Study Title: The Life After Stopping Tyrosine Kinase Inhibitors Study (The LAST Study)

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The Life After Stopping Tyrosine Kinase Inhibitors Study

(The LAST study)

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Protocol Version Summary

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Phase: II

LAST
Life After Stopping TKIs

Confidentiality Statement

This protocol may not be used, published or otherwise disclosed

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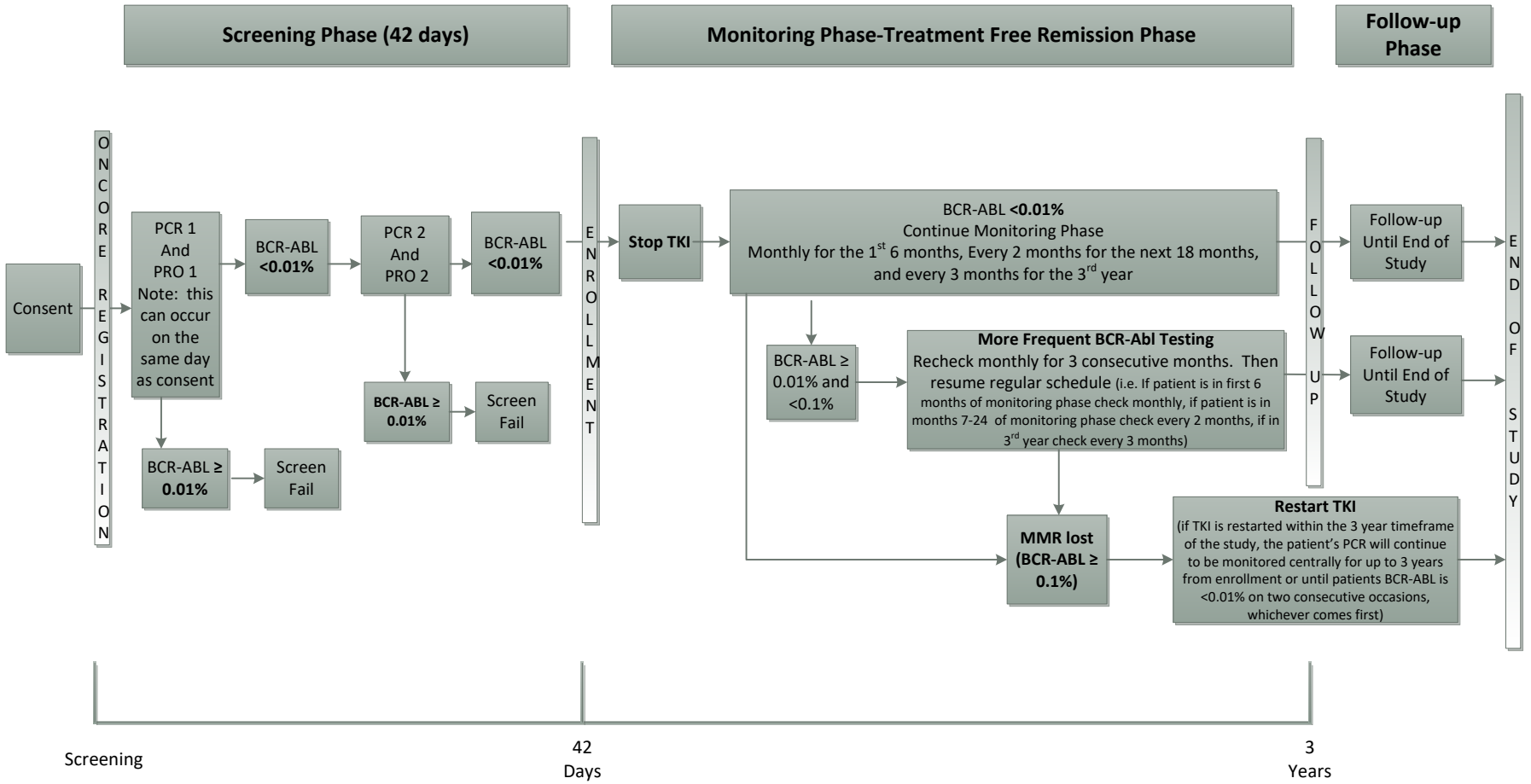
Schedule of Trial Procedures

Month (30 days)[a]	Year 1														Year 2						Year 3				Long Term Follow Up
	S[e]	D1[f]	1	2	3	4	5	6	7	8	9	10	11	12	14	16	18	20	22	24	27	30	33	36	
Eligibility criteria	x																								
Informed consent	x																								
Medical history	X[g]																								
Physical Exam[j]	x							x						x			x			x				x	
Stop TKI		x																							
RQ-PCR[b]	x		x	x	x	x	x	x		x		x		x	x	x	x	x	x	x	x	x	x	x	
PRO assessments[c]	x		x	x	x	x	x	x		x				x			x			x		x		x	
Digital PCR[d]	x		x	x	x	x	x	x		x		x		x	x	x	x	x	x	x	x	x	x	x	
AE assessment[h]	x	→																							
Survival																									X[i]

a. Months after stopping TKI (±4 days for visits month 1-6) (±7 days for visits months 7-36)
b. During screening, RQ-PCR for BCR-ABL will be performed twice at least 21 days apart to confirm that BCR-ABL is <0.01% (MR^4) at the Core Lab. During follow up, if BCR-ABL is ≥ 0.01% for the first time, then PCR testing would be repeated monthly for 3 months. If MMR is lost restart TKI. If no loss of MMR then resume regular schedule of PCR evaluations. i.e. if patient is in first 6 months of study check RQ-PCR monthly, if in month 7-24 then check RQ-PCR q 2 months, if in third year then check RQ-PCR q 3 months. For patients who restart TKI therapy, RQ-PCR will be performed approximately every 3 months at Core Lab until the patient BCR-ABL is <0.01% (MR^4) two consecutive times. Once a patient has two consecutive core lab BCR-ABL < 0.01% (MR^4), the patient will have their RQ-PCR processed locally approximately every 3 months for the remainder of the study.
c. PROs will also be collected twice during the screening period. Refer to section 5.3.2 for patients who restart their TKI.
d. Digital PCR will be performed on the same schedule as RQ-PCR as long as BCR-ABL remains undetectable by RQ-PCR. For patients who restart the TKI, the digital PCR will no longer be performed
e. Screening within 42 days prior to enrollment
f. Day 1 of stopping TKI
g. Baseline data will include age, sex, date of diagnosis, baseline BCR-ABL transcript level, Sokal risk score (see appendix 4) and its components (spleen size, platelet count, the percentage of blasts in the peripheral blood), basophil %, history of prescribed TKIs including any dose reductions or held dosing, time to MR^3, time to undetectable BCR-ABL by PCR, duration undetectable BCR-ABL by PCR.

h. AEs will be followed throughout the study from the time of Informed Consent until restarting TKI. See Section 10.1.2 for AE reporting guidelines
i. Patients will be followed for survival after study completion every 6 months.
j. Once a patient restarts their TKI, physical exams will be performed at the discretion of the treating physician.

Schema


Screening Phase (42 days)
Monitoring Phase-Treatment Free Remission Phase
Follow-up Phase
Consent
ONCORE REGISTRATION
PCR 1 And PRO 1 Note: this can occur on the same day as consent
BCR-ABL ≥ 0.01%
Screen Fail
BCR-ABL <0.01%
PCR 2 And PRO 2
BCR-ABL ≥ 0.01%
Screen Fail
BCR-ABL <0.01%
ENROLLMENT
Stop TKI
BCR-ABL <0.01%
Continue Monitoring Phase
Monthly for the 1st 6 months, Every 2 months for the next 18 months, and every 3 months for the 3rd year
BCR-ABL ≥ 0.01% and <0.1%
More Frequent BCR-Abl Testing
Recheck monthly for 3 consecutive months. Then resume regular schedule (i.e. If patient is in first 6 months of monitoring phase check monthly, if patient is in months 7-24 of monitoring phase check every 2 months, if in 3rd year check every 3 months)
MMR lost (BCR-ABL ≥ 0.1%)
Restart TKI
(if TKI is restarted within the 3 year timeframe of the study, the patient's PCR will continue to be monitored centrally for up to 3 years from enrollment or until patients BCR-ABL is <0.01% on two consecutive occasions, whichever comes first)
FOLLOW UP
Follow-up Until End of Study
Follow-up Until End of Study
END OF STUDY
Screening
42 Days
3 Years

List of Abbreviations and Glossary of Terms

Abbreviation	Term
AE	Adverse event
ANC	Absolute neutrophil count
AP	Accelerated phase
AST	Aspartate aminotransferase
BC	Blast crisis
CBC	Complete blood count
CCyR	Complete cytogenetic response
CML	Chronic myelogenous leukemia
CMR	Complete molecular response
CR	Complete remission
eCRF	Electronic case report forms
CTMS	Clinical Trials Management System
CTO	Clinical trials office
DCR	Death in CR
DSMC	Data safety monitoring committee
ECOG	Eastern Cooperative Oncology Group
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
Hb	Hemoglobin
HCT	Hematopoetic stem cell transplantation
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IRB	Institutional review board
IS	International standardized ratio
MCW	Medical College of Wisconsin
MR	Molecular response
MMR	Major molecular response
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PCR	Polymerase chain reaction
PO	*Per os*; by mouth (orally)
PR	Partial remission
PRO	Patient reported outcomes
PROMIS	Patient Reported Outcomes Measurement Information System
QA	Quality assurance
QOL	Quality of life
RFS	Relapse free survival
SAE	Serious adverse event
TKI	Tyrosine kinase inhibitors
US	United States
WBC	White blood cell

Protocol Summary

Study Title: The Life After Stopping Tyrosine Kinase Inhibitors Study (The LAST study)

Phase: II

Number of Patients: 173

Number of Sites: 14

STUDY OBJECTIVES

Primary Objectives:

1. Proportion of patients with CML who develop molecular recurrence after discontinuing tyrosine kinase inhibitors (TKIs). Molecular recurrence defined as loss of MMR (> 0.1% BCR-ABL^{IS})
2. Compare the patient-reported health status of patients before and after stopping TKIs.

Secondary Objectives:

1. To prospectively determine whether there are disease, patient-related, or treatment-related factors that predict molecular recurrence including sex, age, type of TKI, time to undetectable BCR-ABL by PCR, duration undetectable BCR-ABL by PCR, Sokal risk at diagnosis, and BCR-ABL transcript levels measured by digital PCR.
2. Develop a risk scoring system to predict the patient's risk of molecular recurrence after stopping TKI
3. Assess whether specific time points are more important for clinical prediction of recurrence and develop an optimal follow up schedule.
4. Describe the patient-reported health status of patients after resuming TKIs in patients who restart TKIs.

Overview of Study Design

This is a non-randomized, prospective, single-group longitudinal study. The overall objective is to improve decision making for TKI discontinuation in eligible CML patients. Patients with CML on treatment with imatinib, dasatinib, nilotinib, or bosutinib and in confirmed deep molecular response will stop their TKI. Confirmed deep molecular response is defined as BCR-ABL < 0.01% (>MR^4 i.e. > 4 log reduction) for at least 2 years. The study will closely monitor patients using standard RQ-PCR testing for molecular recurrence, testing them monthly for 6 months, then every other month until 24 months, and then quarterly until 36 months. Concurrently, the study will assess a wide range of patient reported outcomes (PROs) before stopping TKIs and after discontinuation in conjunction with PCR testing, though at fewer time points. Patients who have molecular CML recurrence based on

RQ-PCR will restart imatinib, dasatinib, nilotinib, or bosutinib and will continue to be monitored for disease status and patient-reported health status until the end of the study.

Study population:

Inclusion Criteria:

1. Age 18 or older at time of study entry
2. Willing and able to give informed consent
3. Diagnosed with CML in chronic phase and have either the b3a2 (e14a2) or b2a2 (e13a2) variants that give rise to the p210 BCR-ABL protein
4. Currently taking imatinib, dasatinib, nilotinib or bosutinib
5. Patient has been on TKI therapy for at least 3 years
6. Documented BCR-ABL <0.01% (>MR^4 i.e. >4 log reduction) or undetectable BCR-ABL by PCR for at least 2 years according to the patient's local lab
7. Documented BCR-ABL <0.01% (>MR^4 i.e. >4 log reduction) or undetectable BCR-ABL at least 3 times prior to screening according to the patient's local lab
8. Two (2) Screening PCRs have been completed and both results are < 0.01% (>MR^4 i.e > 4 log reduction) by central lab
9. Has been on any number of TKIs, but has not been resistant to any TKI (changes made for intolerance are allowed)
10. Patient has been compliant with therapy per treating physician

Exclusion Criteria:

1. Prior hematopoietic stem cell transplantation
2. Poor compliance with taking TKI
3. Unable to comply with lab appointments schedule and PRO assessments
4. Life expectancy less than 36 months
5. Patients who have been resistant to previous TKI therapy are not eligible
6. Pregnant or lactating women

Duration of Study: 60 months

Table of Contents

1. Background and Study Rationale

1.1 Background

Tyrosine kinase inhibitors (TKIs) have dramatically improved the survival of patients with chronic myeloid leukemia (CML), leading to an unforeseen increase in prevalence. Current recommendations are to continue therapy indefinitely, sometimes despite significant side effects. Moreover, the costs of TKI therapy are substantial and place a financial burden on the US health care system. Small, single-armed studies from Europe and Australia suggest that some patients with CML in a TKI-induced complete molecular response (MR 4.5) maintain this response after discontinuation of TKIs. Given uncertainty about the patient characteristics associated with maintenance of MR 4.5 versus recurrence of active leukemia, patients and physicians have little basis on which to make the decision to discontinue TKI therapy. Furthermore the impact of discontinuation on patients' experiences of symptoms and the factors driving a patient's choice about discontinuation have not been studied. The Life After Stopping Tyrosine Kinase Inhibitors (LAST) Study will provide answers to these practical questions in a comprehensive, outcome-based approach, thereby generating a rational basis for decision making. With annual costs of $100,000 per patient (1), an estimated prevalence of 70,000 patients in 2010 (2), and with an estimated 36% of patients in stable MR 4.5 (3), a discontinuation rate of 50% could lead to savings of over $500 million to the US health care system in the first year, even with increased monitoring costs and a 50% recurrence rate. Prevalence of CML continues to rise – 180,000 patients are expected by 2050 (2) – increasing the public health relevance of this important issue.

1.2 Chronic myeloid leukemia is treatable with TKIs

CML is caused by the BCR-ABL tyrosine kinase, the product of the t(9;22) translocation visible as the Philadelphia chromosome (Ph). This fusion gene confers a proliferative advantage to the cells acquiring this translocation. Prior to the introduction of imatinib (Gleevec®) in 2001, the only cure for CML was hematopoetic stem cell transplantation, and the median survival of all patients was 4-5 years (4). Since the introduction of imatinib, about 87% of patients are expected to be alive at 8 years of follow up (5). Several other TKIs were subsequently developed and FDA-approved for the treatment of CML patients, including nilotinib (6) and dasatinib (7). As first line therapies, these have been compared head-to-head with imatinib in two phase 3 studies and found to induce faster cytogenetic and molecular responses than imatinib, although it is not known whether this translates into improved long-term survival (8, 9). Response to TKIs usually proceeds in an orderly fashion: first normalization of blood counts and spleen size, followed by the disappearance of Ph-positive metaphases (complete cytogenetic response). Deeper responses at the molecular level are measured by reductions of the BCR-ABL transcripts in the blood or marrow to very low or undetectable levels using real-time quantitative polymerase chain reaction (RQ-PCR) (10, 11). Molecular response (MR) is reported as % BCR-ABL/control gene, with ABL1 being the most commonly used control gene. For BCR-ABL to be considered undetectable, adequate amplification of a quality control gene is needed to ensure that the

measurement is sufficiently sensitive. MR 3.0 is a 3.0 log reduction in BCR-ABL transcripts and is equivalent to BCR-ABL ≤ 0.1%. MR 4.0 is BCR-ABL ≤0.01%, MR 4.5 is BCR-ABL ≤0.0032%, and MR 5.0 is BCR-ABL ≤0.001%.

1.3 Financial impact of TKI therapy

This study has the potential to reduce national expenditures associated with treatment with TKIs. In early 2013, over 100 experts in CML, including many of the co-investigators on this study, called for a reduction in the prices of TKIs to allow greater access to the drugs for more patients and to "maintain sound long-term healthcare policies" in light of the $2.7 trillion spent on health care in the U.S. in 2011(1). As outlined above, savings could top half a billion dollars in the U.S. if half of eligible CML patients discontinued TKIs, even after accounting for recurrence and increased costs of monitoring for patients off therapy. Moreover, the cost savings to patients themselves should not be underestimated. Most patients in the U.S. pay at least some of their medications costs out of pocket; some pay a very large proportion of those costs out of pocket.

1.4 TKIs are associated with reduced quality of life

Imatinib was a significant improvement over previous CML treatments in terms of survival and toxicity (12, 13). Even so, imatinib and other TKIs are associated with diminished patient-reported health status due to multiple side effects of the treatment. While there are relatively few (<10) studies on health status outcomes, patients consistently report increased fatigue and depression, difficulties with sleep, and high symptom burden particularly nausea, diarrhea, pain, fluid retention (puffy face), and skin problems (14), especially as compared to peers without cancer (15). Of particular concern is that patients and physicians may not value health-related quality of life in the same way, further limiting which data are collected in research studies and thus our understanding of the patient's experience. A European study found that while both patients and physicians ranked fatigue as their first concern, other symptoms and concerns were ranked quite differently (16). The issues ranked substantially higher by patients were mostly symptoms – dry mouth, trouble concentrating or remembering, frequent urination, skin problems, and drowsiness, whereas the issues ranked substantially higher by physicians were psychosocial concerns such as interference with daily activities or worry about the treatment schedule. Furthermore, deleterious side effects have been recognized only with longer follow-up, for example, pulmonary hypertension in patients on dasatinib (17) and peripheral arterial occlusive disease in patients on nilotinib (18). These and other side effects are thought to be related to the inhibition of kinases other than the BCR-ABL kinase (19).

1.5 Some patients may not need to continue taking TKIs forever

Current guidelines for the treatment of CML recommend continuation of treatment with TKIs as long as patients are responding and tolerating the drug (20, 21). The French STIM trial (Stop Imatinib) stopped imatinib in 100 patients who had sustained MR^5 for at least 2 years and monitored them closely (22). Patients who had

molecular recurrence restarted imatinib therapy. Molecular recurrence was defined as loss of MR^5 confirmed by a second rising level. With a median follow up of 50 months, 39 patients had maintained their molecular remission and 61 patients had molecular recurrence. Of those 61 patients, all responded to TKI rechallenge; no patient experienced disease progression or died from their disease (22). Similar results have been shown in five other small, non-US studies (23-27). These studies have varied with regard to sample size, definition of recurrence, and TKI therapy before discontinuation. In the TWISTER study conducted in Australia (24), 40 patients with sustained CMR stopped imatinib and were monitored frequently. Treatment was restarted at loss of MMR or two consecutive samples at any level. With a median follow up of 42 months, 18 (45%) of patients had not met the study definition of relapse. In all patients who relapsed, the first sample which tested positive was at a level below loss of MMR. Eight patients lost MMR prior to starting therapy. Of note 5 of the 18 patients who did not meet the pre-specified definition of relapse had detectable levels of BCR-ABL in the blood on one or two occasions, but have not relapsed. All patients who restarted imatinib responded, with all patients having at least one undetectable PCR measurement. No patients progressed to accelerated phase or blast crisis and no patients relapsed. Based on the observation that some patients have a low level detectable disease but have no evidence of disease progression, the A-STIM trial (According to Stop Imatinib) was designed where patients restart TKI therapy at loss of MMR and not when there was detectable disease. In the A-STIM trial patients with chronic phase CML who had been in CMR and/or had weakly positive samples prior to enrollment were eligible (23). In that study, 80 patients were enrolled and stopped their TKI. The median duration of CMR prior to study enrollment was 41 months, and 52% had unstable CMR. With a median follow up of 31 months, 29 patients (36%) lost MMR. Of the patients who lost MMR, only 4 patients lost MMR after 6 months and only one patient lost MMR after 12 months. Overall, 45 patients (51%) lost CMR according to the STIM criteria. Of those, 29 lost MMR for a cumulative incidence of 65% at 24 months for loss of MMR in patients with loss of CMR. Treatment was resumed in 29 patients after loss of MMR and in 2 patients after loss of CMR. With a median follow up of 17 months after treatment restart, 23 patients regained CMR and 8 patients are in MMR. One patient progressed to lymphoid blast crisis. That patient had a long history of CML, was treated with interferon for 4 years, then stopped therapy for intolerance. Seven years later she was started on imatinib, and three years later, imatinib was stopped. CMR was lost 9 months later and MMR was lost one month after. She was started on imatinib and regained CMR, but 8 months later developed lymphoid blast crisis. The authors of the study do not think this was attributed to the design of the study as she lost both CMR and MMR at the same time. In addition, this is consistent with previous data of patients who develop sudden blast crisis while on imatinib(28). In the KIDS study (Korean imatinib discontinuation study), 78 patients with CML who had undetectable BCR-ABL by RQ PCR for at least 2 years and had been on imatinib therapy for at least 3 years discontinued imatinib. Patients who relapsed (defined as loss of MMR on 2 consecutive assessments) resumed TKI. With a median follow up of 14 months, 13 patients lost MMR at 12 months. Of those, 9 restarted imatinib therapy and achieved CMR at a median of 7.5 months. Interestingly none of the patients who had prior HCT relapsed. None of the patients progressed to accelerated phase or blast crisis. In the study by Rea et al,

patients on second generation TKIs (2G-TKI) i.e. dasatinib and nilotinib were enrolled on the study and stopped TKI therapy. Of the 34 patients who had at least 6 months of follow up, 25 patients (74%) received 2G-TKI upfront or for intolerance and 9 (26%) received 2G-TKI due to suboptimal response/resistance to imatinib. The probability of stable MMR was 67% vs 33% for patients who were on 2G-TKI upfront/intolerance vs. suboptimal response/resistance respectively. None of the patients progressed to accelerated phase or blast crisis. More recently, the Euro-SKI study interim analysis results were presented(29). In that study, patients with CML and sustained deep molecular response defined as BCR-ABL <0.01% (MR^4) for at least one year were enrolled in the study. The planned interim analysis of the first 200 patients completing 6 months of follow up was presented. Both duration of CML therapy and duration of deep molecular response were associated with prognostic significance. However, there was no prognostic significance for depth of response at discontinuation when comparing patients at MR^4 vs $MR^{4.5}$ vs. MR^5. Based on this data, this protocol will include patients in confirmed deep molecular response defined as BCR-ABL <0.01% (MR^4 i.e. > 4 log reduction). Taken together, these results are compelling, but the evidence base is not sufficient for a large-scale change in the standard of care for CML patients in the US. Indeed, CML experts recommend that discontinuation be performed on clinical trials only (22, 30, 31).

Table (1) Previously reported stopping TKI studies

	#	TKI	Prior IFN N (%)	Median F/U (months)	Definition of Relapse	Relapse N (%)	Relapse in first 6 months N (%)	Latest relapse (months)
STIM1(22)	100	I	51 (51)	50	detectable *BCR-ABL* on 2 consecutive tests with at least 1 log increase between the 2 or loss of MMR once	61 (61)	58 (95)¥	22
STIM2(27)*	124	I	0	12		48 (39)	45 (94)	12
TWISTER(24)	40	I	21 (52)	42	detectable *BCR-ABL* on 2 consecutive tests at any level or loss of MMR once	22 (52)	15 (68)	27
KIDS(26)**^	78	I	NR	14	loss of MMR on 2 consecutive tests	16 (21)	NR	NR
A-STIM(23)^	80	I	40 (52)	31	Loss of MMR once	29 (36)	25 (31)	17
2G-TKI(25)^	34	D or N	25 (74)	14	Loss of MMR once	15 (44)	NR	29

*No prior therapy with IFN, **21 patients had prior HCT, ^Restarting with loss of MMR only, ¥ 7 months, NR: Not reported, I: imatinib, D: dasatinib, N: nilotinib, NR: Not reported, MMR: Major molecular response, F/U: Follow up, 2G-TKI: Second generation TKI, IFN: Interferon

2. Study Objectives

Primary Objectives:

1. Proportion of patients with CML who develop molecular recurrence after discontinuing tyrosine kinase inhibitors (TKIs). Molecular recurrence defined as loss of MMR (> 0.1% BCR-ABL^{IS})
2. Compare the patient-reported health status of patients before and after stopping TKIs.

Secondary Objectives:

1. To prospectively determine whether there are disease, patient-related, or treatment-related factors that predict molecular recurrence including sex, age, type of TKI, time to undetectable BCR-ABL by PCR, duration undetectable BCR-ABL by PCR, Sokal risk at diagnosis, and BCR-ABL transcript levels measured by digital PCR.
2. Develop a risk scoring system to predict the patient's risk of molecular recurrence after stopping TKI
3. Assess whether specific time points are more important for clinical prediction of recurrence and develop an optimal follow up schedule.
4. Describe the patient-reported health status of patients after resuming TKIs in patients who restart TKIs.

3. Study Design

This is a non-randomized, prospective, single-group longitudinal study. The overall objective is to improve decision making for TKI discontinuation in eligible CML patients. Patients with CML on treatment with imatinib, dasatinib, nilotinib, or bosutinib and are in confirmed deep molecular response will stop their TKI. Confirmed deep molecular response is defined as BCR-ABL < 0.01%, (> MR^4 i.e. > 4 log reduction) for at least 2 years. The study will closely monitor patients using standard RQ-PCR testing for molecular recurrence, testing them monthly for 6 months, then every other month until 24 months, and then quarterly until 36 months. Concurrently, the study will assess a wide range of PROs before stopping TKIs and after discontinuation in conjunction with PCR testing, though at fewer time points, utilizing online and/or phone questionnaires. Patients who have molecular CML recurrence based on RQ-PCR will restart imatinib, dasatinib, nilotinib, or bosutinib and will continue to be monitored for disease status and health status until the end of the study.

Number of Patients: 173 patients

Duration of Study: 60 months
Number of sites: 14 sites and 2 affiliate sites, all in the US

4. Study Population

Inclusion Criteria:

1. Age 18 or older at time of study entry
2. Willing and able to give informed consent
3. Diagnosed with CML in chronic phase and have either the b3a2 (e14a2) or b2a2 (e13a2) variants that give rise to the p210 BCR-ABL protein
4. Currently taking imatinib, dasatinib, nilotinib or bosutinib
5. Patient has been on TKI therapy for at least 3 years
6. Documented BCR-ABL <0.01% (>MR^4 i.e. >4 log reduction) or undetectable BCR-ABL by PCR for at least 2 years according to the patient's local lab
7. Documented BCR-ABL <0.01% (>MR^4 i.e. >4 log reduction) or undetectable BCR-ABL at least 3 times prior to screening according to the patient's local lab
8. Two (2) Screening PCRs have been completed and both results are < 0.01% (>MR^4 i.e > 4 log reduction) by central lab
9. Has been on any number of TKIs, but has not been resistant to any TKI (changes made for intolerance are allowed)
10. Patient has been compliant with therapy per treating physician

Exclusion Criteria:

1. Prior hematopoietic stem cell transplantation
2. Poor compliance with taking TKI
3. Unable to comply with lab appointments schedule and PRO assessments
4. Life expectancy less than 36 months
5. Patients who have been resistant to previous TKI therapy are not eligible
6. Pregnant or lactating women

5. Procedures

5.1 Recruitment Sites and Feasibility

To achieve a geographically diverse sample and reach our needed sample size, 14 sites and 2 affiliate sites are included for recruitment as outlined in **Table 2**.

Table 2. Recruitment Sites and Locations

Site	Location
Medical College of Wisconsin Cancer Center	Milwaukee, WI
University of Chicago Comprehensive Cancer Center Affiliate Site: University of Chicago at Silver Cross	Chicago, IL New Lenox, IL
Huntsman Cancer Institute at University of Utah	Salt Lake City, UT
Dana-Farber Cancer Institute Affiliate Site: Dana-Farber Beth Israel	Boston, MA Boston, MA
Winship Cancer Institute of Emory University	Atlanta, GA
Karmanos Cancer Institute of Wayne State University	Detroit, MI
Duke University Cancer Institute	Durham, NC
Fred Hutchinson Cancer Research Center & Seattle Cancer Care Alliance	Seattle, WA
Memorial Sloan Kettering Cancer Center	New York, NY
Moffitt Cancer Center	Tampa, FL
Weill Medical College of Cornell University	New York, NY
UCSF Helen Diller Family Comprehensive Cancer Center	San Francisco, CA
The University of Texas MD Anderson Cancer Center	Houston, TX
Roswell Park Cancer Institute	Buffalo, NY

5.2 Screening, registration and enrollment:

5.2.1 Pre-Screening

A log of all potential patients will be kept by each site, including individuals who decide not to participate in or who are found to be ineligible for the study.

5.2.2 Screening and Registration

Screening will be performed for potential study patients after they have consented to trial participation. If a patient is screened - regardless of whether or not they are registered to the study – their details should be entered into the MCW Oncore CTMS. Patients will receive a screening ID that will be used to identify the patient throughout the study. At this time patients will be considered registered on the study.

Documentation of both the informed consent process and that the process occurred prior to a subject's entry into this study is recorded in the subject's source documents. The original consent form, signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the investigator's study files at each participating institution.

Patients in screening will be assessed by the PCR Core Lab twice, at least 21 days apart, to confirm that the BCR-ABL is < 0.01% (>MR^4 i.e. > 4 log reduction). Concurrently; patients will take the PRO questionnaires described in Appendix 1 to record their baseline health status.

Participating Sites will upload all de-identified source documents with patient study IDs confirming patient eligibility into Oncore CTMS. The coordinating center will review all documents and confirm eligibility.

5.2.3 Enrollment

Patients will be considered enrolled in the study once the coordinating site has confirmed that all screening eligibility criteria have been met; then the TKI will be stopped within 7 days of enrollment.

5.3 Monitoring phase

After patients are enrolled and stop their TKI, the monitoring phase starts. Patients will have both BCR-ABL assessments and PRO assessments as clarified below (sections 5.3.1 and 5.3.2). The monitoring phase will last for 3 years.

Patients' study participation may be terminated for any of the following reasons:

- Death
- Medically significant event
- Physician discretion
- Withdrawal of consent
- Patient non-compliance with study procedures
- Patient is lost to follow up

5.3.1 Assessment of BCR-ABL

Enrolled patients will have blood draws for RQ-PCR at their local study site laboratory every month for the first 6 months, every 2 months for the next 18 months (until 24 months), and every 3 months for the third year. Patients may be able to get some labs drawn closer to their home. Site will need to complete Appendix 5 if they want permission to send patients to a lab closer to home. Sites local IRB should be consulted as well to determine local IRB reporting requirements. All samples will be shipped to the PCR Core Lab. Specimen Collection and Handling instructions are detailed in Appendix 2. The PCR Core Lab will perform RQ-PCR and digital testing of peripheral blood. Digital PCR will be used for research questions only, with results available to

clinicians only upon conclusion of the study. Thus therapy decisions will be made based on RQ-PCR only, per existing treatment guidelines. During the monitoring phase, if BCR-ABL ≥0.01% for the first time, then PCR testing would be repeated monthly for 3 months. If BCR-ABL ≥0.1% (loss of MMR) restart TKI. If no loss of MMR then resume regular schedule of PCR evaluations. i.e. if patient is in first 6 months of study check RQ-PCR monthly, if in month 7-24 then check RQ-PCR q 2 months, if in third year then check RQ-PCR q 3 months. If BCR-ABL ≥0.1% at any time point, patients will restart TKI therapy. For patients who restart TKI therapy, RQ-PCR will be performed at the central lab approximately every 3 months from the date of restarting their TKI, for a total of 3 years from enrollment or until BCR-ABL is < 0.01% twice, whichever comes first. All PCR Core Lab results will be entered into Oncore CTMS to facilitate secure sharing of data with the Coordinating Center. Following that, BCR-ABL results will be collected locally approximately every 3 months for the duration of the study. These local Lab results will be entered into Oncore CTMS to facilitate secure sharing of data with the Coordinating Center. It may be expected that patients who had been tolerating their previous TKI will resume that drug, but the study will not restrict them from starting a different TKI; this decision will be left to the patient and his or her physician.

5.3.1.1 Assessment of BCR-ABL for GeneXpert Validation

Enrolled patients will have blood draws for their RQ-PCR and Digital PCR that will be shipped to the PCR Core Lab at the time points described in sections 5.3.1. Aliquots of these samples will be taken by the PCR Core Lab for GeneXpert Validation tests. Please see appendix 6 for validation test information.

5.3.2 Assessment of PROs

Baseline assessment of on-therapy PROs will be collected twice before enrollment during screening then for the duration of the study, at months 1, 2, 3, 4, 5, 6, 8, 12, 18, 24, 30, and 36. Because side effects associated with TKIs are expected to diminish in 1-3 months after discontinuation, PRO data will be collected more frequently in the first 6 months of the study. Prior to each scheduled visit, an MCW study coordinator will email the local study coordinator with a link to access a secure platform hosted by MCW using the REDCap platform. For all patients PRO assessments will primarily be administered at the time of blood draws. Ideally, the site coordinator would meet with the patient at the time of blood draws and administer the survey on an electronic tablet provided by the study (though the assessment can also be completed in other ways if necessary, see section 5.4. on Prevention of Missing Data).

For patients who restart their TKI, PRO data will be collected approximately every 3 months for the first 12 months after restarting and then approximately every 6 months until end of study, ideally in conjunction with the PCR blood draws. No protocol deviations need be filed if at least 4 PRO assessments are collected within the first 18 months after TKI restart date. Note that PRO assessments must be collected at least 1 month apart.

5.4 Patient Retention and Prevention of Missing Data

For participants who do not complete their PRO assessment at the clinic, the local site coordinator will either 1) email the REDCap link to the participant to complete the assessment online at home, 2) access the assessment in REDCap and read them to the participant over the phone, reporting the participant's responses directly into the online system, or 3) give the participant a paper version of the assessment and then upload the completed assessment to OnCore.

Every effort will be made to limit study drop out over the 3-year study follow-up. It is expected that patients will want to remain in the study because otherwise they will not have access to the same increased frequency of monitoring. A MCW project coordinator will monitor the collection of biologic data through OnCore in collaboration with the PCR Core Lab to make sure that expected data is being delivered. A MCW project coordinator will monitor the PRO data collection through REDCap, so that local study coordinators can follow up with patients in real time each week if they have missed assessments. If patients have missed more than two assessments of either type (PCR test or PRO assessment), the site PI might be contacted to recruit their assistance in following-up with the participant.

5.5 Follow up and end of study

After completion of the monitoring phase, patients will be followed for survival every 6 months and for transformation to accelerated phase or blast crisis. The RQ-PCRs will be performed by the patient's physician according to standard of care.

6. Measures

6.1 Measurement of BCR-ABL

The Core Lab will use standard molecular RQ-PCR monitoring in all patients on the IS scale. All samples with undetectable BCR-ABL will also be examined using digital PCR, which is a more sensitive nanofluidic PCR system (Fluidigm Corporation, South San Francisco, CA) with an increased sensitivity of > 2 log beyond the standard PCR assay [26, 27]. Digital PCR will follow the same schedule as RQ-PCR monitoring unless CML recurs, then only RQ-PCR testing will be used henceforth. In the digital assay, detection sensitivity is augmented by sample partitioning prior to PCR, such that multiple PCR reactions are performed simultaneously in hundreds of replicates. For example, if a mixture containing 1 molecule of BCR-ABL within 100,000 molecules of control gene is partitioned into 1,000 independent chambers, the chamber containing the single BCR-ABL molecule now only contains ~100 molecules of control gene. This 1,000-fold increase in relative concentration theoretically allows for a 1,000-fold improvement in the detection sensitivity of PCR reactions, thereby facilitating rare copy detection in patient samples. Digital PCR uses the Poisson distribution to calculate BCR-ABL and ABL1 control gene transcript levels.

6.2 Measurement of PROs

The PROMIS measurement system will be used for self-reported health status. PROMIS is the NIH's initiative to standardize measurement of PROs in clinical research across all chronic conditions. Where PROMIS measures are not available to assess CML-specific symptoms, the EORTC QLQ-CML Symptom Burden scale, which covers abdominal pain, dry mouth, skin problems, headaches, joint pain or swelling, eye problems, etc will be used (32). The full battery of items is expected to take fewer than 25 minutes to complete based on our past experience with these measures. The content of the PROs is provided in **Appendix 1**; specific wording changes may be made in response to feedback from the Patient Advisory Panel. In a longer baseline assessment (~30 minutes) sociodemographic characteristics will be collected as well as monthly out of pocket expenses for TKIs. In the 3-month assessment, additional questions about medications will be asked.

7. Statistical Analysis

7.1 Data Management and Analyses

All data will be stored securely at the Coordinating Center. Personal health information will be kept separately and only key personnel will have access to the identifiers linking clinical and personal data. All variable distributions will be reviewed before commencing analysis to identify problematic values. A 2-tailed significance level of $\alpha=0.05$ will be used for all assessments. Statistical analyses will be conducted using SAS 9.3 (SAS Institute, Inc).

7.2 Analysis for predicting recurrence in patients with CML who discontinue TKIs

In terms of **primary objective 1**, the clinical outcomes to be examined in this study include the primary event of CML molecular recurrence (opposite relapse-free survival [RFS]) and death in complete remission (DCR). For the univariate analysis the probabilities of RFS will be calculated using the Kaplan-Meier estimator. Probabilities of molecular recurrence and DCR will be generated using cumulative incidence estimates to account for competing risks. For **secondary objective 1**, Cox proportional hazards model(33) and Fine and Gray's subdistribution hazards model (34) and Fine and Gray's subdistribution hazards model [32] will be used to determine the effect of clinical characteristics on RFS and CML recurrence after TKI discontinuation, respectively. The baseline clinical risk factors that will be considered in regression analyses include sex, age, type of TKI, time to undetectable BCR-ABL by RQ-PCR, duration with undetectable BCR-ABL by RQ-PCR, Sokal Risk at diagnosis (see appendix 4), and BCR-ABL transcript levels measured by digital PCR. The following analysis plan will be implemented. First, for the continuous variables, including time to undetectable BCR-ABL by RQ-PCR, a martingale residual plot will be applied to evaluate the potential threshold cut point(s) for the effect on RFS and the maximum partial likelihood method will be used to identify optimal cut point(s). Second, univariate probability of RFS, molecular relapse, and DCR with 95% confidence interval (CI) will be computed by each clinical risk factor. Third, a Cox regression model building procedure will be used to identity

significant risk factors associated with molecular recurrence. The assumption of proportional hazards for each factor in the Cox model will be tested using time-dependent covariates. When the test indicates differential effects over time (non-proportional hazards), models will be constructed breaking the post-stopping TKI time course into two periods, using the maximized partial likelihood method to find the most appropriate breaking time point. Following this, the proportionality assumptions will be tested again. Factors that are significant at a 5% level will be kept in the final model. The potential interactions between all significant risk factors will be tested. Fourth, in pursuit of **secondary objective 2** and based on the final Cox model, a risk scoring system will be developed to predict the patient's risk of molecular recurrence after stopping TKI. A 3-4 level scoring system will be considered as appropriate for the data. For **secondary objective 3**, we will assess whether specific time points are more important for clinical prediction of recurrence within this schedule. At each pre-scheduled follow-up time, we will calculate the recurrence rate and treatment failure rate (recurrence or DCR) with its 95% CI. The log transfer approach (35) to calculate the CI to force the CI to be within proper range (0, 1) will be used and based on that make recommendations for the optimal follow-up schedule.

7.3 Analysis for patient-reported health status

The components of health status will be analyzed separately (that is, depression separate from fatigue separate from GI symptoms, etc), since combining them into a summary score can dilute the effects of the individual (and not necessarily related) components and thus mask true change. However, this "battery approach" to PRO assessment has the drawback of resulting in multiple, individual component scores and 1) raises the possibility of obtaining conflicting results of the different components and 2) creates a potential multiple comparisons problem for statistical testing. Pre-specifying the major expected relationships and corresponding statistical comparisons minimizes such potential problems.

There are two main objectives for the analysis of PRO measures in this study. The first is to describe what happens to patients' health status after stopping TKI therapy. The second is to describe what happens to the health status of patients who then resume therapy because of a CML recurrence (e.g., how quickly and strongly do side effects of TKI therapy recur). Both objectives will be pursued in the context of a piecewise longitudinal mixed-effects model for each of the PRO endpoints. In this model, each patient's trajectory over time is divided into one "piece" for the assessments up to the point of recurrence and a second "piece" for the assessments that follow recurrence. A similar piecewise model in the analysis of PRO endpoints for the HF-ACTION trial was used(36). This modeling approach offers several advantages: the likelihood-based estimation means that all available data from each patient are used; correlations within patients over time are addressed; any missing data can be considered ignorable conditional upon the observed data; and the piecewise feature allows us to efficiently estimate a single model that can answer multiple questions of interest (37). Model construction will include graphical and polynomial tests for nonlinear effects of time, as well as more general diagnostics for model assumptions.

In terms of the **primary objective 2**, we hypothesize that, following TKI discontinuation, fatigue, depression, sleep disturbance, and GI symptoms will improve by at least 3 points each by 6 months post-discontinuation (corresponding to the standardized effect size of 0.3 used in our sample size estimation, see Required Sample Size section). These hypotheses will be tested by examining the direction and significance of the coefficient for the effect of time in the first "piece" of each PRO domain's model. Trajectories of the remaining PROs will also be described, but there are no *a priori* hypotheses about how they will change. In terms of our **secondary objective 4**, we will examine each PRO domain's change after patients resume TKI therapy following CML recurrence by examining the coefficients corresponding to the intercept shift and temporal slope in the second "piece" of the model (following recurrence). Again, we hypothesize worsening in fatigue, depression sleep disturbance, and GI symptoms by at least 3 points each by 6 months post-reintroduction.

Table 3. Power to Detect differences (Δ) Between Groups (n=165)

Ratio/ group	Δ=20 %	Δ=25 %	Δ=30 %
1 : 1	75	90	97
1 : 1.5	73	89	97
1 : 2	70	87	96

Δ=Difference in CML recurrence after discontinuing TKI therapy

7.4 Managing Missing PRO Data

Missing PRO data will be avoided through regular monitoring, as described above (See Patient Retention and Prevention of Missing Data). Missing data at the item level will be handled using the following approach. If at least 50% of the items per domain were answered, then we will adjust the score to ([Raw sum x number of items in the domain] / number of items answered). If fewer than 50% of the items in a domain were answered, we will treat the domain as missing. We have chosen the longitudinal mixed effects model to allow the inclusion of all cases in our analyses, even those with missing values (38).

7.5 Required Sample Size

For predicting CML recurrence, sufficient power to detect differences by patient characteristics is needed. With 173 patients and assuming 5% loss to follow-up (analysis sample of 165) and a 2-tailed significance level of α=0.05, will have 90% power to detect a difference of 25% between groups of equal size (1:1 ratio) in relapse-free survival (RFS) at 18 months. Using nQuery Advisor, a power analysis with multiple scenarios to detect differences in RFS based on plausible differences between groups (based on the STIM trial), as outlined in was conducted **(Table 3)**. For developing the risk scoring system, a power analysis with multiple scenarios to identify 3 risk level groups, namely low, intermediate, and high risk for CML recurrence was conducted. We have 99%

power to develop a scoring system to stratify patients into low (20% risk for recurrence), intermediate (50% risk for recurrence), and high (80% risk for recurrence). **Table 4** shows the power associated with various effect sizes in CML recurrence rate for groups of equal size (ratio of 1:1:1) as well another plausible ratio (1:2:3).

Table 4. Power to Develop a Risk Scoring System (n=165)

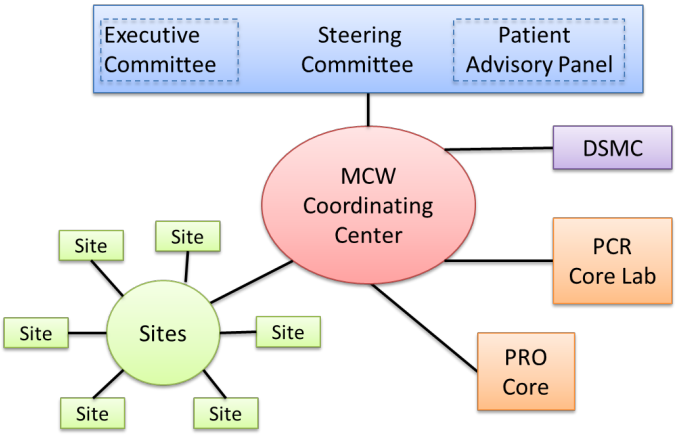
Ratio/ group	CML Recurrence Risk	Power
1 : 1 : 1	80% / 50% / 20%	99
1 : 2 : 3	80% / 50% / 20%	99
1 : 1 : 1	80% / 60% / 30%	99
1 : 2 : 3	80% / 60% / 30%	99
1 : 1 : 1	70% / 60% / 30%	84
1 : 2 : 3	70% / 60% / 30%	80
1 : 1 : 1	75% / 60% / 45%	82
1 : 2 : 3	75% / 60% / 45%	73

For the PRO analysis, we need sufficient power to detect the smallest policy-relevant change in health status, which we estimate as an effect size of 0.3, i.e., corresponding to about 1/3 of a standard deviation. (PROMIS measures are scored on a standardized 0-100-point scale, where 50 corresponds to the average in the general U.S. population with a standard deviation of 10.) We conducted a power analysis using a simulation of a piecewise linear mixed model in SAS 9.3. We chose a piecewise model to accommodate CML recurrence and reintroduction of TKI therapy (see Analysis Plan for Aim 2). Prior to simulation, the sample size was divided by an inflation factor to adjust for potential site clustering effects in PROs (39). We estimated a range of effect sizes that a fixed sample size could detect, and for each hypothetical effect size, through simulation, we generated many (>1200) random sample datasets based on the following assumptions: 13 PRO assessments over 3 years, a median time-to-recurrence of 6 months (40), expected improvement in PROs after TKI discontinuation and decline in PROs after CML recurrence/reintroduction of TKI therapy, known variance and covariance parameters (36), 4 fixed effects (intercept, time before recurrence, recurrence, and time after recurrence), and 2 random effects (random intercept and slope prior to recurrence) to allow baseline and monthly change to vary by patient (41). For each generated sample, we fit the piecewise mixed model to the data, and collected data on rejection of the null hypothesis of no time effect (that is, no difference in PROs over time with TKI discontinuation and reintroduction), and 10% missing data per year to account for dropout and missed assessments. To estimate the power associated with a given effect size, we computed the proportion

of the successful rejection rate. With >90% power, we need 173 patients to detect a change of 0.3. This sample size also provides >85% power to detect a smaller effect size of 0.25.

8. Study Organization and Administration

The LAST study will be conducted using the organizational structure outlined in Figure 1. MCW will serve as the coordinating center. Drs. Atallah and Flynn at the MCW Coordinating Center will serve as the principal investigators. The executive committee will be comprised of Dr. Horowitz, of MCW's CIBMTR, Dr. Schiffer from Wayne State, Dr. Weinfurt, PI of PROMIS at Duke, Dr. Radich, leader of the PCR Core Lab at Fred Hutchinson Cancer Research Center, and Dr. Zhang, lead biostatistician. The MCW Coordinating Center will interface with the MCW Cancer Center Data Safety Monitoring Committee (DSMC, see section 11.0), the PCR Core Lab, the PRO Core, and the 12 individual Sites (see Table 2). The site investigators will participate on the Steering Committee, which will review all aspects of the work at the onset to ensure that our activities are responsive to the emerging needs of CML physicians. The Steering Committee will meet quarterly via web-mediated conference calls for updates on study progress and annually in-person in conjunction with The American Society of Hematology meetings. A Patient Advisory Panel will participate in planning and regular calls to review study progress and provide feedback on acceptability to patients.



8.1 Multi-Site Management

The Multi-Site Research Program is responsible for oversight of regulatory documentation for each Participating Institutions. Documents should be provided to the Multi-Site Research Program either via the Oncore CTMS or LASTstudy@mcw.edu. See address and contact information:

Multi-Site Research Program (Clinical Trials Office)
Medical College of Wisconsin/Cancer Center

9200 W. Wisconsin Avenue
Milwaukee, WI 53226
E-mail: LASTstudy@mcw.edu

After the MCW IRB grants initial approval, the multi-site program staff provides regulatory documents to the Participating Institutions. The Participating Institution will receive a letter/packet explaining the required regulatory documents. Required regulatory documents will include: initial approval documents, consent forms, site initiation forms, amendments, etc.

Each Participating Institution must receive local IRB approval of both the current protocol and consent prior to activation of the study at their site. The Participating Institution may make minor changes to the consent form to reflect their institutional standards. No substantial changes, including changes to the risk language, are allowed. Consent forms and regulatory documents will be reviewed by the Multi-Site Research Program staff for content.

The local IRB approval notice and consent is forwarded to the Multi-Site Research Program staff. Once all of MCW administrative requirements are completed, the Multi-Site Research Program staff issues an Activation Notice for the Participating Institution and subjects can be enrolled in the study. This Activation includes the implementation of Oncore CTMS. Institutional activation documentation will be sent in a formal letter.

8.2 Site Activation

Study Coordinators at each Participating Institution will conduct the Study according to the local policies of the IRB Approved Protocol.

The Participating Institution will receive an activation notice and subjects can be enrolled in the study. Institutional activation documentation will be sent in a formal letter.

8.3 Ongoing Study Management:

• The Multi-Site Research Program will use the OnCore CTMS for collection, management and analysis of data from the Participating Institutions. Source documents must be uploaded without unique identifiers as specified by HIPAA policies. Study documents must include the subject ID number.
• De-identified source documents that support the following data points are required to be uploaded in the OnCore CTMS shortly after obtaining them:

- All eligibility criteria (including the two screening central lab PCR results)
- TKI stop date and TKI restart date
- Local lab results

- Additional source specifically requested by MCW staff, on a case-by-case basis, to support data entry, deviations, or SAEs

8.4 Ongoing Communication with Participating Institution Research Staff

The Participating Institution will receive Oncore CTMS training from the MCW Oncore CTMS Administrator. The Coordinating Site will conduct monthly conference calls to discuss any ongoing questions or concerns regarding the conduct of the study.

8.5 Trial Monitoring/Quality Assurance

8.5.1 Trial Monitoring

The Multi-Site Research Program will be responsible for ongoing oversight, monitoring, source documentation confirmation, protocol compliance, adverse events, etc. The MCW Principal Investigator will have access to the study data for all of the patients entered onto this study. Data storage is carried out according to MCW Institutional Policy.

The MCW Principal Investigator will oversee the conduct of the study.

8.5.2 Quality Assurance

- The study will be reviewed annually by MCW.
- 10% of subject files will be selected randomly for review (max 10 subjects at each monitoring timepoint).
- Consent/eligibility and objective based data will be reviewed for those files selected
- 1 file will be selected randomly for a comprehensive review at each monitoring timepoint.

After each review a letter/report will be provided to the study staff and the DSMC after each QA review. Necessary corrective action or training will be provided to the staff as needed throughout and following each QA review. Directed audits may be requested at any time by the CCCTO QA Staff, DSMC, Research Manager, study staff member, or administrative staff.

9. Regulatory

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

9.1 Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

9.2 Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

10. Adverse Events/Serious Adverse Events Reporting Guidelines

10.1 Adverse Events

10.1.1 Definition

An Adverse Event (AE) is defined as the presence of a new or the worsening of any pre-existing unfavorable and unintended symptoms or medical conditions that occur after consent has been obtained.

10.1.2 Reporting

Any AE that the treating physician determines is related to the stopping of the TKI will be reported on the AE electronic Case Report Forms (eCRF) in Oncore CTMS. During the screening phase of the protocol all AEs will be recorded on the Baseline AE eCRF but will not need to be followed past the stopping point of the TKI. Medical conditions that already existed at the time of informed consent will be recorded in the Baseline AE eCRF. AE monitoring should be continued until restarting TKI or study completion. SAEs should be followed until study completion.

AEs will be evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

10.2 Serious Adverse Events

10.2.1 Definition

A Serious Adverse Event (SAE) is any AE that:

- Results in death.
- Is life-threatening
- Hospitalization or prolongation of an existing hospitalization
- Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is a medically important event. An important medical event that jeopardizes the subject or requires medical or surgical intervention to prevent one of the outcomes listed above

10.2.2 Procedures for Reporting Serious Adverse Events

Serious adverse events experienced after signing consent should only be reported to the Medical College of Wisconsin if the investigator suspects a causal relationship to stopping the patient's TKI. All deaths, disease transformation to accelerated phase, and blast crisis should be reported immediately despite relationship.

A member of the study staff from each site should complete the SAE eCRF within 24 hours of learning of the event and email (LASTstudysae@mcw.edu) or fax (414-805-0596) the completed form signed by the site investigator to the Medical College of Wisconsin.
The initial SAE should be followed until resolution and updated in the SAE eCRF. Follow-up SAE information is sent to the same contacts listed above. Each site is responsible for reporting SAEs to their local Institutional Review Board per institutional guidelines.

11. Data and Safety Monitoring

The Medical College of Wisconsin Cancer Center Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and subject safety for all cancer center investigator initiated clinical trials. A 6 to 8-member Data and Safety Monitoring Committee will complete a review of protocol-specific data safety monitoring reports, to provide recommendations on trial continuation, suspension or termination. The DSMC will review these reports no less than bi-annually. A summary of the DSMC activities are as follows

- Review the clinical trials for data integrity and safety
- Review all adverse events requiring expedited reporting as defined per protocol
- Review all DSM reports
- Submit a summary of any recommendations related to study conduct
- Terminate the study if deemed unsafe for patients

11.1 Study Enrollment Hold Criteria

In the largest study with imatinib in CML patients, the annual rates of progression to accelerated phase (AP) or blast crisis (BC) was 1.5, 2.8, 1.6, 0.9, and 0.5% for years 1, 2, 3, 4, and 5 of therapy, respectively. A total of 173 patients are expected to be enrolled by end of first year of this study, and adverse events of progression to AP or BC will be evaluated at the end of each year. As the rate of disease progression to AP and/or BC is about 1.2% per each year, the study will be put on hold if ≥ 3, 6, 9, 12, and 15 patients develop disease transformation to AP and/or BC at end of year 1, 2, 3, 4, and 5, cumulatively. In the case of a safety event suspending the study, a prompt cumulative examination of all data and circumstances of these events will be conducted by the Medical College of Wisconsin DSMC to determine whether the study should be resumed, whether the protocol will be revised, or whether the study will be discontinued permanently.

Each participating site's IRB will be notified of any event that triggers postponement of enrollment in this study. If the study is suspended for safety reasons and it is deemed appropriate by the sponsor to resume the study, approval from the relevant IRBs will be obtained prior to resuming the study at each participating institution.

Decisions regarding ongoing study participation of patients on study will be made on a case by case basis after discussion with the participating site's Principal Investigator and Study Principal Investigator.

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13. Appendices

Appendix 1: PRO Measurement

Instruction	Part of the purpose of this clinical study is to understand your experiences in your everyday life. Next we are going to ask you questions about how you are feeling and functioning. We will ask you similar questions many times over the course of the 3-year study. **Please answer the questions as best you can, thinking about your daily life in the past 7 days, not just your experience having CML or taking a tyrosine kinase inhibitor (TKI).** If you have any comments about these questions, please provide them in the textbox provided at the end of this set of questions. If you would like a response from the researchers please email us at LASTstudyPRO@mcw.edu.		
Domain	**Recall Period**	**Item Stem**	**Response Options**
New Page			
Location		Are you answering this questionnaire in the lab or clinic, at home or work, or somewhere else?	1=In the lab or clinic 2=At home or work 3=Somewhere else, please specify [textbox]
PROMIS Global 1		In general, would you say your health is…	5=Excellent 4=Very good 3=Good 2=Fair 1=Poor
PROMIS Global 2		In general, would you say your quality of life is…	5=Excellent 4=Very good 3=Good 2=Fair 1=Poor
New Page			
PROMIS Fatigue example questions	In the past 7 days…	I feel fatigued	1, Not at all 2, A little bit 3, Somewhat 4, Quite a bit 5, Very much
	In the past 7 days…	I have trouble starting things because I am tired	1, Not at all 2, A little bit 3, Somewhat 4, Quite a bit 5, Very much
	In the past 7 days…	How run-down did you feel on average?	1, Not at all 2, A little bit 3, Somewhat 4, Quite a bit 5, Very much
	In the past 7 days…	How fatigued were you on average?	1, Not at all 2, A little bit 3, Somewhat 4, Quite a bit 5, Very much
New Page			

Fatigue Context		Thinking about your level of fatigue in the past 7 days, was anything out of the ordinary?	1=No, this was a usual week 2=Things were better than usual 3=Things were worse than usual
	[If above = 2]	Please describe how things were better than usual.	[textbox]
	[If above = 3]	Please describe how things were worse than usual.	[textbox]
New Page			
PROMIS Depression example questions	In the past 7 days...	I felt worthless	1, Never 2, Rarely 3, Sometimes 4, Often 5, Always
	In the past 7 days...	I felt helpless	1, Never 2, Rarely 3, Sometimes 4, Often 5, Always
	In the past 7 days...	I felt depressed	1, Never 2, Rarely 3, Sometimes 4, Often 5, Always
	In the past 7 days...	I felt hopeless	1, Never 2, Rarely 3, Sometimes 4, Often 5, Always
New Page			
Depression Context		Thinking about your level of depression in the past 7 days, was anything out of the ordinary?	1=No, this was a usual week 2=Things were better than usual 3=Things were worse than usual
	[If above = 2]	Please describe how things were better than usual.	[textbox]
	[If above = 3]	Please describe how things were worse than usual.	[textbox]
New Page			
PROMIS Anxiety example questions	In the past 7 days...	I felt fearful	1, Never 2, Rarely 3, Sometimes 4, Often 5, Always
	In the past 7 days...	I found it hard to focus on anything other than my anxiety	1, Never 2, Rarely 3, Sometimes 4, Often 5, Always

	In the past 7 days...	My worries overwhelmed me	1, Never 2, Rarely 3, Sometimes 4, Often 5, Always
	In the past 7 days...	I felt uneasy	1, Never2, Rarely3, Sometimes4, Often5, Always
New Page			
Anxiety Context		Thinking about your level of anxiety in the past 7 days, was anything out of the ordinary?	1=No, this was a usual week 2=Things were better than usual 3=Things were worse than usual
	[If above = 2]	Please describe how things were better than usual.	[textbox]
	[If above = 3]	Please describe how things were worse than usual.	[textbox]
New Page			
PROMIS Sleep Disturbance example questions	In the past 7 days...	My sleep quality was	1, Very poor 2, Poor 3, Fair 4, Good 5, Very good
	In the past 7 days...	My sleep was refreshing	1, Not at all 2, A little bit 3, Somewhat 4, Quite a bit 5, Very much
	In the past 7 days...	I had a problem with my sleep	1, Not at all 2, A little bit 3, Somewhat 4, Quite a bit 5, Very much
	In the past 7 days...	I had difficulty falling asleep	1, Not at all 2, A little bit 3, Somewhat 4, Quite a bit 5, Very much
New Page			
Sleep Disturbance Context		Thinking about your sleep in the past 7 days, was anything out of the ordinary?	1=No, this was a usual week 2=Things were better than usual 3=Things were worse than usual
	[If above = 2]	Please describe how things were better than usual.	[textbox]
	[If above = 3]	Please describe how things were worse than usual.	[textbox]
New Page			

PROMIS Ability to Participate in Social Roles and Activities example questions	In the past 7 days...	I have trouble doing all of my regular leisure activities with others	1, Never 2, Rarely 3, Sometimes 4, Usually 5, Always
	In the past 7 days...	I have trouble doing all of the family activities that I want to do	1, Never2, Rarely3, Sometimes4, Usually5, Always
	In the past 7 days...	I have trouble doing all of my usual work (include work at home)	1, Never 2, Rarely 3, Sometimes 4, Usually 5, Always
	In the past 7 days...	I have trouble doing all of the activities with friends that I want to do	1, Never 2, Rarely 3, Sometimes 4, Usually 5, Always
New Page			
Ability to Participate in Social Roles and Activities Context		Thinking about your work, family, and social activities in the past 7 days, was anything out of the ordinary?	1=No, this was a usual week 2=Things were better than usual 3=Things were worse than usual
	[If above = 2]	Please describe how things were better than usual.	[textbox]
	[If above = 3]	Please describe how things were worse than usual.	[textbox]
New Page			
PROMIS Social Isolation example questions		I feel left out	1, Never 2, Rarely 3, Sometimes 4, Usually 5, Always
		I feel that people barely know me	1, Never 2, Rarely 3, Sometimes 4, Usually 5, Always
		I feel isolated from others	1, Never 2, Rarely 3, Sometimes 4, Usually 5, Always
		I feel that people are around me but not with me	1, Never 2, Rarely 3, Sometimes 4, Usually 5, Always
New Page			

Social Isolation Context		Thinking about your level of lonliness, was anything out of the ordinary?	1=No, this was a usual week 2=Things were better than usual 3=Things were worse than usual
	[If above = 2]	Please describe how things were better than usual.	[textbox]
	[If above = 3]	Please describe how things were worse than usual.	[textbox]
New Page			
PROMIS Physical Function example questions		Are you able to do chores such as vacuuming or yard work?	1, Without any difficulty 2, With a little difficulty 3, With some difficulty 4, With much difficulty 5, Unable to do
		Are you able to go up and down stairs at a normal pace?	1, Without any difficulty 2, With a little difficulty 3, With some difficulty 4, With much difficulty 5, Unable to do
		Are you able to go for a walk of at least 15 minutes?	1, Without any difficulty 2, With a little difficulty 3, With some difficulty 4, With much difficulty 5, Unable to do
		Are you able to run errands and shop?	1, Without any difficulty 2, With a little difficulty 3, With some difficulty 4, With much difficulty 5, Unable to do
New Page			
Physical Function Context		Thinking about your physical abilities, is anything out of the ordinary?	1=No, this is usual 2=Things are better than usual 3=Things are worse than usual
	[If above = 2]	Please describe how things are better than usual.	[textbox]
	[If above = 3]	Please describe how things are worse than usual.	[textbox]
New Page			
PROMIS Sleep Related Impairment example questions	In the past 7 days…	I had a hard time getting things done because I was sleepy	1, Not at all 2, A little bit 3, Somewhat 4, Quite a bit 5, Very much
	In the past 7 days...	When I woke up I felt ready to start the day	1, Not at all 2, A little bit 3, Somewhat 4, Quite a bit 5, Very much

	In the past 7 days...	I felt irritable because of poor sleep	1, Not at all 2, A little bit 3, Somewhat 4, Quite a bit 5, Very much
	In the past 7 days...	I had trouble staying awake during the day	1, Not at all 2, A little bit 3, Somewhat 4, Quite a bit 5, Very much
New Page			
PROMIS Pain Interference example questions	In the past 7 days...	How much did pain interfere with your day to day activities?	1, Not at all 2, A little bit 3, Somewhat 4, Quite a bit 5, Very much
	In the past 7 days...	How much did pain interfere with work around the house?	1, Not at all 2, A little bit 3, Somewhat 4, Quite a bit 5, Very much
	In the past 7 days...	How much did pain interfere with your ability to participate in social activities?	1, Not at all 2, A little bit 3, Somewhat 4, Quite a bit 5, Very much
	In the past 7 days...	How much did pain interfere with your household chores?	1, Not at all 2, A little bit 3, Somewhat 4, Quite a bit 5, Very much
New Page			
PROMIS Pain Intensity	In the past 7 days...	How would you rate your pain on average?	0, No pain 0 1, 1 2, 2 3, 3 4, 4 5, 5 6, 6 7, 7 8, 8 9, 9 10, Worst imaginable pain 10
New Page			
Pain Context		Thinking about your level of pain in the past 7 days, was anything out of the ordinary?	1=No, this was a usual week 2=Things were better than usual 3=Things were worse than usual
	[If above = 2]	Please describe how things were better than usual.	[textbox]
	[If above = 3]	Please describe how things were worse than usual.	[textbox]

New Page			
PROMIS Applied Cognition General Concerns example questions	In the past 7 days…	My thinking has been slow	1, Never 2, Rarely (Once) 3, Sometimes (Two or three times) 4, Often (About once a day) 5, Very often (Several times a day)
	In the past 7 days...	It has seemed like my brain was not working as well as usual	1, Never 2, Rarely (Once) 3, Sometimes (Two or three times) 4, Often (About once a day) 5, Very often (Several times a day)
	In the past 7 days...	I have had to work harder than usual to keep track of what I was doing	1, Never2, Rarely (Once)3, Sometimes (Two or three times)4, Often (About once a day)5, Very often (Several times a day)
	In the past 7 days...	I have had trouble shifting back and forth between different activities that require thinking	1, Never 2, Rarely (Once) 3, Sometimes (Two or three times) 4, Often (About once a day) 5, Very often (Several times a day)
New Page			
Applied Cognition General Concerns Context		Considering your thinking in the past 7 days, was anything out of the ordinary?	1=No, this was a usual week 2=Things were better than usual 3=Things were worse than usual
	[If above = 2]	Please describe how things were better than usual.	[textbox]
	[If above = 3]	Please describe how things were worse than usual.	[textbox]
New Page			
EORTC CML Symptom Burden Scale	During the past week	Have you had abdominal pains or cramps?	1, Not at all 2, A little bit 3, Quite a bit 4, Very much
	During the past week	Have you had a dry mouth?	1, Not at all 2, A little bit 3, Quite a bit 4, Very much
	During the past week	Have you had skin problems (e.g. color changes, itchy, dry or flaking skin)?	1, Not at all 2, A little bit 3, Quite a bit 4, Very much
	During the past week	Have you had headaches?	1, Not at all 2, A little bit 3, Quite a bit 4, Very much
	During the past week	Have you had aches or pains in your muscles or joints?	1, Not at all 2, A little bit 3, Quite a bit 4, Very much

	During the past week	Have you had hair loss?	1, Not at all 2, A little bit 3, Quite a bit 4, Very much
	During the past week	Have you sweated excessively?	1, Not at all 2, A little bit 3, Quite a bit 4, Very much
	During the past week	Have you had acid indigestion or heartburn?	1, Not at all 2, A little bit 3, Quite a bit 4, Very much
	During the past week	Have you felt drowsy?	1, Not at all2, A little bit3, Quite a bit4, Very much
	During the past week	Have you experienced any swelling in certain parts of your body (e.g. ankles, legs or around your eyes)?	1, Not at all 2, A little bit 3, Quite a bit 4, Very much
	During the past week	Have you had to urinate frequently?	1, Not at all 2, A little bit 3, Quite a bit 4, Very much
	During the past week	Have you had problems with your eyes (e.g. burning, watery, irritated or dry)?	1, Not at all 2, A little bit 3, Quite a bit 4, Very much
	During the past week	Have you had muscle cramps?	1, Not at all 2, A little bit 3, Quite a bit 4, Very much
PROMIS GI Symptoms - Diarrhea	In the past 7 days…	How many days did you have loose or watery stools?	0, No days 1, 1 day 2, 2 days 3, 3-5 days 4, 6-7 days
	In the past 7 days...	How often did you feel like you needed to empty your bowels right away or else you would have an accident?	0, Never 1, One time during the past 7 days 2, 2-6 times during the past 7 days 3, Once a day 4, More than once a day
PROMIS GI Symptoms - Nausea	In the past 7 days…	How often did you have nausea–that is a feeling like you could vomit?	1, Never 2, Rarely 3, Sometimes 4, Often 5, Always
Symptoms Context		Thinking about <u>any of the above symptoms in the past 7 days</u>, was anything out of the ordinary?	1=No, this was a usual week 2=Things were <u>better</u> than usual 3=Things were <u>worse</u> than usual

	[If above = 2]	Please describe how things were better than usual.	[textbox]
	[If above = 3]	Please describe how things were worse than usual.	[textbox]
New Page			
PROMIS Alcohol Use	In the past 30 days…	Did you drink any type of alcoholic beverage?	1=Yes 2=No
	In the past 30 days…	In a typical week, I drank…	1=1-7 drinks 2=8-14 drinks 3=15-21 drinks 4=22-28 drinks 5=More than 28 drinks
PROMIS Interest in Sexual Activity	In the past 30 days…	How interested have you been in sexual activity?	1, Not at all2, A little bit3, Somewhat4, Quite a bit5, Very
PROMIS Satisfaction with Sex Life	In the past 30 days…	How satisfied have you been with your sex life?	1, Not at all 2, A little bit 3, Somewhat 4, Quite a bit 5, Very
PROMIS Sexual Activity Screener	In the past 30 days…	Did you have any type of sexual activity? (Examples of sexual activity are masturbation, oral sex, and sexual intercourse.)	1=No 2=Yes
PROMIS Sexual Function Clinical Screener	In the past 12 months	Has there ever been a period of 3 months or more when you had any of the following problems or concerns? Please check all that apply.	1=You wanted to feel more interest in sexual activity 2=You had difficulty with erections (penis getting hard or staying hard) – MEN ONLY 2=Your vagina felt too dry – WOMEN ONLY 4=You had pain during or after sexual activity 8=You had difficulty having an orgasm 16=You felt anxious about sexual activity 32=You did not enjoy sexual activity 64=Some other sexual problem or concern _____ 128=No sexual problems or concerns

		Thinking about all of the questions that you just answered about how you feel and function, please provide any comments or questions below.	[text box]
New Page			
Instruction	**The next questions are about your background. We will not ask these questions at every visit.**		
New Page			
Demographic questions		What is the zip code where you live?	[number field]
		Not including yourself, how many people currently live in your household? Please count people of all ages including babies or small children.	Drop down box [Range 0-15]
		Please indicate the age of the [next] person you live with.	0-5 years 6-15 years 16-25 years 25-35 years 36-45 years 46-55 years 56-65 years 66-75 years over 75 years
		What is your marital status?	1=Married or in a domestic partnership or civil union 2=Widowed 3=Divorced 4=Separated 5=Never married 6=Other [text box]
		Are you of Spanish, Hispanic, or Latino descent?	1=No 2=Yes
		Please check one or more categories below to indicate what race(s) you consider yourself to be.	1=White 2=Black or African American 3=Asian 4=American Indian or Alaska Native 5=Native Hawaiian or other Pacific Islander 6=Some other race – Type in race. [text box]

Socioeconomic Status		The next question is about the total income of your household for the past 12 months. Please include your income PLUS the income of all members living in your household. Please count income BEFORE TAXES, including income from all sources (such as wages, salaries, tips, net income from a business, interest, dividends, child support, alimony, and Social Security, public assistance, pensions, or retirement benefits).What was your total HOUSEHOLD income in the past 12 months?	1 = Less than $20,0002 = $20,000 to $39,9993 = $40,000 to $59,9994 = $60,000 to $79,9995 = $80,000 to $99,9996 = $100,000 to $199,9997 = $200,000 or more
		What is the highest degree or level of school you have completed?	1=No schooling completed 2=Nursery school to 5th grade 3=6th to 8th grade 4=9th to 12th grade (NO DIPLOMA) 5=High school graduate or the equivalent (GED) 10=Some college, no degree 11=Associate's degree 12=Bachelor's degree 13=Master's degree 14=Professional or Doctorate degree
		Which statement best describes your current employment status?	1=Working – as a paid employee 2=Working – self-employed 3=Not working – on temporary layoff from a job 4=Not working – looking for work 5=Not working – retired 6=Not working – on disability 7=Not working – other [text box]
	[If working]	On average, how many hours do you work per week?	1=35 hours or more 2=20-34 hours 3=10-19 hours 4=Less than 10 hours

	[If working]	In the past 30 days, about how many days did you miss work because of illness or injury?Do not include work missed for maternity leave.	[number drop down 0-30]
		In the past 30 days, how difficult was it for you to meet the monthly payments on your bills?	5=Extremely difficult 4=Very difficult 3=Somewhat difficult 2=Slightly difficult 1=Not at all difficult
Health Insurance		Do you currently have any health insurance? Include private plans as well as government programs like Medicare or Medicaid.	1=No 2=Yes 3=I don't know
	[IF above = 2]	What is your main source of health insurance? (Note: Medicare is a health insurance program for persons 65 years or over and for some disabled persons.)	1=Medicare 2=Medicaid 3=A plan provided by an employer or union 4=A plan purchased directly from an insurance company, through an insurance exchange, or through a group such as AARP 5=TRI-CARE, CHAMPUS or CHAMP-VA 6=I get care from the Department of Veterans Affairs (VA) 7=Other
	[If above = 7]	Please describe the other coverage you have.	[text box]
	[IF insurance = Medicare]	Which type(s) of Medicare coverage do you have? Check all that apply. Part A of Medicare covers most hospital expenses. Part B of Medicare covers many doctors' expenses including doctor visits, and the premium is usually deducted from your Social Security. Part D of Medicare covers prescription drugs, usually through a private insurance provider.	1=Part A - Hospital 2=Part B - Medical 3=Part D - Prescription drug 4=I don't know

	[IF above does not equal 3]	Do you have a prescription drug plan from some other source?	1=No2=Yes3=I don't know
	[IF any insurance]	Does this plan cover or provide help with paying for regular prescription drugs?	1=No 2=Yes 3=I don't know
	[If above = 1]	Do you have a prescription drug plan from some other source?	1=No 2=Yes 3=I don't know
	[IF no insurance]	What is the main reason you don't have health insurance?	1=Person in family with health insurance lost job or changed employers 2=Employer doesn't offer health insurance 3=Cost is too high 4=Other
	[IF no insurance]	Please describe the main reason you do not have health insurance.	[text box]
		To treat CML, you have been prescribed a tyrosine kinase inhibitor (TKI) such as imatinib, dasatinib, nilotinib, or bosutinib. On average, about how much do you pay out of pocket for a 30-day supply of your TKI? Do not include money spent on premiums for health insurance. Your best guess is fine.	1=Less than $25 2=$25-$99 3=$100-$299 4=$300-$999 5=$1000 or more 4=I don't know
		Do you regularly take any prescription medications other than your TKI?	1=No 2=Yes 3=I don't know
	[IF above = 2]	Not including your TKI, how many prescription medications do you regularly take each month?	[number drop down]

	[IF above = 2]	On average, about how much do you pay out of pocket for a 30-day supply of your other presciption medications (not including your TKI)?Do not include money spent on premiums for health insurance.Your best guess is fine.	1=Less than $252=$25-$993=$100-$2994=$300-$9995=$1000 or more4=I don't know
	[If don't know above]	Does is amount to less than $200 per month, more than $400 per month, or what?	1=Less than $200 per month 2=$201-$399 per month 3=More than $400 per month 4=I really don't know
		Please provide any comments about health insurance or costs that you would like to share with the researchers.	[text box]
Satisfaction with Health Care		Overall, how satisfied or dissatified are you with the **quality** of your health care?	1=Very satisfied 2=Somewhat satisfied 3=Neutral 4=Somewhat dissatisfied 5=Very dissatisfied
		Overall, how satisfied or dissatified are you with the **cost** of your health care?	1=Very satisfied 2=Somewhat satisfied 3=Neutral 4=Somewhat dissatisfied 5=Very dissatisfied
		Overall, how satisfied or dissatified are you with the **convenience** of your health care?	1=Very satisfied 2=Somewhat satisfied 3=Neutral 4=Somewhat dissatisfied 5=Very dissatisfied
Trust in Provider		Overall, how much trust, if any, do you have in your usual doctor?	1=Complete trust 2=Quite a bit of trust 3=Some trust 4=A little bit of trust 5=No trust
		What factors were most important to you when you decided to join this clinical study?	[text box]

New Page

	When people take a tyrosine kinase inhibitor (TKI) such as imatinib, dasatinib, nilotinib, or bosutinib, they often have side effects from the TKI that need to be treated with additional prescription medications, over-the-counter medications, or supplements. Before you joined the LAST study 3 months ago and stopped taking your TKI, were you taking any medications for symptoms related to side effects from the TKI? Include prescription medications, over-the-counter medications, or supplements.	1=Yes 0=No
	Since you joined the LAST study 3 months ago and stopped taking your TKI, are you still taking any prescription medications for symptoms related to side effects from the TKI or have you stopped taking any prescription medications? Please check all that apply.	
	I am still taking prescription medication for the following symptoms...	1=Nausea 2=Diarrhea 3=Water retention 4=Sleep problems 5=Depression 6=Fatigue 7=Skin problems 8=Muscle cramps 9=Low potassium or magnesium 7=Other [text box]
	I stopped taking prescription medication for the following symptoms...	1=Nausea 2=Diarrhea 3=Water retention 4=Sleep problems 5=Depression 6=Fatigue 7=Skin problems 8=Muscle cramps 9=Low potassium or magnesium 7=Other [text box]

		Since you joined the LAST study 3 months ago and stopped taking your TKI, are you still taking any over-the-counter medications or supplements for symptoms related to side effects from the TKI or have you stopped taking any over-the-counter medications or supplements? Please check all that apply.	
		I am still taking over-the-counter medications or supplements for the following symptoms...	1=Nausea 2=Diarrhea 3=Water retention 4=Sleep problems 5=Depression 6=Fatigue 7=Skin problems 8=Muscle cramps 9=Low potassium or magnesium 7=Other [text box]
		I stopped taking over-the-counter medications or supplements for the following symptoms...	1=Nausea 2=Diarrhea 3=Water retention 4=Sleep problems 5=Depression 6=Fatigue 7=Skin problems 8=Muscle cramps 9=Low potassium or magnesium 7=Other [text box]
		Since you joined the LAST study 3 months ago and stopped taking your TKI, have you started taking any new prescription medications?	1=Yes 0=No
		Which new prescription medications are you taking?	[Text box]
		Since you joined the LAST study 3 months ago and stopped taking your TKI, have you started taking any new over-the-counter medications or supplements?	1=Yes 0=No

		Which new over-the-counter medications or supplements are you taking?	[Text box]
		In your own words, please describe your experience having to restart a tyrosine kinase inhibitor (TKI)	[Text box]

Appendix 2: Specimen Collection & Handling

Specimen Collection
Peripheral PCR blood sample:
A minimum of 20 ml of whole blood in an EDTA vacutainer (lavender top). Due to PCR inhibition, the lab does not accept heparin as a preservative.

Specimen Labeling
All submitted specimens must be labeled with the patient's initials, patient study ID#, patient's date of birth and date/time of specimen collection.

Shipping Requirements
All specimens must be accompanied by a Specimen Shipping Requisition Form.
Samples must be received by Molecular Oncology within 48 hours of draw. The Molecular Oncology lab is open M-F, 8:00am – 4:30 pm. Please do not draw samples on Fridays for delivery on Saturday.
The sample must be placed in a leak proof primary receptacle (ex: vacutainer).
Multiple primary receptacles must be individually wrapped or separated to prevent contact.
The primary receptacle must be placed into a leak proof secondary container (ex: resealable biohazard bag) in such a way that under normal conditions of transport, they cannot break or leak.
Absorbent material, such as paper towels or absorbent pads, must be placed in the secondary container with sufficient capacity to absorb the entire contents of the primary receptacle(s).
The secondary container must be placed into an outer shipping container with suitable cushioning material (bags or envelopes are not allowed). The shipping container must be labeled with the universal biohazard symbol.
The outer packaging must be marked with the name, address, and phone number of both the sender and recipient.
All packages shipped via aircraft must display a 2-inch diamond with "UN3373" inside of the diamond.

Send the container via next day delivery at ambient temperature to:

Molecular Oncology
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue North, Rm. D2-281
Seattle, WA 98109

Please call/email the Molecular Oncology lab as soon as the tracking number is available: (206) 667-2592, molab@fhcrc.org. The Molecular Oncology lab is open M-F, 8:00am – 4:30 pm. Please do not draw samples on Fridays for delivery on Saturday.

Specimen Shipping Requisition Form

Has The Patient Consented to Research Samples? ☐ YES ☐ NO

Patient Information

Patient Initials: _____ Birth Date: _____ Sex: M ___ F___

Study ID #: _____

Check Appropriate Box Below:
□ Screening #: _____
□ Month #: _____
□ Restarted TKI

Sample Information

Date of Sample Collection: _____ Time of Sample Collection: _____

Eligibility for Screening PCRs only:

- ☐ Documented BCR-ABL < 0.1% (> MR^4 i.e. >4 log reduction) or undetectable BCR-ABL by PCR for at least 2 years according to the patient's local lab
- ☐ Documented BCR-ABL < 0.1% (> MR^4 i.e. >4 log reduction) or undetectable BCR-ABL PCR at least 3 times prior to screening according to the patient's local lab
- ☐ Currently taking a TKI (imatinib, dasatinib, nilotinib, or bosutinib)
- ☐ Has not had prior hematopoietic stem cell transplantation
- ☐ Patient has been on a TKI therapy for at least 3 years

Physician Information

Physician's Full Name: _____ NPI # _____

Physician's Phone #: _____ Fax# _____

Physician's Institution: _____

Physician's Address: _____

_____

Person Filling out Requisition: _____ Phone Number_____

Appendix 3: ECOG Status

ECOG PERFORMANCE STATUS	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix 4: Sokal risk score (42)

The score, which is a hazard ratio function, is calculated using the following formula:
EXP 0.0116 x (age* – 43.4)) + 0.0345 (spleen size** – 7.51) + (0.188 x ((platelets^/ 700)^2 – 0.563)) + (0.0887 x (blasts$^{\#}$ – 2.10)).

Low-risk: Sokal score < 0.8
Intermediate-risk: Sokal score 0.8 - 1.2
High-risk: Sokal score > 1.2

*Age in years, **spleen size in cm below costal margin, ^10^9/L, $^{\#}$blast percentage

Appendix 5: Local Lab Draw and PRO Permission Request Form

This option is not for all patients and careful consideration should be used to ensure proper oversight. This form is to be completed and signed off on by the site PI and coordinating site PI for any site that is requesting permission for one of their patients to have blood draws at a location that is **not** the patient's study site (study site includes: any affiliate sites identified under the sites IRB approval). This form must be approved and signed by both the site PI and the coordinating site PI prior to applicable patient visits.

Patient Initials: _____ Birth Date: _____ Study ID #:_____

Month # being Requested (Cannot be requested for visits that require MD visits):

_____

Reason for request (i.e. distance the patient would need to travel):

_____

Eligibility:

- ☐ Study site has corresponded with local lab prior to sending patient to ensure that local lab understands requirements.
  Local Lab Name: _____
- ☐ Blood draw billing information has been discussed with the local lab
- ☐ Patient kits have been prepared which include the shipping materials and Shipping Label with Appropriate billing information
- ☐ Patient has been instructed on how to complete their electronic PROs and has necessary internet access. They have also confirmed they understand the importance of completing PROs as close to the date of the PCR blood draw as possible.
- ☐ PI feels patient has an adequate understanding of the requirements to ensure compliance with the scheduled visits

Site Information

Person Filling out Request: _____ Phone Number_____

Study Site PI Full Name: _____

PI Phone #: _____ Fax# _____

PI's Institution: _____

By signing below site is agreeing that the above eligibility requirements have been addressed and understands that if issues arise approval may be revoked to complete further visits at local lab.

Study Site PI Signature and Date: _____

Final Coordinating Site Decision:
Coordinating Site PI Signature and Date: _____

Appendix 6: GeneXpert Validation tests

Use of BCR-ABL Assays, including GeneXpert BCR-ABL V1 and V2 Assays, in the LAST Trial:

- The use of real time quantitative PCR (RQ-PCR, Q-PCR or RT-Q-PCR) assays for monitoring residual disease, as measured by BCR-ABL1 mRNA quantitation as % Ratio (BCR-ABL1/ABL1), is an important aspect of evaluating response to drug therapies in patients with Chronic Myelogenous Leukemia (CML).

- Although a few specialized academic research laboratories have been able to standardize "standard" homebrew BCR-ABL Q-PCR assays within their own labs using the International Scale (*IS*) developed by the World Health Organization (WHO), there is still a need to standardize the methodology and reporting of BCR-ABL1 by laboratories in the US and around the world, including in resource poor settings in developing countries, in order to improve the care and evaluation of therapeutic treatment options of patients with CML.

- Cepheid, a molecular diagnostics company based in Sunnyvale, CA, has developed the GeneXpert Dx system and cartridge based assays which standardize and simplify highly accurate and reproducible Q-PCR assays for the end user by integrating sample preparation, nucleic acid isolation, detection and quantification of RNA and DNA targets in a variety of infectious diseases and oncology/hematology indications, including BCR-ABL1 testing for CML.

- Cepheid currently has two versions of GeneXpert BCR-ABL Monitoring assays, Version 1 (V1) and Version 2 (V2). These cartridge-based, yet "standard" Q-PCR assays will be evaluated alongside "standard" homebrew Q-PCR and investigational digital PCR assays performed in Dr. Jerry Radich's core laboratory facility in the context of the LAST clinical trial.

It is anticipated that the GeneXpert BCR-ABL Version 2 assay will perform comparably to the other standard homebrew BCR-ABL Q-PCR assay(s) being performed on blood samples from the LAST trial, serving as evidence of analytical validity in comparison to the gold standard Q-PCR assay run in Dr. Radich's Core Lab. These data, as well as the correlation of % Ratio (BCR-ABL1/ABL1) by GeneXpert BCR-ABL V2 and the gold standard Q-PCR assays with clinical endpoints in the study, such as Time to CML molecular recurrence [defined as loss of MMR (> 0.1% BCR-ABL, *IS*) as assessed by standard Q-PCR], Relapse free survival (RFS), and Death in complete remission (DCR), may provide key evidence to support the claim of the GeneXpert BCR-ABL V2 Assay's clinical validity and utility in monitoring CML disease burden and patient response to changes in drug therapy (in this case, discontinuation of therapy), and as such, de-identified study data may be shared with Cepheid and subsequently submitted by the company to the FDA to support pre-market review of the GeneXpert BCR-ABL V2 Assay, allowing widespread use of the assay in laboratories throughout the U.S. Indeed, the FDA has invited Cepheid to submit data for pre-market review that includes a clinical cohort with well-characterized clinical outcomes.

Brief Technical Background and Regulatory Status of GeneXpert BCR-ABL V1 and V2 Assays:

- GeneXpert BCR-ABL Assays utilize standard, but simplified and automated, RT-Q-PCR which is performed in the GeneXpert assay cartridge following several off-board sample preparation steps.

- The GeneXpert® BCR-ABL Monitor Assay(s), Version 1 (V1) or Version 2 (V2), can be performed in de-centralized labs on the Cepheid GeneXpert® Dx System (instrument).

- Both the V1 and V2 assays are currently considered (in the U.S.) Research Use Only (RUO) *in vitro* diagnostic tests for the simultaneous detection and quantitation of the *BCR-ABL1* chromosomal translocation mRNA transcripts (type b2a2 or b3a2) and the *ABL1* endogenous control mRNA transcript in peripheral blood specimens from patients diagnosed with chronic myelogenous leukemia (CML).

- Reporting on International Scale:

  The GeneXpert BCR-ABL Assays (V1 and V2) report BCR-ABL1 mRNA quantitation as % Ratio (BCR-ABL1/ABL1) on the International Scale (*IS*) per WHO Standards.

- GeneXpert Assay Regulatory Status, Sensitivity, and Sample requirements

  1. **The GeneXpert BCR-ABL Monitor V1 Assay**

     - Is not FDA cleared but is available in the United States as a RUO *in vitro* diagnostic assay. This Assay is, however, available for routine clinical use outside the US in those countries that accept diagnostics with CE registration.

     - Blood sample volume and sensitivity: This version (V1) of the assay requires a 0.2 ml whole blood sample collected in EDTA or PAXgene, and can accurately and reproducibly detect and quantify BCR-ABL1/ABL1 % ratios to a 3 log reduction, or 0.1% (*IS*), which defines Major Molecular Response (MMR), per WHO guidelines.

     - Due to the improved sensitivity of the BCR ABL V2 assay (please refer to V2 details below), Cepheid is not seeking FDA pre-market review for the V1 version of the assay.

  2. **The GeneXpert BCR-ABL V2 Assay**

     - Is a RUO *in vitro* diagnostic assay that is not FDA cleared, but Cepheid intends to submit the necessary documentation to FDA to support a pre-market review and, ultimately it is hoped, regulatory clearance as an FDA-cleared assay.

     - Blood sample volume and sensitivity: This version (V2) of the assay requires a 4 ml whole blood sample collected in EDTA or PAXgene, and can accurately and reproducibly detect and quantify BCR-ABL1/ABL1 % ratios to a 4.5-log reduction, or 0.003% (*IS*), which defines Complete Molecular Response (CMR), per WHO guidelines.

GeneXpert Instrument and Cartridges for the LAST study

- Cepheid will supply the Radich Core Laboratory with a GeneXpert 16 module instrument system, as well as all BCR-ABL Assay cartridges to support GeneXpert Q-PCR testing of patient samples at the same time points for which the standard homebrew Q-PCR assay will be tested.
- All instrumentation and cartridges to support the testing of samples in the study will be provided at no cost to the Radich lab or LAST study investigators/NCI.
- Patient de-identified study data and laboratory test results, ("List of Data Elements" as outlined below), may be required to be shared directly with Cepheid for analysis to support FDA submission.

The LAST study: List of Data Elements required for potential Cepheid BCR-ABL Monitor Assay submission to FDA

Note: All peripheral blood samples tested by RQ-PCR and digital PCR assays will have an aliquot also tested in the GeneXpert BCR-ABL Monitor assay performed in the Core Molecular Oncology (Dr. Radich) Lab. All GeneXpert BCR-ABL data, as well as the following data variables, may be required for Cepheid's US-IVD submission to FDA:

1. Patient de-identified baseline data/demographic factors
    a. Study ID #
    b. Age/birthdate
    c. Sex
    d. Race
    e. Date of diagnosis
    f. Sokal risk score and its components (spleen size, platelet count, the percentage of blasts in the peripheral blood), basophil %
    g. ECOG performance status
2. Treatment
    a. History of prescribed TKIs including any dose reductions or held dosing
    b. Current TKI at study screening
    c. Duration of treatment on current TKI at study screening and date
    d. Time to MR 3.0
    e. Time to undetectable BCR-ABL by PCR,
    f. Duration undetectable BCR-ABL by PCR
    g. Side effects requiring medical intervention or referral.
    h. For patients in whom MMR is lost after discontinuing TKI, and who must restart TKI: the type of TKI and date of restarting TKI.
3. Samples - for each blood sample tested:
    a. Study ID#
    b. Date of Sample Collection
    c. Time of Sample Collection
4. BCR-ABL levels at screening:
    a. For patients with *undetectable* BCR-ABL at screening (this category covers all patients who are eligible for study enrollment):
        i. Time to undetectable BCR-ABL by PCR
        ii. Duration of undetectable BCR-ABL by PCR
        iii. BCR-ABL transcript levels measured by digital PCR
    b. For patients with *detectable* BCR-ABL at screening (Screening failures – these patients are not eligible for study enrollment):
        i. BCR-ABL transcript levels at screening by PCR
        ii. BCR-ABL transcript levels at screening by digital PCR
5. BCR-ABL levels for patients on study:
    a. Results of all RQ-PCR and digital PCR testing performed as part of study procedures, including
        i. Both screening visit(s) at least 21 days apart to confirm patient is in MR^4;
        ii. On study: BCR-ABL levels monthly for 6 months, every other month until 24 months, and then quarterly until 36 months
        iii. All BCR-ABL RQ-PCR assessments for patients who lose MMR
        iv. After completion of monitoring phase: as available, BCR-ABL levels every 6 months according to physician's standard of care
6. Outcomes for each patient after TKI discontinuation:
    a. Time to CML molecular recurrence [defined as loss of MMR (> 0.1% BCR-ABL, *IS*)]
    b. Relapse free survival (RFS)
    c. Death in complete remission (DCR)