different TKI treatment [by type of different TKI], or TKI treatment to other CML treatment [by type of other CML treatment]; second line treatment added [including type of second line treatment]); duration of

therapy, monitoring, and reason for TKI treatment discontinuation (including reasons for discontinuation and, if applicable, physician classification criteria and grade of intolerance).

6.3.1.5. Factors associated with initial TKI treatment choice or change in TKI treatment

To meet the final secondary objective, factors associated with initial TKI treatment choice or change in TKI treatment will be summarized by treatment group:

- Demographic and clinical patient characteristics:
    - Age at enrollment
    - Age at advanced/metastatic lung cancer diagnosis
    - Gender
    - Race/Ethnicity
    - Comorbidities at enrollment
    - Geographic location by state in the US
    - Rural/urban residence
    - Previous systemic treatment
        - Transfusion
        - Bone marrow biopsy/aspirate
    - ECOG performance status
    - Past and present smoking status
    - Medical history
    - Framingham Score
    - Sokal score
    - Metabolic lab values
        - BMI
        - Metabolites
        - Cytokines and chemokines from biometric panel (e.g. insulin, glucose, high-sensitivity CRP, GDF-15, homocysteine, insulin, C-Peptide, NT-proBNP, hsTNT, sST2, LOX-1 polymorphism)
        - Moderately increased albuminuria levels
    - Other CV and metabolic parameters of interest
        - Fasting blood glucose
        - HbA1c level
        - Fasting lipid panel (total cholesterol, HDL, LDL, triglycerides),
- Patient characteristics which may lead to a physician to recommend that a patient receive specific TKI drug treatment or change of treatment:
    - Long-term overall survival benefit
    - Lower transformation to accelerated/blast phase
    - Manageable cardiac tolerability profile

- Manageable pulmonary tolerability profile
- Manageable metabolic tolerability profile
- Manageable hepatic tolerability profile
- High patient compliance/adherence to therapy
- Patient achieves responses that meet or exceed NCCN treatment guidelines
- Patient achieves a rapid and deep response
- Other reason.

Descriptive statistics will be provided for patients to identify potential factors that affect physician decision-making in the treatment selection. In addition, univariate and multivariate logistic regression models may be utilized to evaluate the key patient and disease characteristics that influence treatment choice, change in treatment, or treatment discontinuation.

Participants will enter the study at the time of first TKI prescription (index date) and followed until death, leaving clinical care, or the end of the study period of two years.

6.4. Exploratory Objectives

- To identify biomarkers that are predictive of an increased risk for cardiovascular or metabolic disease
- To identify safety imaging parameters that are predictive of increased risk for cardiovascular disease.

6.4.1. Analysis Plan for Exploratory Objectives

Whole blood (collected following 8 hours of fasting) and urine samples will be collected to analyze potential inflammatory molecules in CML first line treatments which may be predictive of clinical outcomes, AEs of special interest, onset of comorbidities, and survival outcomes. Blood samples will be stored and analyses will be performed as needed to assess increased risk for cardiovascular or metabolic disease after completion of sample collection. Diagnostic imaging will be collected to analyze changes in cardiovascular function in CML first-line treatments which may be predictive of clinical outcomes, AEs of special interest, onset of comorbidities, and survival outcomes.

Multivariate logistic regression models may be utilized to evaluate key patient and disease characteristics (i.e., demographic differences in age, gender; prognostic characteristics, biomarkers, imaging results or co-morbidities) that influence the occurrence of CV and metabolic events in TKI treated CML patients. Confounding factors and systematic differences will be considered in any multivariate statistical models if sample size permits.

Sample collection of biomarkers will be summarized, including the number and percent of patients with collected blood sample, and patients with at least one evaluable sample by assay type. In addition, the number and percent of patients will be summarized for each category of patient

demographics and baseline disease characteristics by assay. Summaries will be presented for each treatment group and the total population.

Kaplan-Meier curves and analyses will be performed by assay type on the time-to-event endpoints. Quartiles, survival probabilities (at appropriate time points), and corresponding 95% confidence intervals will be generated. Tumor response rates by assay type will be compared between treatment groups (index vs. switch groups within TKI) using Fisher's exact test.

The distributions of biomarkers with continuous measures, such as gene or protein expression, will be described for each treatment group and total population. Summary statistics will include means, medians, corresponding standard errors, quartiles and ranges. Biomarkers with discrete measures, such as genotype locus, will be summarized in frequency tables for each treatment group and total population.

Associations between clinical endpoints (Assessments of CV and Metabolic disease, Incidence of CV and Metabolic disease, MMR, MMR-RR, CCyR, CCyR-RR, CHR, CHR-RR, OS) and biomarkers will be evaluated using data from patients who have a valid and evaluable sample for the marker of interest. Cox proportional hazard model will be used for the time to events endpoints and logistic regression model will be used for MMR-RR, CCyR-RR and CHR-RR to explore the associations. Markers and their interaction with treatment will be assessed on an individual basis, that is a given marker will be analyzed separately. Discrete measures, such as marker genotype, will be assessed by including these measures along with their interaction with treatment as class effects in the appropriate models. Continuous measures, such as protein expression, the model with the marker treated as a continuous variable and dichotomous variable will be considered separately. Dichotomization of a continuous marker will be based on the method of maximum chi square in which the marker expression level is dichotomized into low and high-expression groups at the point that best associates these groups with the particular clinical outcome. This grouping, along with its interaction with treatment, will be included as a class effect in the appropriate model. That is, the patients will be divided at the point of the distribution that maximizes the association between the marker by treatment interaction and each clinical outcome. Significance of this association will be evaluated using a test for maximal chi-square values (Miller and Siegmund 1982). Also, dichotomization of a continuous marker will be based on a pre-specified cut-off point if deemed appropriate.

6.5. Interim Analysis

6 interim analyses will be planned for this study, at points in time determined by BMS based on when they would like to present data to scientific congresses. BMS and iVH will work through the exact timing and budgeting of these interim analyses.

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8. Appendix

APPENDIX 1: ESTIMATE OF 10-YEAR RISK FOR CORONARY HEART DISEASE FRAMINGHAM POINT SCORESFOR MEN AND WOMEN

1 ESTIMATE OF 10-YEAR RISK FOR MEN

Table 1: Framingham Point Scores by Age Group for Men

Age	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Table 2: Framingham Point Scores by Age Group and Total Cholesterol for Men

Total Cholesterol	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
280+	11	8	5	3	1

Table 3: Framingham Point Scores by Age and Smoking Status for Men

	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

Table 4: Framingham Point Scores by HDL Level for Men

HDL	Points
60+	-1
50-59	0
40-49	1
<40	2

Table 5: Framingham Point Scores by Systolic Blood Pressure and Treatment Status for Men

Systolic BP	If Untreated	If Treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
160+	2	3

Table 6: 10-Year Risk by Total Framingham Point Scores for Men

Point Total	10-Year Risk
< 0	< 1%
0	1%
1	1%
2	1%
3	1%

Table 6: 10-Year Risk by Total Framingham Point Scores for Men

Point Total	10-Year Risk
4	1%
5	2%
6	2%
7	3%
8	4%
9	5%
10	6%
11	8%
12	10%
13	12%
14	16%
15	20%
16	25%
17 or more	≥ 30%

2 ESTIMATE OF 10-YEAR RISK FOR WOMEN

Table 7: Framingham Point Scores by Age Group for Women

Age	Points
20-34	-7
35-39	-3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-79	16

Table 8: Framingham Point Scores by Age Group and Total Cholesterol for Women

Total Cholesterol	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	1
200-239	8	6	4	2	1
240-279	11	8	5	3	2
280+	13	10	7	4	2

Table 9: Framingham Point Scores by Age and Smoking Status for Women

	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

Table 10: Framingham Point Scores by HDL Level for Women

HDL	Points
60+	-1
50-59	0
40-49	1
<40	2

Table 11: Framingham Point Scores by Systolic Blood Pressure and Treatment Status for Women

Systolic BP	If Untreated	If Treated
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
160+	4	6

Table 12: 10-Year Risk by Total Framingham Point Scores for Women

Point Total	10-Year Risk
< 9	< 1%

Table 12: 10-Year Risk by Total Framingham Point Scores for Women

Point Total	10-Year Risk
9	1%
10	1%
11	1%
12	1%
13	2%
14	2%
15	3%
16	4%
17	5%
18	6%
19	8%
20	11%
21	14%
22	17%
23	22%
24	27%
25 or more	≥ 30%

Source: Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001 May 16;285(19):2486-97.