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SWOG

A RANDOMIZED PHASE II STUDY OF RUXOLITINIB (NSC-752295) IN COMBINATION WITH BCR- ABL TYROSINE KINASE INHIBITORS IN CHRONIC MYELOID LEUKEMIA (CML) PATIENTS WITH MOLECULAR EVIDENCE OF DISEASE

NCT #03654768

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AGENTS:

SWOG-Held IND Agents:
Ruxolitinib (Jakafi®) (NSC-752295) (IND-138173)

Commercially Available Agents:
Bosutinib (Bosulif®) (NSC-TBD)
Dasatinib (BMS-354825) (NSC-732517)
Imatinib(Gleevec®) (STI-571)(NSC-716051)
Nilotinib (Tasigna®) (NSC-747599)

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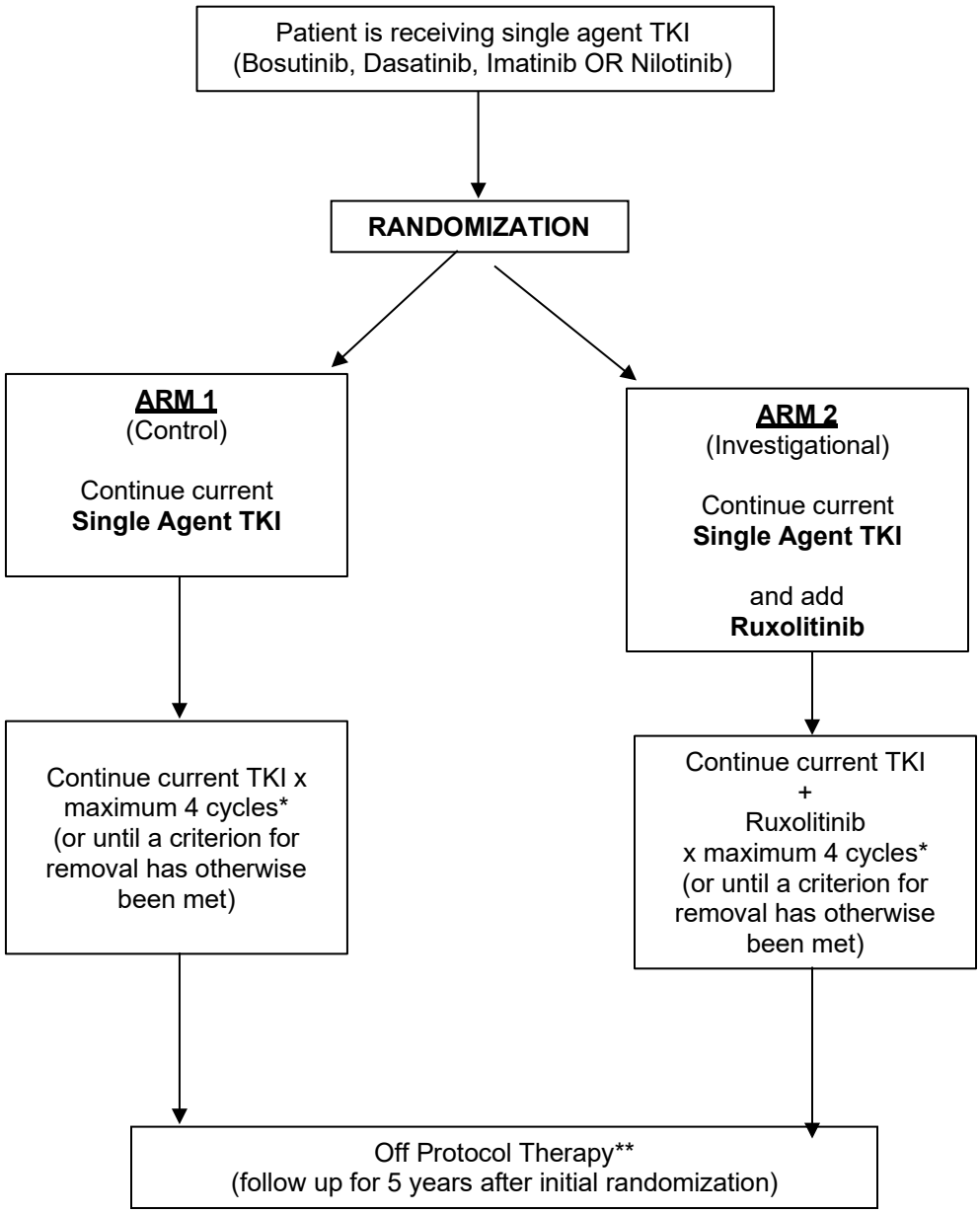
CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further information and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions. Other Tools and Reports: Institutions participating through the CTSU continue to have access to other tools and reports available on the SWOG CRA Workbench via the SWOG website (www.swog.org).
The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For patient eligibility or data submission questions contact the SWOG Statistics and Data Management Center by phone or email: 206/652-2267 leukemiaquestion@crab.org **For treatment or toxicity related questions** contact the Study Chairs: Srinivas K. Tantravahi at 801/585-9682 or Jerald Radich at 206/667-4118.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

SCHEMA



* One Cycle = 90 days.

** After Cycle 4 of protocol therapy, patients will be removed from protocol therapy. After removal from protocol therapy, the patient may remain on single-agent TKI therapy at the discretion of the treating physician; however, it will not be considered “protocol therapy.” Treatment during follow-up will be at the discretion of the treating physician.

1.0 OBJECTIVES

1.1 Primary Objective

a. To compare the rate of molecular response 4.5 (MR4.5) after 12 months of combination therapy with ruxolitinib plus a TKI (bosutinib, dasatinib, imatinib or nilotinib) versus a TKI alone, based on local PCR testing to measure BCR-ABL transcripts in chronic phase CML patients with molecular evidence of disease.

1.2 Secondary Objectives

a. To estimate the frequency and severity of toxicities of each regimen in this patient population.

b. To estimate progression free survival and overall survival of each regimen in this patient population.

1.3 Additional Objectives

a. To describe patterns of MR4.5 and MR4.0 attainment and failure over the 3, 6, 9, and 12-month time points of each regimen in this patient population.

b. To evaluate drug compliance based on patient reported drug intake calendars in this patient population.

c. To describe the kinetics of response in this patient population (as measured by quantitative BCR-ABL/BCR ratio) in both arms over the 3, 6, 9, and 12-month time points.

2.0 BACKGROUND

2.1 Knowledge Gap/Clinical Need to be Addressed

The bone marrow microenvironment in chronic phase CML is believed to contribute to tyrosine kinase inhibitor (TKI) resistance in leukemic stem cells (LSC). Resistance in LSCs results in minimal residual disease (MRD) in CML. This resistance is due to phosphorylation of STAT3, which creates a protective niche in the bone marrow. We hypothesize that the addition of the JAK2 inhibitor, ruxolitinib, to BCR-ABL TKIs in chronic phase CML patients will decrease the phosphorylation of STAT3, which will alter the protective bone marrow microenvironment, causing the LSCs to become susceptible to TKI induced apoptosis. In turn, this would be expected to result in eradication of MRD.

2.2 How Study Results will Help Patients or Lead to New Paradigms in Clinical Cancer Research

Patients with chronic phase CML who have achieved deep molecular responses are often considered eligible to attempt discontinuation of their TKI. A subset of patients is able to successfully remain off protocol treatment, however 50-60% of patients will relapse quickly after stopping treatment, and this is because they harbor MRD in the bone marrow. If ruxolitinib successfully alters the bone marrow microenvironment such that MRD is eradicated, this will lead to more patients with very deep molecular responses to TKI therapy and more patients who are eligible for TKI discontinuation. Without MRD, it would follow that patients could maintain a prolonged treatment free remission and potentially be cured of CML. If this study is positive, follow-up trials could assess whether ruxolitinib can increase treatment-free remissions.

2.3 Background Data to Support the Intervention and/or Endpoint Measurements Selected

Chronic Myeloid Leukemia (CML) is clinically characterized by the presence of the Philadelphia chromosome. The Philadelphia chromosome is the result of a reciprocal translocation between chromosomes 9 and 22 (t(9;22)(q34;q11)) which forms the oncogene BCR-ABL. The expression of BCR-ABL results in the dysregulation of proliferation, differentiation and apoptotic pathways, culminating in the clinical scenario consistent with CML.

The first generation BCR-ABL TKI imatinib, second generation TKIs, nilotinib, dasatinib and bosutinib, as well as the third generation TKI ponatinib have all proven to be very effective at inducing hematologic, cytogenetic and molecular remissions in CML patients. Current practice is to initiate therapy with a BCR-ABL TKI at the time of diagnosis and treatment is continued indefinitely. The initial studies done with imatinib produced an overall survival of 83% at fifteen years. The IRIS trial was the randomized Phase 3 trial comparing imatinib to interferon and low-dose cytarabine as front-line treatment in chronic phase CML. At the time this trial was conducted, regular molecular monitoring of BCR-ABL transcripts using RT-PCR was not standard of care. Therefore, molecular response data is not available on all imatinib treated patients on the IRIS trial. Despite this, 124 patients who had a complete cytogenetic response on imatinib also had blood available from 1 and 4 years. These samples were retrospectively analyzed to measure BCR-ABL transcripts and at 1 year 53% of these patients had a major molecular response (MMR or 3-log reduction in BCR-ABL transcripts) and this increased to 80% by 4 years. At 1 year 22% of these patients had a 4-log reduction in BCR-ABL transcripts (MR4.0) which increased to 41% by 4 years. *(1)*

Bosutinib, dasatinib and nilotinib are approved for use as frontline therapy in CML. Dasatinib received this indication based on results of the DASISION trial in which patients were randomized to receive either imatinib 400mg PO daily or dasatinib 100mg PO daily for newly diagnosed, previously untreated chronic phase CML. Molecular responses were routinely monitored for patients on both arms of this trial, and the annual cumulative incidence of MMR and MR4.5 (4.5 log reduction in BCR-ABL transcripts) are reported in Table 1. *(2)*

Table 1 Annual Cumulative Incidence of MMR and MR4.5 on the DASISION Trial

Time	Dasatinib		Imatinib	
	MMR (%)	$MR^{4,5}$ (%)	MMR (%)	$MR^{4,5}$ (%)
12 months	46	3	28	2
24 months	64	17	46	8
36 months	69	22	55	12
48 months	76	37	63	30
60 months	76	42	64	33

The frontline indication for nilotinib was based on results of the ENESTnd trial which compared nilotinib 300mg PO BID to nilotinib 400mg PO BID to imatinib 400mg PO daily in newly diagnosed, previously untreated chronic phase CML patients. Nilotinib 300mg PO BID was chosen as the standard dose for frontline therapy, therefore all data from this point forward will refer to nilotinib at this dose unless otherwise specified. Annual cumulative incidence of MMR and MR4.5 are reported in Table 2. *(3)*

Table 2 Annual Cumulative Incidence of MMR and MR4.5 on the ENESTnd Trial

Time	Nilotinib		Imatinib	
	MMR (%)	$MR^{4,5}$ (%)	MMR (%)	$MR^{4,5}$ (%)
12 months	44	11	22	1
24 months	71	25	44	9
36 months	73	32	53	15
48 months	76	40	56	23
60 months	77	54	60	31

The frontline indication for bosutinib was based on results of the BFORE trial which compared bosutinib 400mg PO daily to imatinib 400mg PO daily in newly diagnosed, previously untreated chronic phase CML patients. Annual cumulative incidence of MMR and MR4.5 are reported in Table 3. This trial is more recent, therefore, long-term data is not yet available is it is with DASISION and ENESTnd. *(4)*

Table 3 Annual Cumulative Incidence of MMR and MR4.5 on the BFORE Trial

Time	Bosutinib		Imatinib	
	MMR (%)	$MR^{4.5}$ (%)	MMR (%)	$MR^{4.5}$ (%)
12 months	47%	8	37	3

Depending on the sensitivity of the assay being used for RT-PCR, MR4.5 is equivalent to the previously used term, complete molecular response (CMR). This deep level of response has become a clinically relevant milestone as TKI discontinuation in patients with undetectable levels of BCR-ABL has become part of the standard management in CML. The first clinical trial to address the question of TKI discontinuation was the STIM trial which took place between 2007 and 2009. In this trial, CP-CML patients receiving imatinib who had achieved a CMR for a minimum of two years were instructed to discontinue their imatinib. They were monitored closely with monthly PCR in the first 6 months after discontinuation. With a median follow up of 77 months, 61% of patients relapsed, and 58% did so within 7 months of stopping treatment. Thirty-nine percent of patients remained off protocol treatment without a molecular recurrence. No one has relapsed later than 22 months after discontinuing treatment. Importantly, at the time of molecular relapse, all patients were restarted on prior treatment and regained deep levels of molecular response. *(5)* Numerous other studies have looked at the possibility of discontinuing imatinib and the results have remained consistent across multiple trials.

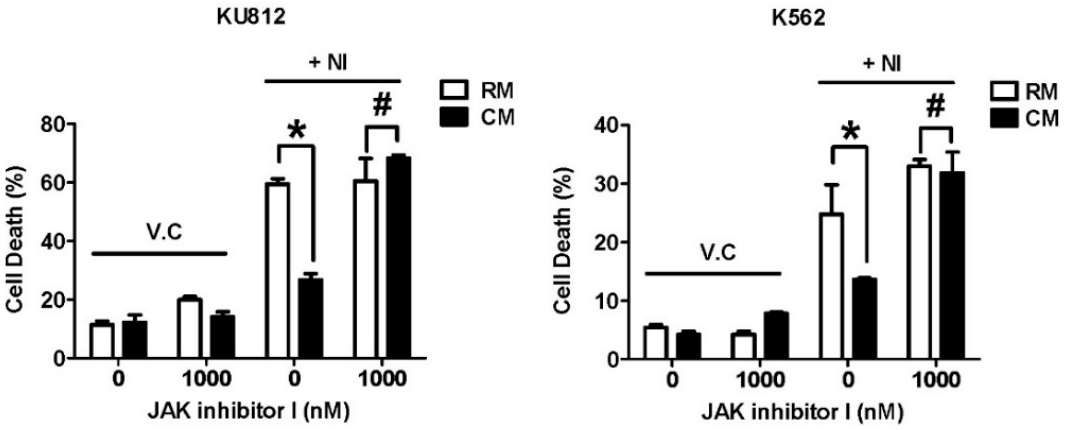
More recent trials have studied the possibility of discontinuing nilotinib, dasatinib and bosutinib. In one trial of 16 patients taking second generation TKIs after imatinib intolerance, had a median follow up of 13 months, and 69% of patients remained off protocol treatment. Of the 31% who relapsed, all did so within the first 4 months after discontinuation, and they all regained their prior response after reinitiating treatment. Large multi-center trials are currently ongoing to address the question of discontinuation of frontline nilotinib and frontline dasatinib. Data from the ENESTFreedom trial was presented at the ASCO annual meeting in 2016. This trial looked at discontinuation of nilotinib in patients who had been on treatment for a minimum of 3 years and had MR4.5 for a minimum of one year. Of the 190 patients who were eligible for discontinuation, 51% remained off protocol treatment without loss of MMR after a median follow up time of 49.4 weeks. The remaining 49% lost MMR and reinitiated treatment with nilotinib. At the time of data cutoff, 98.8% of those who were placed back on therapy had regained MMR, and 88.4% had regained MR4.5. *(6)*

Despite these promising findings, complete eradication of the disease has not been possible in the majority of patients because they harbor minimal residual disease (MRD). The presence of MRD frequently results in relapse of CML after discontinuation of treatment with BCR-ABL TKIs. Preclinical data suggests that MRD is the result of BCR-ABL independent drug resistance. More specifically, CML cells that reside in sanctuary sites such as the bone marrow adhere to fibronectin and demonstrate cell adhesion mediated drug resistance (CAM-DR). Even at increasing doses of BCR-ABL inhibitors, these cells are protected by this mechanism. The conditioned media in the bone marrow contains a variety of cytokines and growth factors which are capable of inducing STAT3-Y705 phosphorylation via the JAK-STAT pathway. This increased phosphorylation, and therefore activity, of STAT3-Y705 is correlated with protection against BCR-ABL TKI-induced cell death. This pathway functions independent from BCR-ABL, and therefore, inhibiting the phosphorylation of STAT3 via alternative pathways is required to eliminate this CAM-DR. *(7)*

In CML cells grown in media conditioned with HS-5 bone marrow stromal cells, JAK2 and TYK2, but not JAK1 or JAK3, were phosphorylated leading to increased STAT3 activation. The inhibition of JAK2 and TYK2 leads to the complete inhibition of STAT3-Y705 phosphorylation, thereby implicating the role of conditioned media-induced activation of JAK2 and TYK2 in STAT3-Y705 phosphorylation and resistance towards BCR-ABL TKI- induced cell death. *(8)*

Studies using CML cell lines have successfully knocked down JAK2 and TYK2 using pan JAK inhibitors, ruxolitinib or siRNA technology. The double knock down of JAK2 and TYK2, but not the individual knock down of JAK2 or TYK2, led to the reversal of drug resistance against BCR-ABL TKIs in CML. *(9)* (Figure 1 * denotes statistical significance, # denotes no significant difference).

Figure 1



These studies led to the belief that pharmacologic inhibition of the JAK2-TYK2-STAT3 pathway could overcome the bone marrow microenvironment-mediated drug resistance leading to the eradication of MRD in patients with CML. Ruxolitinib is an inhibitor of the Janus kinase family of protein tyrosine kinases (JAKs) with selective inhibition of JAK1 and JAK2, and modest to marked selectivity against TYK2. *(10)* Quintarelli et al. published data suggesting that ruxolitinib works synergistically with imatinib, dasatinib and nilotinib in the presence of HS-5 bone marrow stromal cells. Figure 2 demonstrates that the combination of ruxolitinib with imatinib (Figure 2a), dasatinib (Figure 2b) or nilotinib (Figure 2c) showed significantly greater toxicity in K562 cells than a single agent TKI. *(11)*

Figure 2

Figure 2a

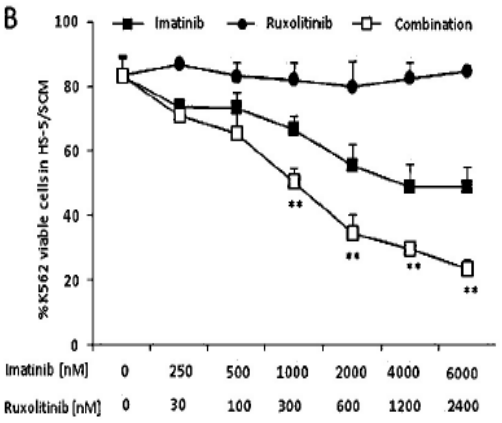
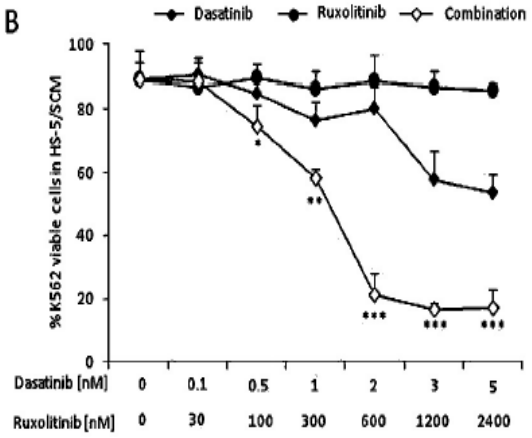
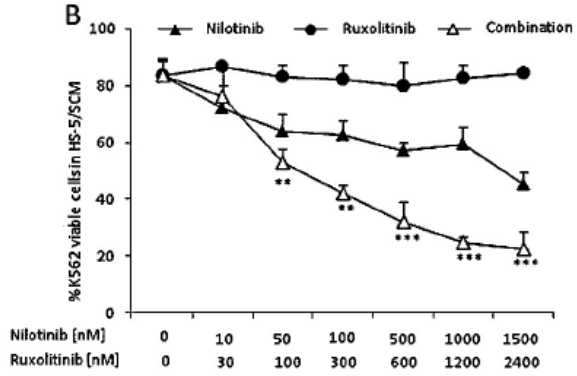


Figure 2b





The synergism was stronger with ruxolitinib plus nilotinib or dasatinib than it was with imatinib. (Figure 3) *(12)* The difference in synergy, as well as the difference in rates of MR4.5 with second generation TKIs compared to imatinib on the ENESTnd and DASISION trials are the primary reasons to study the combination of ruxolitinib plus second generation TKIs rather than imatinib.

Figure 3

K562 cells in HS-5/SCM

Imatinib (nM)	Ruxolitinib (Nm) 0	30	100	300	600	1200	2400
6000	0.38	0.61	0.75	0.71	0.73	0.73	0.71
4000	0.39	0.58	0.55	0.65	0.65	0.63	0.63
2000	0.31	0.56	0.58	0.59	0.57	0.60	0.64
1000	0.17						
500	0.08	0.26	0.27	0.37	0.36	0.37	0.38
250	0.08	0.17	0.18	0.23	0.25	0.21	0.27
0		0.11	0.10				
				0.13	0.15	0.15	0.16
	0.00	0.00	0.00	0.08	0.04	0.09	0.05

K562 cells in HS-5/SCM

Dasatinib (Nm)							
5	0.40	0.55	0.60	0.82	0.79	0.85	0.86
3	0.35	0.63	0.65	0.79	0.87	0.81	0.82
2	0.32	0.48	0.49	0.74	0.76	0.78	0.80
1	0.34	0.26	0.23	0.35	0.36	0.44	0.44
0.5	0.05	0.09	0.16	0.15	0.16	0.17	0.18
0.1	0.01	0.01	0.03	0.02	0.01	0.04	0.04
0.00	0.00	0.03	0.02	0.03	0.01	0.03	0.04
	0	**30**	**1000**	**300**	**600**	**1200**	**2400**

Ruxolitinib (Nm)

K562 cells in HS-5/SCM

Nilotinib (Nm)							
1500	0.47	0.47	0.46	0.67	0.74	0.75	0.74
1000	0.31	0.33	0.44	0.60	0.70	0.71	0.69
500	0.34	0.34	0.47	0.63	0.63	0.65	0.69
100	0.18	0.25	0.30	0.45	0.48	0.44	0.47
50	0.16	0.20	0.30	0.39	0.39	0.42	0.46
10	0.05	0.00	0.05	0.17	0.09	0.05	0.04
0	0.00	0.00	0.00	0.08	0.04	0.09	0.05
	0	**30**	**100**	**300**	**600**	**1200**	**2400**

Ruxolitinib (Nm)

A Phase I clinical trial using ruxolitinib in combination with nilotinib in patients with chronic phase CML was recently completed at Moffitt Cancer Center. This was a dose escalation trial of 11 chronic phase CML patients being treated with nilotinib. Ruxolitinib dosing was 5mg BID, 10mg BID and 15 mg BID in cohorts 1-3, respectively. Combination therapy was continued for six months, at which point ruxolitinib was discontinued. No DLTs occurred at any dose level, and no dose reductions were needed. Only one grade 3/4 treatment emergent adverse event occurred, which was hypophosphatemia that was replaced with oral supplementation. Ruxolitinib 15 mg BID was considered safe and tolerable in this patient population. Of the first 10 patients on study, 4 (40%) of them achieved MR4.5, after six months on trial. Fatigue assessments were completed in seven patients prior to beginning combination therapy, and again after 3 and 6 months on study, and there was a non-significant improvement in fatigue severity scores with combination therapy. Patient plasma was collected from four patients at baseline and again after ≥28 days of ruxolitinib therapy. A plasma inhibitory assay was run using the patient samples in KU812 cells to measure the change in STAT3-Y705 phosphorylation before and after ruxolitinib treatment. A significant decrease in pSTAT3-Y705 was noted with all four patient samples, thus proving the on-target effect of ruxolitinib. Furthermore, a Phase I trial using ruxolitinib in combination with imatinib, dasatinib or nilotinib is ongoing at MD Anderson Cancer Center. The results of this trial are forthcoming.

2.4 RT-PCR for BCR-ABL

Chronic myeloid leukemia is characterized by the Philadelphia chromosome which is the

result of a reciprocal translocation between chromosomes 9 and 22. This translocation results in the fusion gene BCR-ABL1. BCR-ABL1 is integral to the pathogenesis of CML and causes constitutive ABL tyrosine kinase activity which results in dysfunctional proliferation, differentiation and a block in apoptosis. *(13)*

Treatment of chronic phase CML is with BCR-ABL1 tyrosine kinase inhibitors. These drugs bind in the ABL kinase domain thereby inhibiting the function of BCR-ABL and restoring normal proliferation, differentiation and apoptosis.

Close monitoring of response in CML is imperative to the management of these patients. Responses are assessed as hematologic, cytogenetic and molecular responses, with a hematologic assessment being the least sensitive method of monitoring disease status, and molecular assessment using reverse transcriptase polymerase chain reaction (RT-PCR) being the most sensitive. Cytogenetic response is assessed by using standard G-banding karyotype testing on the bone marrow aspirate, and the ideal response to TKI therapy is a complete cytogenetic response (CCyR) after 12 months of treatment. A CCyR indicates that none of the 20 metaphases tested show the presence of the Philadelphia chromosome. Once patients have achieved a CCyR, monitoring of response to therapy can only be done using RT-PCR to measure the level of BCR-ABL transcripts in the peripheral blood. *(14)* The National Comprehensive Cancer Network guidelines for the management of CML recommended monitoring patients with RT-PCR in the peripheral blood every 3 months. Responses must be reported using the International Scale (IS) which uses a conversion factor to standardize PCR results so they may be compared across different laboratories. Unfortunately, not all laboratories in the United States use the IS, and therefore results from those labs are not comparable to those reported on IS. *(15,16)*

Responses are measured based on the BCR-ABL transcript log-reduction from a standardized baseline (100% on the international scale, IS). The desired response is dependent on the length of time a patient has been treated with TKIs. Typically, the sensitivity of the PCR assay ranges from a 4 to 5-log reduction from the 100% IS, and in many cases, anything beyond a 4.5-log reduction becomes undetectable. *(17,18)*

All subjects on this study must have detectable BCR-ABL transcripts identified by RT-PCR done on the peripheral blood in order to be eligible to enroll. Per the NCCN guidelines, RT-PCR for BCR-ABL will be done on the peripheral blood every 3 months while on trial for routine monitoring of disease status. The primary endpoint of this study is a 4.5 log reduction in BCR-ABL transcripts from 100% IS after 12 months on study. It is known that there is some variability in PCR testing between different laboratories based on the control gene used as well as the sensitivity of the assay. *(19)* In order to reduce variability, all assays must be performed in CLIA approved laboratories that report results using the International Scale.

2.5 Inclusion of Women and Minorities

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

Note that the anticipated accrual data is based on the accrual for the most recent SWOG CML study, **S0325**

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	1	0	0	0	1
Native Hawaiian or Other Pacific Islander	0	1	0	0	1
Black or African American	1	2	0	0	3
White	27	49	1	1	78
More Than One Race	0	1	0	0	1
Total	29	53	1	1	84

3.0 DRUG INFORMATION

Investigator Brochures

For information regarding Investigator Brochures, please refer to SWOG Policy 15.

For this study, bosutinib, dasatinib, imatinib and nilotinib are commercially available; therefore, Investigator Brochures are not applicable to these drugs. Information about commercial drugs is publicly available in the prescribing information and other resources.

For this study, ruxolitinib is investigational and is being provided under an IND held by SWOG. For INDs filed by SWOG, the protocol serves as the Investigator Brochure for the performance of the protocol. In such instances submission of the protocol to the IRB should suffice for providing the IRB with information about the drug. However, in cases where the IRB insists on having the official Investigator Brochure from the company, further information may be requested by contacting the SWOG Operations Office at 210/614-8808.

3.1 Bosutinib

a. PHARMACOLOGY

Mechanism of Action: Bosutinib is a tyrosine kinase inhibitor. Bosutinib inhibits the Bcr-Abl kinase that promotes CML; it is also an inhibitor of Src-family kinases including Src, Lyn, and Hck. Bosutinib inhibited 16 of 18 imatinib-resistant forms of Bcr-Abl expressed in murine myeloid cell lines. Bosutinib did not inhibit the T315I and V299L mutant cells. In mice, treatment with bosutinib reduced the size of CML tumors relative to controls and inhibited growth of murine myeloid tumors expressing several imatinib-resistant forms of Bcr-Abl.

b. PHARMACOKINETICS

1. Absorption - Following administration of a single dose of BOSUTINIB 500 mg with food in patients with cancer, the median time to-peak concentration (tmax) was 4-6 hours. Bosutinib exhibits dose proportional

increases in AUC and Cmax, over the dose range of 200 to 800 mg. After 15 daily doses of BOSUTINIB (500 mg) with food in patients with CML, the mean (SD) Cmax value was 200 (12) ng/mL, and the mean (SD) AUC was 3650 (425) ng•h/mL. When given with a high fat meal, the Cmax and AUC of bosutinib increased 1.8- and 1.7-fold, respectively. Following administration of a single dose of BOSUTINIB (500 mg) with food to healthy subjects, the absolute bioavailability was 34%.

2. Distribution - After administration of a single dose of BOSUTINIB 500 mg with food in patients with CML, bosutinib had a mean apparent volume of distribution ± standard deviation of 6080 ± 1230 L. Bosutinib was highly bound to human plasma proteins in vitro (94%) and ex vivo in healthy subjects (96%), and binding was not concentration-dependent.

3. Metabolism - Bosutinib is primarily metabolized by CYP3A4. The major circulating metabolites identified in plasma are oxydechlorinated (M2) bosutinib (19% of parent exposure) and N-desmethylated (M5) bosutinib (25% of parent exposure), with bosutinib N-oxide (M6) as a minor circulating metabolite. All the metabolites were deemed inactive.

4. Elimination - In patients with CML given single oral doses of BOSUTINIB 500 mg with food, the mean terminal phase elimination half-life (t1/2) was 22.5 (1.7) hours, and the mean (SD) clearance (Cl/F) was 189 (48) L/h. In six healthy male subjects given a single oral dose of [14C] radiolabeled bosutinib, 91.3% of the dose was recovered in feces and 3% of the dose recovered in urine.

c. ADVERSE EVENTS

1. Adverse effects reported in > 20% of subjects treated with bosutinib include: diarrhea, nausea, thrombocytopenia, rash, vomiting, abdominal pain, respiratory tract infection, anemia, pyrexia, liver test abnormalities, fatigue, cough, and headache.

2. Adverse effects reported in 4% to 20% of subjects include: febrile neutropenia, pericardial effusion, tinnitus, hypertension, gastritis, gastrointestinal hemorrhage (anal hemorrhage, gastric hemorrhage, gastrointestinal hemorrhage, hematemesis, hematochezia, intestinal hemorrhage, lower gastrointestinal hemorrhage, melena, rectal hemorrhage, upper gastrointestinal hemorrhage), pain, hepatotoxicity (includes allergic hepatitis, ascites, cholestasis, drug-induced liver injury, hepatic steatosis, hepatitis toxic, hepatocellular injury, hepatotoxicity, liver disorder, liver injury) drug hypersensitivity, electrocardiogram QT prolonged (includes electrocardiogram QT prolonged, long QT syndrome), blood creatine phosphokinase increased, amylase increased, hyperkalemia, dehydration, hypophosphatemia, myalgia, dysgeusia, urticaria, pruritus, renal impairment, body fluid retention, leukopenia.

3. Serious adverse effects reported in ≤ 3% of subjects include: granulocytopenia, pericarditis, acute pancreatitis, anaphylactic shock, respiratory failure, pulmonary hypertension, pulmonary edema, erythema multiforme, exfoliative rash, drug eruption, Stevens-Johnson syndrome.

4. Due to potential drug interactions, a complete patient medication list, should be screened prior to initiation of and during treatment with bosutinib.

   CYP3A inhibitors: Avoid the concomitant use of strong or moderate CYP3A inhibitors with BOSUTINIB as an increase in bosutinib plasma concentration is expected.

   CYP3A Inducers: Avoid the concomitant use of strong or moderate CYP3A inducers with BOSUTINIB as a large reduction in exposure is expected.

   Proton Pump Inhibitors: In a dedicated cross-over drug-interaction trial in healthy volunteers. Consider using short-acting antacids or H2 blockers instead of PPIs to avoid a reduction in bosutinib exposure. Separate antacid or H2 blocker dosing and bosutinib dosing by more than 2 hours.

5. Pregnant and lactation: Pregnancy Category D. It is not known whether bosutinib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from bosutinib, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

d. DOSING AND ADMINISTRATION

   Dosing – See treatment plan (Section 7.2).

   Administration: Administer orally, with food. Patients should not take antacids, proton pump inhibitors or H2 antagonists. If antacids are absolutely necessary, they must be taken at least 2 hours before or 2 hours after dosing of bosutinib.

e. HOW SUPPLIED

   Bosutinib is commercially available and will not be supplied. Refer to the current FDA-approved package insert.

f. STORAGE, PREPARATION & STABILITY

   Refer to the current FDA-approved package insert.

3.2 Dasatinib (BMS-354825) (NSC-732517)

a. PHARMACOLOGY

Mechanism of Action: BMS-354825 is a potent, broad spectrum ATP-competitive inhibitor of 5 critical oncogenic tyrosine kinase families: BCR-ABL, SRC family kinases, c-KIT, ephrin (EP) receptor kinases, and PDGFβ receptor. Each of these protein kinases has been strongly linked to multiple forms of human malignancies.

b. PHARMACOKINETICS

Approximate Solubility: BMS-354825 is insoluble in water and slightly soluble in ethanol and methanol.

c. ADVERSE EFFECTS

1. Adverse Effects

The following is a description of major adverse events associated with BMS-354825 therapy. A list of Comprehensive Adverse Events and Potential Risks (CAEPR) in NCI-CTCAE Version 5.0 terms is listed below. For additional information, see the Investigator Brochure and the package insert.

Comprehensive Adverse Events and Potential Risks list (CAEPR) For Dasatinib (BMS-354825, Sprycel, NSC 732517)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' https://ctep.cancer.gov/protocolDevelopment/adverse_effects.htmfor further clarification.

Frequency is provided based on 2937 patients.

Below is the CAEPR for dasatinib (BMS-354825).

Version 2.7, September 10, 2018

Adverse Events with Possible Relationship to Dasatinib (BMS-354825, Sprycel) (CTCAE 5.0 Term) [n= 2937]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia	Febrile neutropenia	
CARDIAC DISORDERS		
	Pericardial effusion	Heart failure
		Left ventricular systolic dysfunction
		Myocardial infarction
GASTROINTESTINAL DISORDERS		
Diarrhea	Abdominal distension	
Nausea	Abdominal pain	
	Anal mucositis	
	Constipation	
	Dyspepsia	
	Gastrointestinal hemorrhage[2]	
	Mucositis oral	
	Rectal mucositis	
	Small intestinal	
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		

Adverse Events with Possible Relationship to Dasatinib (BMS-354825, Sprycel) (CTCAE 5.0 Term) [n= 2937]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious**
Fatigue	Edema limbs	
	Fever	
	General disorders and administration site conditions - Other (superficial	
	Generalized edema	
	Non-cardiac chest pain	
	Pain	
INFECTIONS AND INFESTATIONS		
	Infection[3]	
INVESTIGATIONS		
Neutrophil count decreased	Alanine aminotransferase increased	Electrocardiogram QT corrected interval prolonged
Platelet count decreased	Aspartate aminotransfera se increased	
	Weight gain	
	Weight loss	
	White blood cell	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	Tumor lysis syndrome
	Hypocalcemia	
	Hypokalemia	
	Hypophosphatemia	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Myalgia	Arthralgia	Growth suppression [4]
		Musculoskeletal and connective tissue disorder – Other
		Musculoskeletal and connective tissue disorder
NERVOUS SYSTEM DISORDERS		
Headache	Dizziness	Intracranial
		Leukoencephalopathy
		Reversible posterior leukoencephalopat
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
		Gynecomastia[2]
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Dyspnea	Cough	

Adverse Events with Possible Relationship to Dasatinib (BMS-354825, Sprycel) (CTCAE 5.0 Term) [n= 2937]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious**
Pleural effusion	Laryngeal mucositis	
	Pharyngeal mucositis	
	Pneumonitis	
	Tracheal mucositis	Pulmonary hypertension
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Rash maculo-papular	Alopecia	Erythema multiforme
	Pruritus	Stevens-Johnson
	Rash acneiform	Toxic Epidermal
VASCULAR DISORDERS		
	Flushing	

1 This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

2 Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

3 Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

4 Effects on growth and development have been observed in pediatric patients and may include epiphyses delayed fusion, osteopenia, growth retardation, and gynecomastia

5 Gastrointestinal ulcer includes Anal ulcer, Colonic ulcer, Duodenal ulcer, Esophageal ulcer, Gastric ulcer, Ileal ulcer, Jejunal ulcer, Rectal ulcer, and Small intestine ulcer under the GASTROINTESTINAL DISORDERS SOC.

Adverse events reported on Dasatinib (BMS-354825, Sprycel) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Dasatinib (BMS-354825, Sprycel) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia)

CARDIAC DISORDERS - Atrial fibrillation; Cardiac disorders - **Other** (cardiomegaly); Cardiac disorders - Other (heart rate increased); Chest pain - cardiac; Myocarditis; Palpitations; Pericarditis; Sinus tachycardia; Ventricular tachycardia
CONGENITAL, FAMILIAL AND GENETIC DISORDERS - Congenital, familial and genetic disorders - Other (Keratosis follicular)
EAR AND LABYRINTH DISORDERS - Ear pain; Middle ear inflammation; Tinnitus; Vertigo
EYE DISORDERS - Blurred vision; Dry eye; Eye disorders - Other (optic nerve neuritis); Periorbital edema
GASTROINTESTINAL DISORDERS - Anal fissure; Ascites; Colitis; Dry mouth; Dysphagia; Esophagitis; Flatulence; Gastritis; Gastrointestinal disorders - Other (enteritis); Gastrointestinal disorders - Other (oral soft tissue disorder); Gastrointestinal disorders - Other (tongue eruption); Gastrointestinal ulcer[3]; Ileus; Oral pain; Pancreatitis; Periodontal disease; Stomach pain
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS -Chills; Edema face; Edema trunk; Flu like symptoms; Gait disturbance; General disorders and administration site conditions - Other (temperature intolerance); Localized edema; Malaise
HEPATOBILIARY DISORDERS - Cholecystitis; Hepatobiliary disorders - Other (cholestasis)
IMMUNE SYSTEM DISORDERS - Anaphylaxis
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising
INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; Cardiac troponin T increased; CD4 lymphocytes decreased; CPK increased; Creatinine increased; Electrocardiogram T wave abnormal; GGT increased; Investigations – Other (bone densitometry);Investigations - Other (thermometry abnormal); Lymphocyte count decreased; Lymphocyte count increased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperkalemia; Hyperuricemia; Hypoalbuminemia; Hypomagnesemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Back pain; Bone pain; Chest wall pain; Generalized muscle weakness; Muscle cramp; Musculoskeletal and connective tissue disorder Other (muscle stiffness); Musculoskeletal and connective tissue disorder Other (nuchal rigidity); Musculoskeletal and connective tissue disorder - Other (tendonitis); Myositis; Osteoporosis; Pain in extremity; Rhabdomyolysis
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL **CYSTS AND POLYPS)** - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (hemangiomatosis)
NERVOUS SYSTEM DISORDERS - Acoustic nerve disorder NOS; Amnesia; Cognitive disturbance; Concentration impairment; Dysarthria; Dysgeusia; Ischemia cerebrovascular; Lethargy; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Somnolence; Syncope; Transient ischemic attacks; Tremor
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia; Libido decreased; Suicidal ideation
RENAL AND URINARY DISORDERS - Acute kidney injury; Proteinuria; Urinary frequency
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Bronchospasm; Epistaxis; Hypoxia; Oropharyngeal pain; Pulmonary edema; Sore throat
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Bullous dermatitis; Dry skin; Hair color changes; Hyperhidrosis; Nail loss; Pain of skin; Palmar-plantar erythrodysesthesia syndrome; Photosensitivity; Purpura; Skin and subcutaneous tissue disorders - Other (acute febrile neutrophilic dermatosis); Skin and subcutaneous tissue disorders - Other (panniculitis); Skin ulceration; Urticaria
VASCULAR DISORDERS - Hematoma; Hot flashes; Hypertension; Hypotension; Phlebitis; Superficial thrombophlebitis; Thromboembolic event; Vasculitis

Note: Dasatinib (BMS-354825, Sprycel) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

2. Drug Interactions: BMS-354825 is primarily metabolized by the human CYP3A4 enzyme, is a significant inhibitor of CYP3A4, and is a weak inhibitor of CYP1A2, CYP2D6, CYP2C9, and CYP2C19. It may decrease the metabolic clearance of drugs that are significantly metabolized by the CYP3A4 enzyme. Due to the potential of BMS-354825 to prolong the QT/QTc, use caution when administering BMS-354825 with other potential QTc-prolonging medications. Due to the possibility of gastrointestinal, cardiac, and cutaneous hemorrhage, avoid using medications that inhibit platelet function or anticoagulants with BMS-354825.

   BMS-354825 is not a P-glycoprotein inhibitor.

3. Pregnancy and Lactation: Females of child bearing potential should avoid pregnancy, which may include use of effective contraception during treatment and for 30 days after the final dose.

d. DOSING AND ADMINISTRATION

See Section 7.0 Treatment Plan.

Administration: Administer orally, with or without food. Tablets should be swallowed whole and cannot be crushed or broken. Grapefruit juice should not be consumed during study drug therapy, as P450 enzyme inhibition may increase drug exposure. In vitro solubility data indicate that dasatinib may have decreased solubility and absorption at pH > 4. Patients should not take antacids, proton pump inhibitors or H2 antagonists. If antacids are absolutely necessary, they must be taken at least 2 hours before or 2 hours after dosing of dasatinib.

e. HOW SUPPLIED

Dasatinib is commercially available and will not be supplied. Refer to the current FDA-approved package insert.

f. STORAGE, PREPARATION & STABILITY

Refer to the current FDA-approved package insert.

3.3 Imatinib (Gleevec®)(STI-571) (NSC-716051)

a. PHARMACOLOGY

Mechanism of Action: Imatinib is a tyrosine kinase inhibitor that inhibits the BCR-ABL tyrosine kinase, the constitutive abnormal gene product of the Philadelphia chromosome in chronic myeloid leukemia (CML). Inhibition of this enzyme blocks proliferation and induces apoptosis in BCR-ABL positive cell lines. Imatinib also

inhibits tyrosine kinases for platelet-derived growth factor (PDGF), stem cell factor (SCF), c-Kit, and cellular events mediated by PDGF and SCF.

b. PHARMACOKINETICS

1. Absorption: Imatinib is well absorbed after oral administration. Cmax occurs within 2-4 hours after dosing. Mean absolute bioavailability is 98%.

2. Distribution: Plasma protein binding, predominately to albumin and α1- acid glycoprotein, is approximately 95% for imatinib and its primary metabolite.

3. Metabolism: Imatinib is primarily metabolized by CYP3A4, with minor contributions by CYP1A2, CYP2D6, CYP2C9, and CYP2C19. CGP74588, the main circulating active metabolite formed predominantly by CYP3A4, demonstrates in vitro potency similar to the parent drug. The elimination half-lives of imatinib and CGP74588 are approximately 18 and 40 hours, respectively, following oral administration.

4. Elimination: Imatinib is eliminated predominately in the feces and mostly as metabolites. Approximately 81% of the dose is eliminated within 7 days, in feces (68% of dose) and urine (13% of dose). Unchanged imatinib accounted for 25% of the dose (5% urine, 20% feces). Typically, clearance of imatinib in a 50-year-old patient weighing 50 kg is expected to be 8 L/h, while for a 50-year-old patient weighing 100 kg the clearance will increase to 14 L/h. The inter-patient variability of 40% in clearance does not warrant initial dose adjustment based on body weight and/or age but indicates the need for close monitoring for treatment-related toxicity.

c. ADVERSE EFFECTS

1. Possible Side Effects of Commercial Drug Name:
Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

Adverse effects reported in > 20% of subjects treated with imatinib include: edema, weight gain, nausea, diarrhea, vomiting, pain, rash, fatigue, headache, nasopharyngitis and upper respiratory tract infections, cough, myalgia, cytopenias, and hemorrhage.

Adverse effects reported in 4% to 20% of subjects include: hepatotoxicity, renal toxicity, gastrointestinal perforations, dizziness, hearing loss, insomnia, sinusitis, pyrexia, and dyspepsia.

Serious adverse effects reported in ≤ 3% of subjects include: heart failure and left ventricular dysfunction, bullous dermatologic reactions (e.g., erythema multiforme and Stevens-Johnson syndrome), tumor lysis

syndrome, new malignancy, swelling of the brain, and reports of motor vehicle accidents.

2. Pregnancy and Lactation:
Based on human and animal data, imatinib crosses the placenta and can cause fetal harm, including teratogenicity, spontaneous abortions, and congenital anomalies. Pregnancy should be avoided during imatinib treatment and highly effective contraception should be used for at least two weeks after stopping treatment. Imatinib and its active metabolite are excreted into human milk; a breastfed infant could receive up to 10% of the maternal therapeutic dose based on body weight. Women should not breastfeed during treatment and for one month after the last imatinib dose. The risk of infertility in females or males of reproductive potential has not been studied in humans.

3. Drug Interactions: Imatinib is primarily metabolized by CYP3A4, with minor contributions by CYP1A2, CYP2D6, CYP2C9, and CYP2C19. Concomitant administration of imatinib with inhibitors and inducers of CYP3A may alter the pharmacokinetic or pharmacodynamics properties of imatinib. Imatinib is a potent competitive inhibitor of CYP2C9, CYP2D6, and CYP3A4/5. Imatinib will increase plasma concentrations of CYP3A4 metabolized drugs (e.g., triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, etc.). Use caution when administering imatinib with CYP2C9, CYP2D6, and CYP3A4/5 substrates that have a narrow therapeutic window (e.g. warfarin). Grapefruit juice may also increase plasma concentrations of imatinib; avoid grapefruit juice. See Section 7.3 for details.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

e. HOW SUPPLIED

1. Imatinib (Gleevec®) is commercially available and will not be supplied. Refer to the current FDA-approved package insert.

f. DRUG ORDERING & ACCOUNTABILITY

2. Refer to the current FDA-approved package insert.

3.4 Nilotinib (Tasigna®) (NSC-747599)

a. PHARMACOLOGY

Mechanism of Action: Nilotinib (Tasigna®) is an inhibitor of the BCR-ABL kinase. Nilotinib binds to and stabilizes the inactive conformation of the kinase domain of ABL protein. Nilotinib inhibited BCR-ABL mediated proliferation of murine leukemic cell lines and human cell lines derived from patients with Ph+ CML. Under the conditions of the assays, nilotinib was able to overcome imatinib resistance resulting from BCR-ABL kinase mutations. Nilotinib inhibits the auto-phosphorylation of the following kinases at IC50 values as indicated: BCR-ABL (20 to 60 nM), PDGFR (69 nM), c-KIT (210 nM), CSF-1R (125 to 250 nM), and DDR1 (3.7 nM).

b. PHARMACOKINETICS

1. Absorption: The absolute bioavailability of nilotinib has not been determined. As compared to an oral drink solution (pH of 1.2 to 1.3), relative bioavailability of nilotinib capsule is approximately 50%. Peak concentrations of nilotinib are reached 3 hours after oral administration. Steady-state nilotinib exposure was dose-dependent with less than dose-proportional increases in systemic exposure at dose levels higher than 400 mg given as once daily dosing. Compared to the fasted state, the systemic exposure (AUC) increased by 82% when the dose was given 30 minutes after a high fat meal. The bioavailability of nilotinib is increased with food, thus nilotinib must not be taken with food. No food should be consumed for at least 2 hours before and for at least 1 hour after the dose is taken.

2. Distribution: Single dose administration of two 200mg nilotinib capsules each dispersed in 1 teaspoon of applesauce and administered within 15 minutes was shown to be bioequivalent to a single dose administration of two 200mg intact capsules. The blood-to-serum ration of nilotinib is 0.68. Serum protein binding is approximately 98% on the basis of in vitro experiments. Median steady-state trough concentration of nilotinib was decreased by 53% in patients with total gastrectomy compared to patients who had not undergone surgeries

3. Metabolism: Main metabolic pathways identified in healthy subjects are oxidation and hydroxylation. Nilotinib is the main circulating component in the serum. None of the metabolites contribute significantly to the pharmacological activity of nilotinib.

4. Elimination: The apparent elimination half-life estimated from the multiple dose pharmacokinetic studies with daily dosing was approximately 17 hours. Inter-patient variability in nilotinib AUC was 32% to 64%. Steady state conditions were achieved by Day 8. An increase in serum exposure to nilotinib between the first dose and steady state was approximately 2-fold for daily dosing and 3.8-fold for twice daily dosing. After a single dose of radiolabeled nilotinib in healthy subjects, more than 90% of the administered dose was eliminated within 7 days: mainly in feces (93% of the dose). Parent drug accounted for 69% of the dose. Age, body weight, gender, or ethnic origin did not significantly affect the pharmacokinetics of nilotinib.

c. ADVERSE EFFECTS

1. Possible Side Effects of nilotinib:

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on*

737 patients. Below is the CAEPR for Nilotinib.

Version 2.0, September 6, 2022[1]

Adverse Events with Possible Relationship to Nilotinib (CTCAE 5.0 Term) [n= 737]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
	Eosinophilia	
	Febrile neutropenia	
CARDIAC DISORDERS		
	Chest pain - cardiac	
		Pericardial effusion
GASTROINTESTINAL DISORDERS		
Abdominal pain		
		Ascites
Constipation		
Diarrhea		
	Dyspepsia	
		Gastric hemorrhage
Nausea		
	Pancreatitis	
Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Edema limbs	
Fatigue		
Fever		
	Non-cardiac chest pain	
	Pain	
INFECTIONS AND INFESTATIONS		
Upper respiratory infection		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
	Bruising	
INVESTIGATIONS		
	Alanine aminotransferase increased	
	Blood bilirubin increased	
	CPK increased	
	Cholesterol high	
		Electrocardiogram QT corrected interval prolonged
	GGT increased	

Adverse Events with Possible Relationship to Nilotinib (CTCAE 5.0 Term) [n= 737]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Lipase increased	
	Lymphocyte count decreased	
Neutrophil count decreased		
Platelet count decreased		
	Serum amylase increased	
	Weight gain	
	White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
	Hyperglycemia	
	Hyperkalemia	
	Hyperlipidemia	
	Hypertriglyceridemia	
	Hypocalcemia	
	Hypokalemia	
	Hyponatremia	
	Hypophosphatemia	
		Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Arthralgia		
	Back pain	
	Bone pain	
	Chest wall pain	
	Flank pain	
	Generalized muscle weakness	
	Muscle cramp	
Myalgia		
	Neck pain	
	Pain in extremity	
NERVOUS SYSTEM DISORDERS		
	Aphonia	
	Dizziness	
	Dysesthesia	
	Dysgeusia	
Headache		
	Paresthesia	

Adverse Events with Possible Relationship to Nilotinib (CTCAE 5.0 Term) [n= 737]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Peripheral motor neuropathy	
	Peripheral sensory neuropathy	
PSYCHIATRIC DISORDERS		
	Insomnia	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Cough		
	Dyspnea	
	Epistaxis	
	Oropharyngeal pain	
		Pleural effusion
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Alopecia	
	Dry skin	
	Eczema	
	Hyperhidrosis	
Pruritus		
	Rash acneiform	
Rash maculo-papular		
VASCULAR DISORDERS		
	Hypertension	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]The relative early occurrence of some of these deaths relative to the initiation of Tasigna (nilotinib) suggests the possibility that ventricular repolarization abnormalities may have contributed to their occurrence.

Adverse events reported on Nilotinib trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Nilotinib caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia)
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Atrioventricular block complete; Palpitations; Sinus bradycardia; Sinus tachycardia; Ventricular arrhythmia
EAR AND LABYRINTH DISORDERS - Vertigo
EYE DISORDERS - Dry eye; Eye disorders - Other (eyelid edema); Eye disorders - Other (eye pruritis); Vitreous hemorrhage

GASTROINTESTINAL DISORDERS - Abdominal distension; Flatulence
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; Malaise; Sudden death NOS[2]
HEPATOBILIARY DISORDERS - Hepatobiliary disorders - Other (hepatic function abnormal)
INFECTIONS AND INFESTATIONS - Conjunctivitis; Folliculitis; Infections and infestations - Other (gastroenteritis)
INVESTIGATIONS - Alkaline phosphatase increased; Aspartate aminotransferase increased; Investigations - Other (globulins decreased); Weight loss
METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Hyperphosphatemia; Hypoalbuminemia; Hypomagnesemia; Metabolism and nutrition disorders - Other (diabetes mellitus)
PSYCHIATRIC DISORDERS - Anxiety; Depression
RENAL AND URINARY DISORDERS - Urinary frequency
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Pulmonary edema
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Urticaria
VASCULAR DISORDERS - Flushing

Note: Nilotinib in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

2. Pregnancy and Lactation: Pregnancy Category D. Based on its mechanism of action and findings in animals, nilotinib may cause fetal harm when administered to a pregnant woman. Women should be advised to avoid becoming pregnant while on nilotinib. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should use effective contraceptives if taking nilotinib. Sexually active female patients taking nilotinib should use adequate contraception.

   It is not known whether nilotinib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from nilotinib, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

3. Drug Interactions: Nilotinib undergoes metabolism by CYP3A4, and concomitant administration of strong inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) or inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) of CYP3A4 can increase or decrease nilotinib concentrations significantly. The administration of nilotinib with agents that are strong CYP3A4 inhibitors should be avoided. Concomitant use of nilotinib with medicinal products and herbal preparations (e.g., St. John's Wort) that are potent inducers of CYP3A4 is likely to reduce exposure to nilotinib to a clinically relevant extent. Therefore, in patients receiving

nilotinib, concomitant use of alternative therapeutic agents with less potential for CYP3A4 induction should be selected.

Ketoconazole: In healthy subjects receiving ketoconazole, a CYP3A4 inhibitor, at 400 mg once daily for 6 days, systemic exposure (AUC) to nilotinib was increased approximately 3-fold.

Rifampicin: In healthy subjects receiving the CYP3A4 inducer, rifampicin, at 600 mg daily for 12 days, systemic exposure (AUC) to nilotinib was decreased approximately 80%.

Nilotinib has pH-dependent solubility, with decreased solubility at higher pH. Drugs such as proton pump inhibitors that inhibit gastric acid secretion to elevate the gastric pH may decrease the solubility of nilotinib and reduce its bioavailability. In healthy subjects, co-administration of a single 400 mg dose of nilotinib with multiple doses of esomeprazole (a proton-pump inhibitor) at 40 mg daily decreased the nilotinib AUC by 34%. Increasing the dose of nilotinib when co-administered with such agents is not likely to compensate for the loss of exposure. Since proton pump inhibitors affect pH of the upper GI tract for an extended period, separation of doses may not eliminate the interaction. The concomitant use of proton pump inhibitors with nilotinib is not recommended. In healthy subjects, no significant change in nilotinib pharmacokinetics was observed when a single 400 mg dose of nilotinib was administered 10 hours after and 2 hours before famotidine (an H2 blocker). Therefore, when the concurrent use of a H2 blocker is necessary, it may be administered approximately 10 hours before and approximately 2 hours after the dose of nilotinib. Administration of an antacid (aluminum hydroxide/magnesium hydroxide/simethicone) to healthy subjects, 2 hours before or 2 hours after a single 400 mg dose of nilotinib did not alter nilotinib pharmacokinetics. Therefore, if necessary, an antacid may be administered approximately 2 hours before or approximately 2 hours after the dose of nilotinib.

Avoid administration of nilotinib with agents that may increase nilotinib exposure (e.g., strong CYP3A4 inhibitors) or anti-arrhythmic drugs (including, but not limited to amiodarone, disopyramide, procainamide, quinidine and sotalol) and other drugs that may prolong QT interval (including, but not limited to chloroquine, clarithromycin, haloperidol, methadone, moxifloxacin and pimozide).

Nilotinib is a substrate of the efflux transporter P-glycoprotein (P-gp, ABCB1). If nilotinib is administered with drugs that inhibit P-gp, increased concentrations of nilotinib are likely, and caution should be exercised.

In vitro studies also suggest that nilotinib may induce CYP2B6, CYP2C8 and CYP2C9, and decrease the concentrations of drugs which are eliminated by these enzymes.

Avoid grapefruit products and other foods that are known to inhibit CYP3A4.

Due to potential drug interactions, a complete patient medication list should be screened prior to initiation of and during treatment with nilotinib. See Section 8.0 Toxicities to be Monitored and Dosage Modifications

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

e. HOW SUPPLIED

Nilotinib is commercially available and will not be supplied. Refer to the current FDA-approved package insert.

3.5 Ruxolitinib (Jakafi®) (NSC-752295) (IND-138173)

a. PHARMACOLOGY

Mechanism of Action: Ruxolitinib, a kinase inhibitor, inhibits Janus Associated Kinases (JAKs) JAK1 and JAK2 signaling associated with myelofibrosis and polycythemia vera. JAK signaling involves recruitment of STATs (signal transducers and activators of transcription) to cytokine receptors, activation and subsequent localization of STATs to the nucleus leading to modulation of gene expression.

b. PHARMACOKINETICS

1. Absorption: Ruxolitinib appears to be well absorbed; oral absorption was estimated to be at least 95%. Maximal ruxolitinib plasma concentrations are achieved within 1 to 2 hours after oral administration.

2. Distribution: The mean volume of distribution at steady state in patients with myelofibrosis and polycythemia vera is 72 L (intersubject variability of 29%) and 75 L (intersubject variability of 23%), respectively. In vitro, it is approximately 97% bound to plasma proteins, mostly to albumin.

3. Metabolism: Ruxolitinib is metabolized primarily by CYP3A4 and lesser extent by CYP2C9.

4. Elimination: After a single oral radiolabeled dose to healthy adults, elimination was primarily through metabolism with 74% of radioactivity excreted in urine and 22% excreted in feces. Unchanged drug accounted for less than 1% of the excreted total radioactivity. The mean elimination half-life of ruxolitinib is approximately 3 hours, and the mean half-life of ruxolitinib with metabolites is approximately 5.8 hours.

c. ADVERSE EFFECTS

1. Adverse Effects:

Adverse Events with Possible Relationship to Ruxolitinib		
Likely (> 20%)	**Less Likely (4 – ≤ 20%)**	**Rare but Serious (≤ 3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia Thrombocytopenia	Hematoma Platelet count decreased	
CARDIAC DISORDERS		
	Hypertension	
GASTROINTESTINAL DISORDERS		

Adverse Events with Possible Relationship to Ruxolitinib		
Likely (> 20%)	**Less Likely (4 – ≤ 20%)**	**Rare but Serious (≤ 3%)**
Diarrhea	Constipation Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue	Cough Night sweat Insomnia	
INFECTIONS AND INFESTATIONS		
	Bronchitis Pneumonia Urinary tract infection Upper respiratory tract infection Herpes zoster	
METABOLISM AND NUTRITION DISORDERS		
	Decrease appetite	
MUSCULOSKELETAL AND CONNECTIVE TISSURE DISORDERS		
	Muscle spasm Musculoskeletal pain Pain in extremity Back pain	Arthralgia
NERVOUS SYSTEM DISORDERS		
	Dizziness	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Dyspnea	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Pruritis Rash	

2. Pregnancy and Lactation:

Ruxolitinib has a rating of pregnancy risk category C. There are no adequate and well-controlled studies of ruxolitinib in pregnant women. Ruxolitinib was embryotoxic and fetotoxic in rats and rabbits (increases in post-implantation loss and reduced fetal weights). The potential risk of teratogenicity for humans is unknown. The use of ruxolitinib during pregnancy should be avoided. Women of childbearing potential should use effective contraceptives while taking ruxolitinib.

Women taking ruxolitinib should not breast-feed. In lactating rats, ruxolitinib and/or its metabolites were excreted into the milk with a concentration that was 13-fold higher than the maternal plasma concentration. It is not known whether ruxolitinib is excreted in human milk.

3. Drug Interactions:

Ruxolitinib is metabolized primarily by CYP3A4 and lesser extent by CYP2C9. Therefore, co-medications inhibiting CYP3A4 and CYP2C9 enzymes might increase the exposure to ruxolitinib.

Agents that may alter plasma concentration of ruxolitinib:
Strong CYP3A4 inhibitors: in healthy subjects receiving ketoconazole, a

strong CYP3A4 inhibitor, at 200 mg twice daily for four days, the AUC of ruxolitinib increased by 91% and the half-life was prolonged from 3.7 to 6.0 hours.

When administering ruxolitinib with strong CYP3A4 inhibitors, the total daily dose of ruxolitinib should be reduced to approximately 50% of the dose rounding up to the nearest dosage strength. Patients should be closely monitored for cytopenias and the dose should be titrated based on safety and efficacy.

Mild or moderate CYP3A4 inhibitors: in healthy subjects receiving erythromycin, a moderate CYP3A4 inhibitor, at 500 mg twice daily for four days, there was a 27% increase in the AUC of ruxolitinib. No dose adjustment is recommended when ruxolitinib is co administered with mild or moderate CYP3A4 inhibitors (e.g. erythromycin). Patients should be closely monitored for cytopenias when initiating therapy with a moderate CYP3A4 inhibitor.

Concomitant moderate CYP2C9 and CYP3A4 inhibitors (including a dual enzyme inhibitor as a single agent, e.g. Fluconazole): Based on in silico modeling, an AUC increase of ruxolitinib of 102%, 190% or 330% is predicted when co-administered with 100 mg, 200 mg or 400 mg fluconazole, respectively. A 50% dose reduction should be considered when concomitantly administering medicinal products which are moderate inhibitors of CYP2C9 and CYP3A4. Avoid the concomitant use of JAKAVI with fluconazole doses of greater than 200 mg daily.

Due to potential drug interactions, a complete patient medication list, including investigational drug name, should be screened prior to initiation of and during treatment with investigational drug name. See Section 8.0.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

e. HOW SUPPLIED

1. Ruxolitinib is investigational for this study and will supplied free of charge by Incyte, Corporation for distribution by Catalent.

2. For this study, ruxolitinib tablets will be supplied at a strength of 5 mg. Each bottle will contain 60 tablets.

f. STORAGE, PREPARATION & STABILITY

1. Based on available stability data, ruxolitinib should be stored in tight packaging (water permeation < 5 mg/day/liter), controlled room temperature between 15°C to 30°C (59°F to 86°F) and protected from light. The immediate release drug product should be stored in high density polyethylene (HDPE) bottles with induction sealing and child-resistant closure under the storage condition of “Do not store above 30°C”. Additionally, an in-use period is assigned to all dosage strengths. The product packaging in which drug is provided from the

manufacturer/distributor meets the necessary storage requirements; no on- site repackaging is required.

g. DRUG ORDERING & ACCOUNTABILITY

1. Sites may order a starter supply of ruxolitinib at the time of local IRB approval of the protocol. Drug is not patient-specific, so one order of drug may be used for multiple patients. Sites should re-order drug as necessary based on local patient and site study needs.

   Drug may be ordered by submitting the completed Ruxolitinib Drug Order Form, according to the instructions on the form. The order form may be accessed from the protocol abstract page of the SWOG website (www.swog.org) or from the CTSU website (www.ctsu.org).

2. Drug Handling and Accountability

   a. The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return or disposal of all drugs received from the supplier using the NCI Drug Accountability Record Form (DARF) available at http://ctep.cancer.gov.

   b. Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI DARF. If the trial is a placebo control trial – indicate that separate DARFs are needed for each patient to also include the placebo drug supply.

3. Drug Return and/or Disposition Instruction

   a. Drug Returns: Unused drug supplies must NOT be returned. Unused drug must be disposed of per local institutional guidelines.

   b. Drug expiration: Indicate drug expiration date on the DARF under Manufacturer and Lot # and use the drug lots with shorter expiration date first).

4. Contact Information

   Questions about drug orders, transfers, returns, or accountability should be addressed to Jozefa Lomski at Catalent (jozefa.lomski@catalent.com).

4.0 DIAGNOSTIC CRITERIA

4.1 Diagnostic Criteria

All stages of CML require confirmation of the Philadelphia chromosome or variants of the (9;22) translocation by cytogenetics or by FISH, or patients must test positive for BCR-ABL by RT-PCR. Secondary chromosomal abnormalities in addition to the Philadelphia chromosome will not result in a change in phase of disease. Only the criteria in Section 4.2 below will be used to determine diagnosis of Chronic Phase disease. Definitions for Accelerated Phase and Blast Phase are located in protocol Section 10.2.

4.2 Chronic Phase

Chronic Phase is defined by the presence of all of the following criteria:

a. < 15% blasts in peripheral blood and bone marrow.

b. < 30% blasts plus promyelocytes in peripheral blood and bone marrow.

c. < 20% basophils in the peripheral blood. d. ≥ 100 x 109/L (≥ 100,000/mm3) platelets.

d. No evidence of extramedullary leukemic involvement, with the exception of hepatosplenomegaly.

e. If the marrow is inaspirable ("dry tap"), then all requirements in Sections 4.2a - 4.2e above must be met, except for the marrow requirements in 4.2a - b, and a bone marrow biopsy must be performed and read as consistent with chronic phase.

4.3 Risk Category Based on Hasford Score and Sokal Score

Hasford and Sokal score calculators are available at http://bloodref.com/myeloid/cml/sokal- hasford.

The risk category is determined from the Hasford Score as follows:

Score	Risk Category
Score ≤ 780	Low risk
780 < Score ≤ 1480	Intermediate risk
1,480 < Score	High risk

The risk category is determined from the Sokal Score as follows:

Score	Risk Category
Score < 0.8	Low risk
0.8 < score ≤ 1.2	Intermediate risk
1.2 < score	High risk

The advantage of using the Hasford score is that the Sokal score contains a subset of this data (age, spleen size, blast % and platelet count). Accordingly, collection of this more complete data set will allow both scores to be analyzed for prognostic information; however, whichever score was calculated at patient's initial diagnosis will be collected.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for randomization. For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the SWOG Statistics and Data Management Center in Seattle at 206/652-2267 or leukemiaquestion@crab.org prior to randomization. NCI policy does not allow for waiver of any eligibility criterion (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm).

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 7 or 21 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 Disease Related Criteria

a. Patients must have a diagnosis of chronic phase chronic myeloid leukemia without any history of progression to accelerated or blast phase CML (as defined in Section 4.0). No new bone marrow aspiration and biopsy is needed to prove diagnosis prior to randomization; however, documentation stating the patient is in chronic phase is required.

b. Patients must have detectable BCR-ABL transcripts measured by RT-PCR at a CLIA-approved laboratory and reported on the International Scale (IS) with a value of > 0.0032% IS and ≤ 1.0% IS within 21 days prior to randomization. The RT- PCR assay must have the sensitivity to detect a 4.5 log reduction in BCR-ABL transcripts from 100% IS (must be able to detect (0.0032% IS or lower).

5.2 Prior/Concurrent Therapy Criteria

a. Patients must have been on TKI therapy for CML for at least 12 months prior to randomization. Hydroxyurea prior to initiation of TKI is allowed.

b. Patients must be currently receiving treatment with bosutinib (within the allowable dose range of 200-500 mg daily), nilotinib (within the allowable dose range of 150-400 mg BID or a cumulative daily dose of 300-800 mg), imatinib (within the allowable dose range of 300-400 mg daily), or dasatinib (within the allowable dose range of 40-140 mg daily). They must have received their current TKI for a minimum of 6 months prior to randomization and must be expected to remain on the same TKI for the next 12 months.

c. Patient must not have a history of resistance to any prior TKI drug. If patient has received more than one TKI, the reason for changing treatment must have been something other than resistance or inadequate response to the prior TKI (for example, intolerance to the prior TKI) and the treatment change must have occurred ≥6 months prior to randomization.

d. Patients must not be receiving any other investigational agents.

5.3 Clinical/Laboratory Criteria

a. Patients must be ≥ 18 years of age.

b. Patients must have complete history and physical examination within 28 days prior to randomization.

c. If clinically indicated, patients must have QTcF interval < 500 ms (by Fridericia calculation) on a 12-lead EKG within 7 days prior to randomization.

$$QTcF = QT/(RR)^{0.33}$$

(QTcF = QT interval divided by the cube root of the RR [heart rate] in seconds)

d. Patients must have platelets ≥ 100,000/mm3 (100.0 x 109/L), ANC > 1,000/mm3 (1.0 x 109/L), and hemoglobin ≥ 8 g/dL within 7 days prior to randomization.

e. Patients must have ALT and AST ≤ 2.5 x IULN within 7 days prior to randomization.

f. Patients must have total bilirubin ≤ 1.5 x IULN within 7 days prior to randomization (unless the patient has a known diagnosis of Gilbert's Syndrome).

g. Patients must have a serum creatinine ≤1.5 x IULN within 7 days prior to randomization.

h. Prior malignancy is allowed providing it does not require concurrent therapy. ***Exception:*** Active hormonal therapy is allowed.

i. Patients must not be pregnant or nursing due to the teratogenic potential of the drugs used on this study. Women of child-bearing potential must have a negative serum pregnancy test within 7 days prior to randomization. Women/men of reproductive potential must have agreed to use an effective contraceptive method during treatment and for 30 days after discontinuation of study drug. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

j. Patients known to be HIV+ are eligible provided they meet all other eligibility criteria and have undetectable HIV viral loads on their most recent viral load test which must have been performed in the last 6 months.

5.4 Specimen Submission Criteria

Pre-randomization specimens for 5.4b (central BCR-ABL quantification) may be drawn at the same time or within 21 days of the specimens for 5.4a (local BCR-ABL quantification).

a. Specimens (peripheral blood) must be collected and submitted to a CLIA-approved laboratory as outlined in Section 15.1, within 21 days prior to randomization. BCR- ABL transcripts must be measured using RT-PCR and results must be reported using the International Scale. The RT-PCR assay must have the sensitivity to detect a 4.5 log reduction in BCR-ABL transcripts from 100% IS (must be able to detect0.0032% IS or lower).

b. Patients must be offered participation in submission of specimens for central BCR- ABL quantification and banking for future research. This submission is highly encouraged as an important protocol endpoint. With patient's consent, specimens must be collected as outlined in Section 15.2, within 42 days prior to randomization.

5.5 Regulatory Criteria

a. Patients ***must*** be informed of the investigational nature of this study and must sign and give informed consent in accordance with institutional and federal guidelines.

b. As a part of the OPEN registration process (see Section 13.3 for OPEN access instructions) the treating institution's identity is provided in order to ensure that

the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

6.0 STRATIFICATION FACTORS

A dynamic allocation scheme will be used to balance the randomization on the following stratification factors. *(20)*

6.1 Time on TKI therapy prior to randomization (≥ 1 and < 4 years versus ≥ 4 years). Note: This will be total time on any TKI therapy.

6.2 Current TKI (bosutinib versus dasatinib versus imatinib versus nilotinib).

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Dr. Srinivas K. Tantravahi at 801/585-9682 or Dr. Jerald Radich at 206/667-4118. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then select "About" on the menu and then click on "Policies & Procedures" and choose Policy 38).

7.1 Treatment

Refer to the NCCN guidelines for complete supportive care and prophylactic guidelines for treatment of patients with TKI (https://www.nccn.org/patients/guidelines/cml/).

Prior to initiation of protocol therapy, all patients must have serum lipase and serum amylase testing to establish baseline values. After the baseline visit, the serum lipase and the serum amylase need to be drawn and checked only on the patients taking nilotinib.

a. Arm 1: Single Agent TKI

For patients in Arm 1: Cycle 1, Day 1 is defined as the day of randomization.

Agent	Dose	Route	Day	Schedule*
Bosutinib	200-500 mg^	PO	1-90	Daily, every cycle
OR				
Dasatinib	40-140 mg^	PO	1-90	Daily, every cycle
OR				
Imatinib	300-400 mg^	PO	1-90	Daily, every cycle
OR				
Nilotinib	150-400 mg^	PO	1-90	BID, every cycle
	OR			
	Cumulative daily dose of at least 300mg^	PO	1-90	Daily, every cycle
	(total daily dose is between 300 mg – 800 mg)			

* Note: One cycle = 90 days
^ Within the outlined dose range, dose is at the discretion of the treating physician, and should be the same as the dose the patient was receiving prior to randomization. Patients who have had dose modifications prior to study enrollment may continue to be treated at the modified dose (the dose they were receiving at the time of randomization), but no further dose reductions/modifications are allowed (see Section 8.0).

b. Arm 2: TKI + Ruxolitinib

For patients in Arm 2: Cycle 1, Day 1 is defined as the first day of ruxolitinib administration. Prior to initiation of protocol therapy, patients in Arm 2 must also have lipid profile testing, to include total cholesterol, LDL cholesterol and triglycerides to establish baseline values.

Agent	Dose	Route	Day	Schedule*
Ruxolitinib	15 mg (total daily dose is 30 mg)	PO	1-90	BID, every cycle
AND				
TKI (bosutinib, dasatinib, imatinib, or nilotinib)				
Bosutinib	200-500 mg^	PO	1-90	Daily, every cycle
OR				
Dasatinib	40-140 mg^	PO	1-90	Daily, every cycle
OR				
Imatinib	300-400 mg^	PO	1-90	Daily, every cycle
OR				
Nilotinib	150-400 mg^ OR	PO	1-90	BID, every cycle
	Cumulative daily dose of at least 300 mg^ (total daily dose is between 300 mg – 800 mg)	PO	1-90	Daily every cycle

* Note: One cycle = 90 days
^ Within the outlined dose range, dose is at the discretion of the treating physician, and should be the same as the dose the patient was receiving prior to randomization. Patients who have had dose modifications prior to study enrollment may continue to be treated at the modified dose (the dose they were receiving at the time of randomization), but no further dose reductions/modifications are allowed (see Section 8.0).

7.2 Drug Compliance Documentation

Drug compliance will be recorded by patients in the Intake Calendar (see Appendices 18.1-18.5). Institutional CRAs will review and ascertain patient adherence with protocol therapy at the end of treatment for each cycle. Calendar should be kept in the patient's research chart. Sites utilizing the CIRB must use the Intake Calendar provided Sites not utilizing the CIRB may utilize institutional pill diaries or other source documentation in place of the Intake Calendar at the discretion of the treating physician.

7.3 Concomitant and Prohibited Therapies and Supportive Care

a. Concomitant Therapies

Supportive care measures will be provided per local institutional policies and procedures in accordance with NCCN guidelines.

b. Prohibited Therapies

The following should not be taken with Ruxolitinib:

- Grapefruit juice
- Potent systemic inhibitors of CYP3A4. See Appendix 18.7.
- Fluconazole doses > 200 mg

The following medications are contraindicated with TKIs, however if the patient is already taking these medications at study entry then they are allowed to continue. If they need to start one of these medications while on trial than approval must be obtained from the study chair.

Lists of CYP inhibitors or inducers are accessible from: https://drug-interactions.medicine.iu.edu/MainTable.aspx OR consult local institutional pharmacists.

TKI	Interactions
Bosutinib	• H2 antagonists or proton pump inhibitors • Potent systemic inhibitors of CYP3A4 such as but not limited to boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) • Potent systemic inducers of CYP3A4 such as but not limited to rifampin, phenytoin, carbemazepime, phenobarbital, rifabutin, dexamethasone, St John's Wort
Dasatinib	• H2 antagonists or proton pump inhibitors • Potent systemic inhibitors of CYP3A4 such as but not limited to boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) • Potent systemic inducers of CYP3A4 such as but not limited to rifampin, phenytoin, carbemazepime, phenobarbital, rifabutin,

TKI	Interactions
Imatinib	• H2 antagonists or proton pump inhibitors • Warfarin • Potent systemic inhibitors of CYP2C9, CYP2D6, and CYP3A4/5 • Potent systemic inhibitors of CYP3A4, and to a lesser extent of CYP1A2, CYP2D6, CYP2C9, and CYP2C19, such as but not limited to alfentanil, boceprevir, clarithromycin, cyclosporine, conivaptan, diergotamine, ergotamine, fentanyl, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, pimozide, posaconazole, quinidine, ritonavir, saquinavir, sirolimus, tacrolimus, telaprevir, telithromycin, voriconazole) • Potent systemic inducers of CYP3A4 such as but not limited to rifampin, phenytoin, carbemazepime, phenobarbital, rifabutin, dexamethasone, St John's Wort
Nilotinib	• H2 antagonists or proton pump inhibitors • Drugs known to prolong the QT interval • Avoid food 2 hours before and 1 hour after taking a dose • Warfarin • Potent systemic inhibitors of CYP3A4 such as but not limited to boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) • Potent systemic inducers of CYP3A4 such as but not limited to rifampin, phenytoin, carbemazepime, phenobarbital, rifabutin, dexamethasone, St John's Wort

c. Management of Ruxolitinib Withdrawal Syndrome

Following discontinuation of ruxolitinib, patients with Myelofibrosis (MF) and Polycythemia Vera (PV) have experienced recurrence of symptoms related to their myeloproliferative neoplasms over a period of approximately one week. Some patients with MF have experienced one or more of the following adverse events after discontinuing ruxolitinib: fever, respiratory distress, hypotension, DIC or multi-organ failure. If one or more of these occur after discontinuation of, or while tapering the dose of ruxolitinib, evaluate for and treat any intercurrent illness and consider restarting or increasing the dose of ruxolitinib. Patients should not interrupt or discontinue ruxolitinib without consulting their physician.

7.4 Criteria for Removal from Protocol Treatment

a. Progression of disease or treatment failure/loss of response to treatment (as defined in Sections 10.2 and 10.3).

b. Unacceptable toxicity.

c. Treatment delay (either TKI or ruxolitinib) for any reason > 28 consecutive days.

d. Patient completes 4 cycles of protocol therapy.

e. Change in TKI therapy while on protocol therapy.

f. The patient may withdraw from the protocol treatment at any time for any reason.

7.5 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Protocol Treatment Notice.

7.6 Follow-Up Period

All patients will be followed until death or 5 years after randomization, whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

a. Serious Adverse Event (SAE) reporting and Routine toxicity reporting

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 5.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0.

8.2 General Considerations

a. TKI dose modifications are allowed as outlined below and as approved by the Study Chair. For modifications made with Study Chair approval, written documentation of the approval must be obtained, kept in the patient chart, and submitted as outlined in Section 14.4.

b. Missed doses will not be made up.

c. If multiple toxicities are experienced, dose modifications will be based on the toxicity requiring the largest dose reduction.

d. Reductions are based on the dose being given at the end of the preceding cycle and are based on toxicities observed since the prior toxicity evaluation. Patients will be monitored according to NCTN guidelines; however, patients on Arm 2 (TKI + Ruxolitinib) should have toxicity evaluations every 30 days for the first cycle of protocol therapy.

e. If a drug must be permanently discontinued, the patient must be removed from protocol therapy (see Section 7.4).

f. For dose reductions of oral medications, dose should be reduced to the nearest available pill/tablet/capsule strength to the calculated reduction.

g. For infections requiring hospitalization or patients requiring transfer to an intensive care unit, discuss with the Study Chair to determine whether dose modification or removal from protocol therapy is required. Any such discussion must be documented in the patient chart.

8.3 Dose Modifications

a. Bosutinib, Dasatinib, Imatinib, and Nilotinib

In the event of the occurrence of an adverse event known to be related to TKI use, the TKI dose will be modified as per the respective label. Any additional dose modifications must be approved by the Study Chair. The dose modification should be noted on the **S1712** Treatment Form.

Patients who have had dose modifications prior to study enrollment may continue to be treated at the modified dose (the dose they were receiving at the time of randomization).

b. Ruxolitinib

1. Dose Level Table

Dose Level	Dose
0 (starting dose)	15 mg PO BID (30 mg total daily)
-1	10 mg PO BID (20 mg total daily)
-2	5 mg PO BID (10 mg total daily)
-3	Hold drug

2. Dose Modifications

a. *Thrombocytopenia or Neutropenia*

Interrupt treatment for platelets counts less than 50 x 10^9/L or absolute neutrophil count (ANC) less than 0.5 x 10^9/L.

After recovery of platelet counts to > 50 x 10^9/L and ANC to > 0.75 x 10^9/L, dosing may be restarted. The table below shows the maximum allowable dose of ruxolitinib that may be used when restarting after a dose interruption.

Current Platelet Count	Ruxolitinib Dose
75 - <100 x 10^9/L	Next lower dose level for at least 14 days and if platelets remain ≥ 75 x 10^9/L, may increase by one dose level

50 - < 75 x 10^9/L	Decrease dose level by 2 levels for at least 14 days; if platelets remain ≥ 50 x 10^9/L may increase dose by one dose level
< 50 x 10^9/L	Hold ruxolitinib

Following treatment interruption for ANC below 0.5 x 10^9/L, after ANC recovers to 0.75 x 10^9/L or greater, restart dosing at one dose level below the dose being given at the time of interruption.

b. *Dose Modifications for Anemia*

Patients with a baseline hemoglobin ≥ 10 g/dL

Hemoglobin	**Ruxolitinib Dose***
10 - < 12 g/dL	No dose reduction required
8 - < 10 g/dL	Reduce by 1 dose level for at least 14 days; if patient is asymptomatic from anemia, or if hemoglobin returns to ≥ 10 g/dL, may increase dose back up by 1 dose level.
< 8 g/dL	Hold ruxolitinib until hgb > 8g/dL then resume ruxolitinib at one dose level below the previous dose.

*Maximum doses are displayed. When restarting, begin with a dose that is one dose level below the dose being given at the time of interruption.

Patients with a baseline hemoglobin of 8-10 g/dL

If hemoglobin falls > 1 g/dL below baseline, reduce ruxolitinib by one dose level for at least 14 days. If hemoglobin returns to within
1 g/dL of baseline level, may increase ruxolitinib back to the previous dose. If hemoglobin falls > 1 g/dL again, permanently reduce ruxolitinib dose by one dose level.

c. *Dose Modifications for Non-Hematologic Toxicity*

Adverse Event Grade	**Dose Adjustments**
Any Grade 1 or 2 toxicity	No dose reduction required. Monitor patient closely and manage with supportive care as needed
Any Grade 3 toxicity*	Hold ruxolitinib until toxicity resolves to ≤ Grade 1 or baseline. May resume ruxolitinib at the previous dose or at one dose level below the previous dose at the discretion of the treating physician.
Any recurrent Grade 3 toxicity after 2 dose reductions	Discontinue ruxolitinib; remove from protocol therapy

Any Grade 4 toxicity	Dose Level -3 (hold ruxolitinib) until toxicity resolves to ≤ Grade 1 or baseline, then resume at Dose Level -1.

* Dose modifications are not required for electrolyte abnormalities that resolve, with or without intervention, to < Grade 2.

8.4 Dose Modification Contacts

For treatment or dose modification questions, please contact DrSrinivas K. Tantravahi at 8001/585-9682 or Dr. Jerald Radich at 206/667-4118.

8.5 Adverse Event Reporting Requirements

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct; and
- AEs are recorded and complete (no missing fields) and the form is query free (fields added to the form during study build do not need to be query free for the integration call with CTEP-AERS to be a success).

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form.

In the rare occurrence, that Internet connectivity is lost; a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the deep link from Medidata Rave.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

If you have questions about this process, please contact the SAE Program Manager 210- 614-8808 or email adr@swog.org.

The CTEP-AERS electronic reporting system “Help” feature has detailed instructions in the section "Submitting Reports for RAVE Users".

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse

events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol.

b. Reporting method

This study requires that expedited adverse events be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS Web-based application located at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 8.1) via CTEP-AERS. When Internet connectivity is disrupted, a 24-hour notification is to be made to SWOG by telephone at 210-614-8808 or by email at adr@swog.org. Once Internet connectivity is restored, a 24-hour notification that was made by phone or using adr@swog.org must be entered electronically into CTEP-AERS by the original submitter at the site.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event, as specified in Table 8.1 or 8.2, as applicable.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. Expedited reporting for commercial agents

Commercial reporting requirements are provided in Table 8.1. The commercial agents used in this study are dasatinib, nilotinib, imatinib and bosutinib. If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Program at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Note that while Arm 2 utilizes the same commercial agents as Arm 1, Arm 2 will not utilize the expedited reporting for commercial agent instructions, as commercial agents are not administered independently of investigational agent on Arm 2.

Table 8.1. Expedited reporting requirements for adverse events experienced by patients on study Arm 1 who have received the commercial drugs listed in 8.5e above within 30 days of the last administration of the commercial agent.

ATTRIBUTION	Grade 4		Grade 5[a]	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			**CTEP-AERS**	**CTEP-AERS**
Possible, Probable, Definite	**CTEP-AERS**		**CTEP-AERS**	**CTEP-AERS**

CTEP-AERS: Indicates an expedited report is to be submitted via CTEP-AERS within 10 calendar days of learning of the event[b]

.

a **This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.**

b **Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent within 5 calendar days by fax to 210-614-0006.**

f. Expedited reporting for investigational agents

Expedited reporting is required if the patient has received at least one dose of the investigational agent as part of the trial. Reporting requirements are provided in Table 8.2. The investigational agents used in Arm 2 of this study is ruxolitinib. If there is any question about the reportability of an adverse event or if on-line CTEP- AERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 8.2: Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a Non-CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention[1] Ruxolitinib (Arm 2)

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in Section 8.5f.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

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g. Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Late Phase 2 and Phase 3 Studies Utilizing an Agent under a non-CTEP-IND (Arms 1 and 2):

1. Group-specific instructions.

   Supporting Documentation Submission - Within 5 **calendar days** submit the following to the SWOG Operations Office by fax to 210-614-0006 or mail to the address below:
   - Printed copy of the first page of the CTEP-AERS report
   - Copies of clinical source documentation of the event
   - If applicable, and they have not yet been submitted to the SWOG Statistics and Data Management Center, and, copies of Off Treatment Notice and/or Notice of Death.

2. The adverse events listed below also require expedited reporting for this trial:
   - Grade 3 or 4 anemia requiring transfusion of packed red blood cells
   - Grade 4 thrombocytopenia requiring transfusion of platelets
   - Grade 4 neutropenia requiring ruxolitinib dose modifications

h. Reporting Secondary Malignancy, including AML/ALL/MDS

1. A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

   SWOG requires all secondary malignancies that occur following treatment with an agent under a Non-NCI IND to be reported via CTEP-AERS. Three options are available to describe the event.

   - Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
   - Myelodysplastic syndrome (MDS)
   - Treatment-related secondary malignancy

   Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

   Second Malignancy: A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

   For more information see: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

2. Any supporting documentation should be submitted to CTEP per NCI guidelines for AE reporting located at: **http://ctep.cancer.gov/protocolDevelopment/electronic_applications/d ocs/aeguidelines.pdf.**

A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 days by fax to 210-614-0006 or mail to the address below:

- a copy of the pathology report confirming the AML/ALL/MDS diagnosis
- (if available) a copy of the cytogenetics report

SWOG
ATTN: SAE Program
4201 Medical Drive, Suite 250
San Antonio, Texas 78229

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

i. Reporting Pregnancy, Fetal Death, and Death Neonatal

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)" under the Pregnancy, puerperium and perinatal conditions** SOC.

   Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Pregnancy Loss** Pregnancy loss is defined in CTCAE as "Death in utero." Pregnancy loss should be reported expeditiously as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC.

   A Pregnancy loss should **NOT** be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

3. **Death Neonatal** Death neonatal is defined in CTCAE as "Newborn death occurring during the first 28 days after birth. A neonatal death should be reported expeditiously as **Grade 4 "Death neonatal"** under the **General disorders and administration** SOC.

Neonatal death should **NOT** be reported as a Grade 5 event under the General disorders and administration SOC as currently CTEP-AERS recognizes this event as a patient death.

NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301-230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

The Pregnancy Information Form is available at:
http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm

9.0 STUDY CALENDARS

Study calendars for each treatment arm are below. Please note the following for both treatment arms:

- Forms are found on the protocol abstract page on the SWOG website (www.swog.org) and on the CTSU website (www.ctsu.org). Forms submission guidelines are found in Section 14.0.

- Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in https://www.swog.org/sites/default/files/docs/2017-10/Best%20Practices%20upddate.pdf.

9.1 Arm 1: Single Agent TKI

	Pre Reg[J]	Cycle 1 (Days 1-90)	Cycle 2 (Days 91-180)	Cycle 3 (Days 181-270)	Cycle 4 (Days 271-360)	End of Treatment Visit	Follow Up A
REQUIRED STUDIES							
History / Physical Exam	X[N]	X[N]	X	X	X	X	X
Performance Status	X						
Toxicity Notation[B]	X[N]	X[N]	X	X	X	X	X[I]
Intake Calendar[C]			X	X	X	X	
LABORATORY STUDIES							
CBC, Diff Plts[B]	X[H]	X[H]	X	X	X	X	
Comprehensive Metabolic Panel[B,D]	X	X[IH]	X	X	X	X	
Serum Lipase[L]		X[H]	X	X	X	X	X
Serum Amylase[L]		X[H]	X	X	X	X	X
Serum Pregnancy Test	X[K]						
Disease Assessment (Local BCR-ABL)[E]	X		X	X	X	X	X
X-RAYS / SCANS							
12-Lead EKG[M]	X						
SPECIMEN SUBMISSION							
Whole Blood for Central BCR-ABL & Banking	X		X	X	X	X	X
PROTOCOL TREATMENT[G]							
Bosutinib, Dasatinib, Imatinib or Nilotinib		X	X	X	X	X[G]	X[G]

Click here for Footnote.

NOTE: For patients in Arm 1: Cycle 1, Day 1 is defined as the day of randomization.

Footnotes for Calendar 9.1

A Patients will be followed for up to 5 years from initial randomization. Follow up should be per NCCN standard of care guidelines and per institutional standards. **Prior to progression:** At minimum, the patient must be seen every 3-6 months and PCR for BCR-ABL quantification must be performed. BCR-ABL quantification results will be reported according to Section 14.4c. **Post-progression:** Patients will be followed for survival and must be seen every 6 months until 2 years after registration and then annually until 5 years after registration.

B Patients on Arm 1 will be managed according to NCCN guidelines for treatment of chronic phase CML. At minimum, patients will be examined in the outpatient setting every 3 months (or more often if clinically indicated, at the discretion of the treating physician).

C CRA will review the Intake Calendar at the end of each cycle (see Appendices 18.1-18.5).

D To include measurements of ALT, AST, total bilirubin, serum creatinine, magnesium, and phosphorus.

E See Section 15.1. For pre-registration only, may be drawn within 21 days or at same time as central BCR ABL. For all other time points, must be drawn at the same time as central BCR-ABL.

F See Section 15.2. For pre-registration only, may be drawn within 21 days or at the same time of the local BCR ABL. For all other time points, must be drawn at the same time as local BCR-ABL.

G Patient will be treated with the TKI and at the dose they were receiving prior to randomization (see Section 7.1). After Cycle 4 of protocol therapy, patients will be removed from protocol therapy. After removal from protocol therapy, treatment during follow-up will be at the discretion of the treating physician (including continued single-agent TKI).

H To be completed prior to treatment on Cycle 1 Day 1 for safety assessment; however, if the test/assessment has been performed within 7 days prior to Cycle 1 Day 1, it need not be repeated prior to treatment.

I Report AEs of interest (new non-melanoma skin cancer, hepatitis reactivation, worsening of musculoskeletal pain, second malignancies, Herpes zoster, or hospital admission for sepsis) on the **S1712** Follow-up form during follow up.

J Preregistration laboratory assessments must be completed within 7 days prior to registration. See Section 5.0.

K Pregnancy testing is required for females of childbearing potential. See Section 5.3h.

L Serum amylase and serum lipase testing is required for all patients prior to treatment initiation. During the study treatment, continued serum amylase and serum lipase testing is required only for patients taking nilotinib and must be performed monthly while on protocol treatment, and per drug label, NCCN guidelines, and institutional standards during follow-up.

M If clinically indicated.

N See Section 5.3b. Patients must have toxicity notation within 28 days prior to randomization.

9.2 Arm 2: TKI + Ruxolitinib

	Pre Reg[K]	Cycle 1 (Days 1-90)	Cycle 2 (Days 91-180)	Cycle 3 (Days 181-270)	Cycle 4 (Days 271-360)	End of Treatment Visit	Follow Up [A]
REQUIRED STUDIES							
History / Physical Exam	X [P]	Monthly [P]	X	X	X	X	X
Performance Status	X						
Toxicity Notation	X [P]	Monthly [P]	X	X	X	X	X [I]
Intake Calendar [C]			X	X	X	X	
LABORATORY STUDIES							
CBC, Diff Plts [B]	X [H]	Monthly [B, H]	X	X	X	X	
Comprehensive Metabolic Panel [B, D]	X [H]	Monthly [B, H]	X	X	X	X	
Serum Lipase[N]		X[H]	X	X	X	X	X
Serum Amylase[N]		X[H]	X	X	X	X	X
Serum Pregnancy Test	X[L]						
Lipid Panel [H, M]		X					
Disease Assessment (Local BCR-ABL) E	X		X	X	X	X	X
X-RAYS / SCANS							
12-Lead EKG[O]	X	X[J]					
SPECIMEN SUBMISSION							
Whole Blood for Central BCR-ABL & Banking [F]	X		X	X	X	X	X
PROTOCOL TREATMENT [G]							
Bosutinib, Dasatinib Imatinib or Nilotinib		X	X	X	X	X **G**	X **G**
Ruxolitinib		X	X	X	X		

Click here for footnotes.
NOTE: For patients in Arm 2: Cycle 1, Day 1 is defined as the first day of ruxolitinib administration.

Footnotes: Calendar 9.2

A Patients will be followed for up to 5 years from initial randomization. Follow up should be per NCCN standard of care guidelines and per institutional standards. **Prior to progression:** At minimum, the patient must be seen every 3-6 months and PCR for BCR-ABL quantification must be performed. BCR-ABL quantification results will be reported according to Section 14.4c. **Post-progression:** Patients will be followed for survival and must be seen every 6 months until 2 years after registration and then annually until 5 years after registration.

B **Patients on Arm 2 will have CBC with differential and CMP every two weeks for the first two months of treatment and monthly thereafter for the duration of protocol treatment.** Otherwise, patients will be managed according to NCCN guidelines for treatment of chronic phase CML.

C CRA will review the Intake Calendar at the end of each cycle (see Appendices 18.1-18.5).

D To include measurements of ALT, AST, total bilirubin, serum creatinine, magnesium, and phosphorus.

E See Section 15.1. For pre-registration only, may be drawn within 21 days or at same time as central BCR ABL. For all other time points, must be drawn at the same time as central BCR-ABL.

F See Section 15.2. For pre-registration only, may be drawn within 21 days or at the same time of the as local BCR-ABL. For all other time points, must be drawn at the same time as local BCR-ABL.

G Patient will be treated with the TKI and at the dose they were receiving prior to randomization (see Section 7.1). After Cycle 4 of protocol therapy, patients will be removed from protocol therapy. After removal from protocol therapy treatment during follow-up will be at the discretion of the treating physician (including continued single-agent TKI).

H To be completed prior to treatment on Cycle 1 Day 1 for safety assessment; however, if the test/assessment has been performed within 7 days prior to Cycle 1 Day 1, it need not be repeated prior to treatment.

I Report AEs of interest (new non-melanoma skin cancer, hepatitis reactivation, worsening of musculoskeletal pain, second malignancies, Herpes zoster, or hospital admission for sepsis) on the **S1712** Follow-up form during follow up.

J For patients taking nilotinib, to be performed seven days after beginning ruxolitinib, with any dose changes and regularly during treatment at the discretion of the treating physician to assess drug interaction effects on QTc interval. This is performed for patient safety, as potential interaction of ruxolitinib with TKI is not well characterized. For patients on bosutinib, dasatinib, or imatinib, to be performed as clinically indicated.

K Preregistration laboratory assessments must be completed within 7 days prior to registration. See Section 5.0.

L Pregnancy testing is required for females of childbearing potential. See Section 5.3h.

M Patients must be fasting for at least 8 hours. Lipid panel must include total cholesterol, LDL cholesterol and triglycerides. Lipid panel must be performed 8-12 weeks after initiation of ruxolitinib therapy.

N Serum amylase and serum lipase testing is required for all patients prior to treatment initiation. During the study treatment, continued serum amylase and serum lipase testing is required only for patients taking nilotinib and must be performed monthly while on protocol treatment, and per drug label, NCCN guidelines, and institutional standards during follow-up.

O If clinically indicated.

P See Section 5.3b. Patients must have toxicity notation within 28 days prior to randomization.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

10.1 Molecular Response

RT-PCR to measure BCR-ABL transcripts will be evaluated on the peripheral blood to assess for molecular response. This will be done in commercial labs as standard of care monitoring. All labs must report the results using the International Scale (IS) and the RT-PCR assay must have the sensitivity to detect a 4.5 log reduction in BCR-ABL transcripts from 100% IS (must be able to detect at least 0.0032% IS or lower).

a. Molecular Response 4.5 (MR4.5)

The patient's BCR-ABL/BCR ratio must be at least 31,623 times (4.5 logs) smaller than100% IS, i.e., must demonstrate a 4.5-log reduction relative to 100% IS. When reported on the International Scale, this response is equivalent to a value of ≤ 0.0032%.

b. Molecular Response 4.0 (MR4.0)

The patients BCR-ABL/BCR ratio must be at least 10,000 times (4.0 logs) smaller than100% IS , i.e., must demonstrate a 4.0-log reduction relative to100% IS. When reported on the International Scale, this response is equivalent to a value of ≤ 0.01%.

c. Complete Cytogenetic Response (CCyR)

On the International Scale, this response is equivalent to a value of ≤1%.

d. Major Molecular Response (MMR)

On the International Scale, this response is equivalent to a value of ≤0.1%.

10.2 Progression

Progression to accelerated or blast phase CML at any time while on trial therapy.

a. Accelerated Phase

Accelerated Phase is defined by any of the following:

1. ≥ 15% blasts in the peripheral blood or bone marrow, but < 30% blasts in both the peripheral blood and bone marrow.

2. ≥ 30% blasts plus promyelocytes in peripheral blood and bone marrow.

3. ≥ 20% basophils in the peripheral blood.

b. Blast Phase

Blast Phase is defined by any of the following:

1. ≥ 30% blasts in peripheral blood or bone marrow.

2. Appearance of extramedullary involvement proven by biopsy (other than hepatosplenomegaly, which does not require biopsy) (e.g., chloroma).

10.3 Treatment Failure/Loss of Response**

Any of the following events occurring while a patient is continuously on TKI therapy would constitute treatment failure:

- Loss of complete cytogenetic response at any point in time.

  For patients whose pre-randomization PCR is above MMR (0.1%), a rise above 1% should be followed by a repeat PCR in 2-4 weeks. If the repeat is again above 1%, this will be considered a loss of response.

- Loss of major molecular response (MMR) at any point in time.

  In patients with a pre-randomization PCR below MMR (<0.1%), a rise above 0.1% should be followed by a repeat PCR in 2-4 weeks. If the repeat is again above 0.1%, this will be considered a loss of response.

** For treatment failure/loss of response assessment, the increase in PCR should be confirmed with a second test to be performed within 2-4 weeks of the initial test, before the patient is removed from protocol therapy.

10.4 Progression-Free Survival (PFS)

Progression-free survival is measured from the date of randomization on study until the first of treatment failure/loss of response, progression, (see Section 10.3) or death from any cause. Observations are censored at the date of last follow-up for patients last known to be alive without report of treatment failure/loss of response or progression.

10.5 Overall Survival (OS)

Overall survival will be measured for all patients from the date of randomization until death from any cause with observations censored at the date of last contact for patients last known to be alive.

10.6 Performance Status

Patients will be graded according to the Zubrod performance status scale.

POINT	DESCRIPTION
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 housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of 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.

11.0 STATISTICAL CONSIDERATIONS

11.1 Primary Endpoint: Rate of MR4.5 at 12 Months

Molecular response will be assessed pre-randomization and after each cycle of protocol therapy. Patients who achieve and then lose MR4.5 status before 12 months will be considered MR4.5 failures for the primary endpoint. Patients without 12-month MR4.5 data will be considered failures with respect to the primary endpoint. The number of patients with missing 12-month MR4.5 data will be summarized descriptively for each arm.

11.2 Study Design Justification

The primary objective of this randomized Phase II trial is to compare the rate of MR4.5 at 12 months in the combination arm with that of the single agent arm. Patients will be randomized 1:1 with randomization stratified by single-agent TKI (bosutinib versus dasatinib versus imatinib versus nilotinib) and number of prior years of single-agent therapy (≥ 1 and < 4 years versus ≥ 4 and ≤ 10 years). The investigators will also evaluate molecular response levels at 3, 6, and 9 months after randomization. For each time point, measurements collected within ±1 month of the landmark time will be used in analyses.

Based on the data from cumulative incidence of MR4.5 in the DASISION and ENESTnd trials, the study assumes a 12-month MR4.5 rate of 10% in the single agent arm (null hypothesis) and the study is powered to detect a 12-month MR4.5 rate of 35% in the combination arm (alternative hypothesis). The true conversion rate to MR4.5 may depend on how long patients have been on single-agent therapy before randomization and their current TKI, so randomization will be stratified by number of prior years of single-agent therapy (≥ 1 and < 4 years versus ≥ 4 and ≤ 10 years) and current TKI. The 25% absolute difference in MR4.5 rate (10% versus 35%) was selected as clinically significant.

Up to 37 eligible patients per arm will be accrued. After 19 patients have 12-month MR4.5 data on each arm, an interim analysis will be performed. If the MR4.5 rate in the single-agent TKI arm is higher than the MR4.5 rate in the combination arm, accrual to the trial will be stopped with the conclusion that the combination therapy does not improve 12-month MR4.5 rates. The final analysis will use a logistic regression model stratified by the randomization stratification factors. Seventy-four (74) eligible patients (37 per arm) and a one-sided significance level of 10% provide 89% power. If there is no difference in the MR4.5 rates between arms (null hypothesis), the probability of stopping the trial early is 39%. If the MR4.5 rates in the two arms are 10% (single-agent) versus 35% (combination, alternative hypothesis), the probability of stopping the trial early is 2%. Patients will be enrolled in one stage.

11.3 Secondary and Other Analyses

In each arm, overall survival and progression-free survival will be estimated using the Kaplan-Meier method. In each arm, any toxicity occurring with at least a 5% probability is likely to be observed at least once (85% probability).

In each arm, patterns of MR4.5 and MR 4.0 attainment and failure over the 3, 6, 9, and 12 months will be summarized descriptively.

Drug compliance will be summarized descriptively for each arm.

BCR-ABL/BCR will be analyzed as a quantitative endpoint, with the endpoint transformed as appropriate. Linear regression models will be used to assess associations between treatment arm and the quantitative endpoint.

11.4 Sample Size and Accrual Rate

a. Estimate of Sample Size:

74 eligible patients. If 10 patients enrolled are ineligible, a total of 84 patients will be required.

b. Estimate of Accrual Rate:

Intergroup study **S0325** for newly diagnosed CML patients enrolled 293 patients over 27 months, or approximately 11 patients per month. Based on historical data, approximately 65% of newly diagnosed CML patients could potentially be eligible for this trial one year after diagnosis. Eligible patients must have been on their current TKI for a minimum of 6 months and on any TKI for a minimum of 1 year and a maximum of 10 years at the time of enrollment. Based on this data, we estimate that we could enroll 5 patients per month on this trial and complete accrual within 1.5 years.

11.5 Data and Safety Monitoring Committee

A Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of the SWOG, 3 SWOG members, 3 non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every 6 months from the SWOG Statistics and Data Management Center, and will meet at the Group's bi-annual meetings as necessary. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study.

Toxicity will be monitored on an ongoing basis. Starting when there are at least 15 eligible patients on each arm, twice a year (for the semi-annual SWOG DSMC meeting), the study team will compare between arms the rates of Grade 3 or higher anemia, neutropenia, or thrombocytopenia possibly, probably, or definitely related to treatment. If the observed toxicity rate is more than 15% higher in the combination arm compared to the single-agent arm, the DSMC will consider early closure of the study due to excess toxicity on the combination arm. In the case that the toxicity rate is more than 15% higher in the combination arm compared to the single-agent arm, the study team may propose changes to the protocol to manage toxicities on the combination arm for DSMC review and potential approval to allow the study to continue accrual under the different management guidelines.

12.0 DISCIPLINE REVIEW

Discipline review is not necessary for this study.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patients must be registered prior to initiation of protocol treatment (no more than seven calendar days prior to planned start of treatment).

For patients in Arm 1: Cycle 1, Day 1 is defined as the day of randomization.

For patients in Arm 2: Cycle 1, Day 1 is defined as the first day of ruxolitinib administration.

NOTE: If a patient was assigned a SWOG patient ID prior to registration, that patient ID

must be used at the time of study registration. For questions about entering a previously assigned patient ID, please contact the Statistics and Data Management Center, at 206/652-2267.

13.2 Investigator/Site Registration

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet to CTEP.

13.3 CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored clinical trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr).

RCR utilizes five-person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., Roster Update Management System (RUMS), OPEN, Rave);
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	□	□			
Financial Disclosure Form	□	□	□		
NCI Biosketch (education, training, employment, license, and certification)	□	□	□		
GCP training	□	□	□		
Agent Shipment Form (if applicable)	□				
CV (optional)	□	□	□		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster;
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (i.e., Alliance).

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

13.4 CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

a. **IRB Approval:**

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval (applies to US and Canadian sites only) and on at least one participating roster;

- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

b. **Additional Requirements**

Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

c. **Downloading Site Registration Documents:**

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS). To participate, the institution and its associated investigators and staff must be associated with the LPO or a PO on the protocol.

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of your screen
  - Enter the protocol number in the search field at the top of the protocol tree, or
  - Click on the By Lead Organization folder to expand, then select *[Corresponding Organization]*, and protocol number *[NCI Protocol #]*;
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

d. **Submitting Regulatory Documents:**

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log on to the CTSU members' website Regulatory Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

e. **Checking Your Site's Registration Status:**

You can verify your site's registration status on the members' side of the CTSU website.

- Log on to the CTSU members' website;
- Click on Regulatory at the top of your screen;
- Click on Site Registration;

- Enter your 5-character CTEP Institution Code and click on Go.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks..

13.5 Oncology Patient Enrollment Network (OPEN) Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

OPEN will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Credit Investigator

f. Patient Initials

g. Patient's Date of Birth

h. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

i. Country of Residence

j. ZIP Code

k. Gender (select one):
- Female Gender
- Male Gender

l. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

m. Method of Payment (select one):
- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self Pay (No Insurance)
- No Means of Payment (No Insurance)
- Other
- Unknown

n. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White
- Unknown

All site staff will use OPEN to enroll patients to this study. Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org, https://open.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

13.6 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see below for details.

14.3 Data Submission Procedures

a. Data collection for this study will be done exclusively through the Medidata Rave® clinical data management system. Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. To access Rave via iMedidata:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account; and
- Assigned one of the following Rave roles on the relevant Lead Protocol Organization (LPO) or Participating Organization roster at the enrolling site: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.
  - To hold Rave CRA or Rave CRA (Lab Admin) role, site staff must hold a minimum of an AP registration type;
  - To hold Rave Investigator role, the individual must be registered as an NPIVR or IVR; and
  - To hold Rave Read Only role, site staff must hold an Associates (A) registration type.

If the study has a Delegation of Tasks Log (DTL), individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the “accept” link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by

clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the Rave EDC link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

b. You may also access Rave® via the SWOG CRA Workbench via the SWOG website (www.swog.org).

For difficulties with the CRA Workbench, please email technicalquestion@crab.org.

c. Institutions participating through the Cancer Trials Support Unit (CTSU), please refer to the CTSU Participation Table.

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS AFTER RANDOMIZATION:

Submit the following:

S1712 Onstudy Form

Bone marrow biopsy report confirming diagnosis (upload reports via the Source Documentation: Baseline form in Rave®)

RT-PCR report from CLIA-certified laboratory with baseline BCR-ABL transcript levels reported on the International Scale (upload reports via the Source Documentation: Baseline form in Rave®)

Specimens as outlined in Section 15.0

b. ARM 2 ONLY: WITHIN 15 DAYS AFTER EACH OF THE FOLLOWING TIME POINTS DURING CYCLE 1: WEEK 1, DAY 1; WEEK 12, DAY 1:

Submit the following:

S1712 Lipid Profile Results form

c. ARM 2 ONLY: WITHIN 15 DAYS AFTER EACH OF THE FOLLOWING TIME POINTS DURING CYCLE 1: WEEK 1, DAY 1; WEEK 3, DAY 1; WEEK 5, DAY 1; WEEK 7, DAY 1; WEEK 9, DAY 1:

Submit the following:

S1712 CBC with Differential Results form

d. WITHIN 15 DAYS AFTER EACH CYCLE OF TREATMENT**:

Submit the following:

S1712 Treatment Form

S1712 Adverse Event Form**

** For patients in Arm 2: The **S1712** Adverse Event Form is submitted MONTHLY for the first 3 months of protocol therapy.

If EKG was performed, the **S1712** EKG Results Form (Note that for Arm 2, the **S1712** EKG Results Form is required on Cycle 1, Day 8 for patients taking nilotinib.)

S1712 Disease Assessment Form

RT-PCR report from CLIA-certified lab with BCR-ABL transcript level reported on the International Scale. (Upload reports via the Source Documentation: Follow-up form in Rave®.)

Specimens as outlined in Section 15.0

e. WITHIN 28 DAYS OF DISCONTINUATION OF TREATMENT:

Submit the following:

Off Protocol Treatment Notice

Final **S1712** Treatment Form

Final **S1712** Adverse Event Form

f. WITHIN 15 DAYS OF PROGRESSION OR LOSS OF RESPONSE:

Submit the following:

S1712 Disease Assessment Form (if the patient was still on protocol treatment)

or

S1712 Follow-Up Form (if the patient was off protocol treatment) documenting date, site and method for determining progression or loss of response.

RT-PCR report from CLIA-certified lab with BCR-ABL transcript level reported on the International Scale. (Upload reports via the Source Documentation: Follow-up form in Rave®.)

If applicable, bone marrow exam, pathology, cytogenetics, mutational analysis, FISH and flow cytometry reports (whichever are performed). (Upload reports via the Source Documentation: Follow-up form in Rave®.)

g. AFTER OFF PROTOCOL THERAPY, EVERY 3-6 MONTHS* UNTIL 5 YEARS AFTER RANDOMIZATION:

Submit the following:

S1712 Follow Up Form

Late Effects Form (if prior to treatment for progression or relapse or a second primary, and prior to non-protocol treatment, the patient experiences any severe [Grade ≥ 3] long term toxicity that has not been previously reported)

* Patients will be followed per NCCN standard of care guidelines and per institutional standards. At minimum, the patient must be seen every 3-6 months and PCR for BCR-ABL quantification must be performed. BCR-ABL quantification results will be reported on the **S1712** Follow Up Form each time the quantification is performed.

h. WITHIN 28 DAYS OF KNOWLEDGE OF DEATH:

Submit the following:

Notice of Death

Forms listed in Section 14.4d (if the patient was still on protocol treatment) or **S1712** Follow-Up Form (if the patient was off protocol treatment).

15.0 SPECIAL INSTRUCTIONS

Specimen	**Pre-Reg** (within 21 days prior to registration)	**Pre-Reg** (within 42 days prior to registration)	**Cycle 2** (prior to initiation of therapy on Cycle 2)	**Cycle 3** (prior to initiation of therapy on Cycle 3)	**Cycle 4** (prior to initiation of therapy on Cycle 4)	**End of Treatment** (within 28 days after completion of therapy on Cycle 4)	**Follow Up**
Local BCR- ABL (required) ***	X		X	X	X	X	X*
Central BCR-ABL & Banking (optional for patient)		X	X	X	X	X	X**
NOTES	(Central may be drawn at same time or within 21 days of the local draw)	(Central may be drawn at same time or within 21 days of the local draw)	(Local and central must be drawn together)	(Local and central must be drawn together)	(Local and central must be drawn together)	(Local and central must be drawn together)	See footnotes

* Every 3-6 months until 5 years after randomization.
** 6 months after off protocol treatment, at the same time specimens are being drawn for local BCR-ABL quantification, if possible.
*** Local specimens are NOT submitted to the repository.

NOTE: Pre-registration specimen submissions require a patient ID prior to randomization.

To obtain a patient ID prior to registration: Use the SWOG specimen tracking system https://crawb.crab.org/TXWB/ctsulogon.aspx. Select "Specimen Tracking" and use the "Log a Specimen" link from the Specimen Tracking Home page. Use the "No Patient ID yet?" link and enter demographic information for the patient on the next page. This will assign a SWOG patient ID number which will remain the patient's ID number. If the patient does register to the study, it is important to remember to use this patient ID number on the OPEN system so the specimens will match with the correct patient. Specimens will be destroyed if the patient is not subsequently registered to the study.

Note: Testing of banked biospecimens will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

15.1 Local BCR-ABL Quantification (REQUIRED)

For pre-registration only, specimens for central BCR-ABL quantification may be collected/drawn at the same time or within 21 days of the local BCR-ABL quantification (for patients consenting to central BCR-ABL specimen submission). At every other time point, the specimens for local BCR-ABL quantification and central BCR-ABL quantification must be collected/drawn together.

Specimens for local BCR-ABL quantification by RT-PCR must be submitted to the site's preferred local CLIA-approved laboratory. The RT-PCR assay must have the sensitivity to detect a 4.5 log reduction (at least 0.0032 % IS).

a. Collect the volume of blood required by the local laboratory. Peripheral blood must be collected and submitted at the following times (see Section 9.0):

1. Pre-registration* (within 21 days prior to randomization)
2. Cycle 2 (prior to initiation of therapy on Cycle 2)
3. Cycle 3 (prior to initiation of therapy on Cycle 3)**
4. Cycle 4 (prior to initiation of therapy on Cycle 4)**
5. End of Treatment (within 28 days after completion of therapy on Cycle 4)**
6. Every 3-6 months until 5 years after randomization

* See Section 15.0 for instructions on obtaining a SWOG patient ID prior to randomization for pre-registration specimen submission.
** Only submitted if the patient completes treatment on the specified cycle.

b. Specimen Collection and Submission

Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

Sites will collect and submit specimens per local institutional standard procedures.

c. BCR-ABL Quantification Results (on the International Scale)

The BCR-ABL quantification result on the International Scale (IS) must be reported

on the appropriate eCRF in Rave and the associated report must be uploaded as a PDF file to the appropriate Source Documentation form in Rave (see Section 14.4).

15.2 Specimens for Translational Medicine (Central BCR-ABL Quantification) and Banking (Optional for Patient)

For pre-registration only, specimens for central BCR-ABL quantification may be collected/drawn at the same time or within 21 days of the local BCR-ABL quantification (for patients consenting to central BCR-ABL specimen submission). At every other time point, the specimens for local BCR-ABL quantification and central BCR-ABL quantification must be collected/drawn together.

With patient's consent, specimens for translational medicine and banking must be submitted to the SWOG Biospecimen Bank – Leukemia Division, Lab #200.

a. With patient's consent, peripheral blood must be submitted at the following times (see Section 9.0)

1. Pre-registration* (within 42 days prior to randomization)
2. Cycle 2 (prior to initiation of therapy on Cycle 2)**
3. Cycle 3 (prior to initiation of therapy on Cycle 3)**
4. Cycle 4 (prior to initiation of therapy on Cycle 4)**
5. End of Treatment (within 28 days after completion of therapy on Cycle 4)**
6. Six months after off protocol treatment, at the same time specimens are being drawn for local BCR-ABL quantification, if possible.

* See Section 15.0 for instructions on obtaining a SWOG patient ID prior to randomization for pre-registration specimen submission.
** Only submitted if the patient completes treatment on the specified cycle.

b. Specimen Collection Instructions

Collect approximately 30 mL of whole blood in EDTA vacutainer tubes (purple/lavender top) and gently invert to mix (5-10 times). No additional processing of specimens is required. Do not freeze.

Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

c. Specimen Submission Instructions

All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. Complete specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen- processing-and-submission-procedures#LeukemiaBank).If any submission instructions on the webpage are discrepant from protocol instructions, the protocol instructions should be followed.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

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:

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.

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).

Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

17.0 BIBLIOGRAPHY

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18.0 APPENDIX

18.1 Intake Calendar - Bosutinib

18.2 Intake Calendar - Dasatinib

18.3 Intake Calendar – Imatinib

18.4 Intake Calendar – Nilotinib

18.5 Intake Calendar - Ruxolitinib

18.6 Specimen Banking Instructions for the SWOG Biospecimen Bank

18.7 Drugs Known to be Metabolized by CYP450 Isoenzyme 3A4

18.1 Intake Calendar – Bosutinib

SWOG Patient ID_____ Patient Initials (L, F, M) _____ ***SWOG Study #_***

Institution/Affiliate _____ Physician _____

Instructions for the participant:
This is a monthly calendar on which you are to record the number of tablets you take each day. Be sure you have enough calendars to last until your next appointment. If you develop any side effects from the tablets, mark this on the calendar on the day you note the effect. Bring you calendars with you each time you have an appointment.

If you have questions contact: _____ Telephone: _____

Your next appointment is: _____ Date Dispensed: _____

- Bosutinib should be taken once daily with food.
- Your nurse or doctor will review your prescribed dose with you.
- Record all doses or missed doses in this pill diary.
- Tablets should be swallowed whole and not crushed, cut or broken.
- Tablets can be taken in the morning or evening but should be taken at approximately the same time.
- If a dose is missed beyond 12 hours, skip the dose and take the usual prescribed dose on the following day.
- If you miss a dose mark down as “0” and write the reason for missing your dose under the “comments” below.
- Several drugs and supplements interact with bosutinib and need to be avoided while you are taking it. Your doctor/nurse will give you a handout with complete information about what drugs and supplements to avoid that you should refer to while taking bosutinib.
- Avoid grapefruit, grapefruit juice, and supplements that contain grapefruit extract during treatment with bosutinib.
- Avoid antacid medicines.
- Open only one bottle at a time when taking out your dose. Do not transfer pills from one bottle to another.
- Store bottles at room temperature and protect from light.
- If you think you are having any side effects, feel sick, or have any other questions about your pills, please call your doctor/nurse at the number above.
- Take your doses this cycle as your doctor has written them in the special instructions below.

Special instructions: ***[Note to Investigators: Please include instructions for when to take dose, as appropriate to each patient at each visit.]***

BOSUTINIB INTAKE CALENDAR (page 1 of 3)

Date	Day	Was Dose Taken?	Total # of Tablets Taken?	Dose of Tablets	What Time?
__/ /__	**1**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**2**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**3**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**4**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**5**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**6**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**7**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**8**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**9**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**10**	□ Yes □ No		_____ mg	___:___am/pm
Comments:					
Clinician Review – date and initials					

BOSUTINIB INTAKE CALENDAR (page 2 of 3)

Date	Day	Was Dose Taken?	Total # of Tablets Taken?	Dose of Tablets	What Time?
__/ /__	**11**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**12**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**13**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**14**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**15**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**16**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**17**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**18**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**19**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**20**	□ Yes □ No		_____mg	___:___am/pm
Comments:					
Clinician Review – date and initials					

BOSUTINIB INTAKE CALENDAR (page 3 of 3)

Date	Day	Was Dose Taken?	Total # of Tablets Taken?	Dose of Tablets	What Time?
__/ /__	**21**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**22**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**23**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**24**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**25**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**26**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**27**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**28**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**29**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**30**	□ Yes □ No		_____ mg	___:___am/pm
Comments:					
Clinician Review – date and initials					

BOSUTINIB END OF CYCLE (90-DAY) INVENTORY – *FOR CLINIC USE*

Cycle _____ FINAL REVIEW AND COLLECTION NOTES:
Patient Signature:_____Date: / / ___ MD/RN Signature:_____Date: / / ____

[Note to investigators: Cycles of bosutinib are longer than 30 days, so please distribute additional calendar pages with adjusted calendar days to be as patient-friendly as possible. Please ensure that patients understand the length of the cycle that they are to take.]

18.2 Intake Calendar - Dasatinib

SWOG Patient ID_____Patient Initials (L, F, M)_____**SWOG Study #**_____

Institution/Affiliate_____Physician _____

Instructions for the participant:
The chart below is a 30-day intake calendar for dasatinib on which you are to record the number of dasatinib tablets you take each day. Be sure you have enough calendars to last until your next appointment. If you develop any side effects from the tablets, mark this on the calendar on the day you note the effect. Bring your calendars with you each time you have an appointment.

If you have questions contact:_____Telephone: _____
Your next appointment is:_____Date Dispensed: _____

- Dasatinib should be taken once daily
- Your nurse or doctor will review your prescribed dose with you.
- Record all doses or missed doses in this pill diary.
- Tablets may be taken with or without food, but should be taken with a glass of water. They should be swallowed whole and not crushed or broken. Avoid grapefruit or grapefruit juice.
- Tablets can be taken in the morning or evening but should be taken at approximately the same time each day.
- If you miss a dose mark down as “0” and write the reason for missing your dose under the “comments” below.
- If doses are missed because of side effects, they should not be made up. If vomiting occurs within 30 minutes of taking a dose, that dose may be repeated.
- You should skip doses that are missed by more than 12 hours.
- Open only one bottle at a time when taking out your dose. Do not transfer pills from one bottle to another.
- Store bottles at room temperature and protect from light.
- Bring your study pills and this diary to every clinic visit.
- If you think you are having any side effects, feel sick, or have any other questions about your pills, please call your doctor/nurse at the number above.
- Take your doses this cycle as your doctor has written them in the special instructions below.
- Several drugs and supplements interact with dasatinib and need to be avoided while you are taking it. Your doctor/nurse will give you a handout with complete information about what drugs and supplements to avoid that you should refer to while taking dasatinib.
- You should avoid grapefruit, grapefruit juice and antacids while taking dasatinib.

Special instructions: ***[Note to Investigators: Please include instructions for when to take dose, as appropriate to each patient at each visit.]***

DASATINIB INTAKE CALENDAR (page 1 of 3)

Date	Day	Was Dose Taken?	Total # of Tablets Taken?	Dose of Tablets	What Time?
__/ /__	**1**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**2**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**3**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**4**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**5**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**6**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**7**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**8**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**9**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**10**	□ Yes □ No		_____ mg	___:___am/pm
Comments:					
Clinician Review – date and initials					

DASATINIB INTAKE CALENDAR (page 2 of 3)

Date	Day	Was Dose Taken?	Total # of Tablets Taken?	Dose of Tablets	What Time?
__/ /__	**11**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**12**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**13**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**14**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**15**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**16**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**17**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**18**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**19**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**20**	□ Yes □ No		_____ mg	___:___am/pm
Comments:					
Clinician Review – date and initials					

DASATINIB INTAKE CALENDAR (page 3 of 3)

Date	Day	Was Dose Taken?	Total # of Tablets Taken?	Dose of Tablets	What Time?
__/ /__	**21**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**22**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**23**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**24**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**25**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**26**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**27**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**28**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**29**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**30**	□ Yes □ No		_____ mg	___:___am/pm
Comments:					
Clinician Review – date and initials					

DASATINIB END OF CYCLE (90-DAY) INVENTORY – *FOR CLINIC USE*

Cycle _____ FINAL REVIEW AND COLLECTION NOTES:
Patient Signature:_____Date: / / ___ MD/RN Signature:_____Date: / / ____

[Note to investigators: Cycles of dasatinib are longer than 30 days, so please distribute additional calendar pages with adjusted calendar days to be as patient-friendly as possible. Please ensure that patients understand the length of the cycle that they are to take.]

18.3 Intake Calendar - Imatinib

SWOG Patient ID_____Patient Initials (L, F, M)_____**SWOG Study #**_____

Institution/Affiliate_____Physician _____

Instructions for the participant:
The chart below is a 30-day intake calendar for imatinib on which you are to record the number of imatinib tablets you take each day. Be sure you have enough calendars to last until your next appointment. If you develop any side effects from the tablets, mark this on the calendar on the day you note the effect. Bring your calendars with you each time you have an appointment.

If you have questions contact:_____Telephone: _____
Your next appointment is:_____Date Dispensed: _____

- Imatinib should be taken once daily
- Your nurse or doctor will review your prescribed dose with you.
- Record all doses or missed doses in this pill diary.
- All doses of imatinib should be taken with a meal and a large glass of water. Imatinib can be dissolved in water or apple juice for patients having difficulty swallowing.
- Tablets can be taken in the morning or evening but should be taken at approximately the same time each day.
- If you miss a dose mark down as “0” and write the reason for missing your dose under the “comments” below.
- If doses are missed because of side effects, they should not be made up. If vomiting occurs within 30 minutes of taking a dose, that dose may be repeated.
- You should skip doses that are missed by more than 12 hours.
- Do not take any other medications 2 hours before or 2 hours after taking imatinib.
- Open only one bottle at a time when taking out your dose. Do not transfer pills from one bottle to another.
- Store bottles at room temperature and protect from light.
- Bring your study pills and this diary to every clinic visit.
- If you think you are having any side effects, feel sick, or have any other questions about your pills, please call your doctor/nurse at the number above.
- Take your doses this cycle as your doctor has written them in the special instructions below.
- Several drugs and supplements interact with imatinib and need to be avoided while you are taking it. Your doctor/nurse will give you a handout with complete information about what drugs and supplements to avoid that you should refer to while taking imatinib.
- You should avoid grapefruit, grapefruit juice and antacids while taking imatinib.

Special instructions: ***[Note to Investigators: Please include instructions for when to take dose, as appropriate to each patient at each visit.]***

IMATINIB INTAKE CALENDAR (page 1 of 3)

Date	Day	Was Dose Taken?	Total # of Tablets Taken?	Dose of Tablets	What Time?
__/ /__	**1**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**2**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**3**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**4**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**5**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**6**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**7**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**8**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**9**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**10**	□ Yes □ No		_____ mg	___:___am/pm
Comments:					
Clinician Review – date and initials					

IMATINIB INTAKE CALENDAR (page 2 of 3)

Date	Day	Was Dose Taken?	Total # of Tablets Taken?	Dose of Tablets	What Time?
__/ /__	**11**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**12**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**13**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**14**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**15**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**16**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**17**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**18**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**19**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**20**	□ Yes □ No		_____ mg	___:___am/pm
Comments:					
Clinician Review – date and initials					

IMATINIB INTAKE CALENDAR (page 3 of 3)

Date	Day	Was Dose Taken?	Total # of Tablets Taken?	Dose of Tablets	What Time?
__/ /__	**21**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**22**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**23**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**24**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**25**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**26**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**27**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**28**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**29**	□ Yes □ No		_____mg	___:___am/pm
__/ /__	**30**	□ Yes □ No		_____ mg	___:___am/pm
Comments:					
Clinician Review – date and initials					

IMATINIB END OF CYCLE (90-DAY) INVENTORY – *FOR CLINIC USE*

Cycle _____ FINAL REVIEW AND COLLECTION NOTES:
Patient Signature:_____Date: / / ___ MD/RN Signature:_____Date: / / ___

[Note to investigators: Cycles of imatinib are longer than 30 days, so please distribute additional calendar pages with adjusted calendar days to be as patient-friendly as possible. Please ensure that patients understand the length of the cycle that they are to take.]

18.4 Intake Calendar - Nilotinib

SWOG Patient ID_____Patient Initials (L, F, M)_____**SWOG Study #**_____

Institution/Affiliate_____Physician _____

Instructions for the participant:
The chart below is a 30-day intake calendar for nilotinib on which you are to record the number of nilotinib capsules you take each day. Be sure you have enough calendars to last until your next appointment. If you develop any side effects from the capsules, mark this on the calendar on the day you note the effect. Bring your calendars with you each time you have an appointment.

If you have questions contact:_____Telephone: _____
Your next appointment is:_____Date Dispensed: _____

- Nilotinib should be taken twice daily
- Your nurse or doctor will review your prescribed dose with you.
- Record all doses or missed doses in this pill diary.
- Capsules should be taken without food on an empty stomach and should be taken with a glass of water. Avoid eating food for at least two hours before and at least one hour after the dose is taken. Avoid grapefruit or grapefruit juice.
- Capsules should be swallowed whole and not crushed or broken.
- Capsules should be taken in the morning and in the evening at approximately the same time each day.
- If you miss a dose mark down as “0” and write the reason for missing your dose under the “comments” below.
- If doses are missed because of side effects, they should not be made up.
- You should skip doses that are missed by more than 6 hours.
- Do not take any other medications 2 hours before taking nilotinib.
- Open only one bottle at a time when taking out your dose. Do not transfer pills from one bottle to another.
- Store bottles at room temperature and protect from light.
- Bring your study capsules and this diary to every clinic visit.
- If you think you are having any side effects, feel sick, or have any other questions about your capsules, please call your doctor/nurse at the number above.
- Take your doses this cycle as your doctor has written them in the special instructions below.
- Several drugs and supplements interact with nilotinib and need to be avoided while you are taking it. Your doctor/nurse will give you a handout with complete information about what drugs and supplements to avoid that you should refer to while taking nilotinib.

Special instructions: ***[Note to Investigators: Please include instructions for when to take dose, as appropriate to each patient at each visit.]***

NILOTINIB INTAKE CALENDAR (page 1 of 3)

Date mm/dd/yy	DAY	Was Dose Taken?	Total # of Capsules Taken?	Dose of Capsules	What Time?
__/ /__	**1 first dose**	□ Yes □ No		mg	: am/pm
	1 second dose	□ Yes □ No		mg	___:___am/pm
__/ /__	**2 first dose**	□ Yes □ No		mg	: am/pm
	2 second dose	□ Yes □ No		mg	: am/pm
__/ /__	**3 first dose**	□ Yes □ No		mg	: am/pm
	3 second dose	□ Yes □ No		mg	: am/pm
__/ /__	**4 first dose**	□ Yes □ No		mg	: am/pm
	4 second dose	□ Yes □ No		mg	: am/pm
__/ /__	**5 first dose**	□ Yes □ No		mg	: am/pm
	5 second dose	□ Yes □ No		mg	: am/pm
__/ /__	**6 first dose**	□ Yes □ No		mg	: am/pm
	6 second dose	□ Yes □ No		mg	: am/pm
__/ /__	**7 first dose**	□ Yes □ No		mg	: am/pm
	7 second dose	□ Yes □ No		mg	: am/pm
__/ /__	**8 first dose**	□ Yes □ No		mg	: am/pm
	8 second dose	□ Yes □ No		mg	: am/pm
__/ /__	**9 first dose**	□ Yes □ No		mg	: am/pm
	9 second dose	□ Yes □ No		mg	: am/pm
__/ /__	**10 first dose**	□ Yes □ No		mg	: am/pm
	10 second dose	□ Yes □ No		mg	: am/pm
Comments:					
Clinician Review – date and initials					

NILOTINIB INTAKE CALENDAR (page 2 of 3)

Date mm/dd/yy	DAY	Was Dose Taken?	Total # of Capsules Taken?	Dose of Capsules	What Time?
__/ /__	**11 first dose**	□ Yes □ No		mg	: am/pm
	11 second dose	□ Yes □ No		mg	: am/pm
__/ /__	**12 first dose**	□ Yes □ No		mg	: am/pm
	12 second dose	□ Yes □ No		mg	: am/pm
__/ /__	**13 first dose**	□ Yes □ No		mg	: am/pm
	13 second dose	□ Yes □ No		mg	: am/pm
__/ /__	**14 first dose**	□ Yes □ No		mg	: am/pm
	14 second dose	□ Yes □ No		mg	: am/pm
__/ /__	**15 first dose**	□ Yes □ No		mg	: am/pm
	15 second dose	□ Yes □ No		mg	: am/pm
__/ /__	**16 first dose**	□ Yes □ No		mg	: am/pm
	16 second dose	□ Yes □ No		mg	: am/pm
__/ /__	**17 first dose**	□ Yes □ No		mg	: am/pm
	17 second dose	□ Yes □ No		mg	: am/pm
__/ /__	**18 first dose**	□ Yes □ No		mg	: am/pm
	18 second dose	□ Yes □ No		mg	: am/pm
__/ /__	**19 first dose**	□ Yes □ No		mg	: am/pm
	19 second dose	□ Yes □ No		mg	: am/pm
__/ /__	**20 first dose**	□ Yes □ No		mg	: am/pm
	20 second dose	□ Yes □ No		mg	: am/pm
Comments:					
Clinician Review – date and initials					

NILOTINIB INTAKE CALENDAR (page 3 of 3)

Date mm/dd/yy	DAY	Was Dose Taken?	Total # of Capsules Taken?	Dose of Capsules	What Time?
__/ /__	**21 first dose**	□ Yes □ No		mg	: am/pm
	21 second dose	□ Yes □ No		mg	: am/pm
__/ /__	**22 first dose**	□ Yes □ No		mg	: am/pm
	22 second dose	□ Yes □ No		mg	: am/pm
__/ /__	**23 first dose**	□ Yes □ No		mg	: am/pm
	23 second dose	□ Yes □ No		mg	: am/pm
__/ /__	**24 first dose**	□ Yes □ No		mg	: am/pm
	24 second dose	□ Yes □ No		mg	: am/pm
__/ /__	**25 first dose**	□ Yes □ No		mg	: am/pm
	25 second dose	□ Yes □ No		mg	: am/pm
__/ /__	**26 first dose**	□ Yes □ No		mg	: am/pm
	26 second dose	□ Yes □ No		mg	: am/pm
__/ /__	**27 first dose**	□ Yes □ No		mg	: am/pm
	27 second dose	□ Yes □ No		mg	: am/pm
__/ /__	**28 first dose**	□ Yes □ No		mg	: am/pm
	28 second dose	□ Yes □ No		mg	: am/pm
__/ /__	**29 first dose**	□ Yes □ No		mg	: am/pm
	29 second dose	□ Yes □ No		mg	: am/pm
__/ /__	**30 first dose**	□ Yes □ No		mg	: am/pm
	30 second dose	□ Yes □ No		mg	: am/pm
Comments:					
Clinician Review – date and initials					

NILOTINIB END OF CYCLE (90-DAY) INVENTORY – *FOR CLINIC USE*

Cycle _____ FINAL REVIEW AND COLLECTION NOTES:
Patient Signature:_____Date: / / ___ MD/RN Signature:_____Date: / / ____

[Note to investigators: Cycles of nilotinib are longer than 30 days, so please distribute additional calendar pages with adjusted calendar days to be as patient-friendly as possible. Please ensure that patients understand the length of the cycle that they are to take.]

18.5 Intake Calendar - Ruxolitinib

SWOG Patient ID_____Patient Initials (L, F, M)_____**SWOG Study #**_____

Institution/Affiliate_____Physician _____

Instructions for the participant:
The chart below is a 30-day intake calendar for ruxolitinib on which you are to record the number of ruxolitinib tablets you take each day. Be sure you have enough calendars to last until your next appointment. If you develop any side effects from the tablets, mark this on the calendar on the day you note the effect. Bring your calendars with you each time you have an appointment.

If you have questions contact:_____Telephone: _____
Your next appointment is:_____Date Dispensed: _____

- Ruxolitinib should be taken twice daily
- Your nurse or doctor will review your prescribed dose with you.
- Record all doses or missed doses in this pill diary.
- Tablets may be taken with or without food but should be taken with a glass of water. Avoid eating food for eat least one hour after the dose is taken. Avoid grapefruit or grapefruit juice.
- Tablets should be swallowed whole and not crushed or broken.
- Tablets should be taken in the morning and in the evening at approximately the same time each day.
- If you miss a dose mark down as “0” and write the reason for missing your dose in the comments column next to the dose that was missed.
- If doses are missed because of side effects, they should not be made up.
- You should skip doses that are missed by more than 6 hours.
- Open only one bottle at a time when taking out your dose. Do not transfer tablets from one bottle to another.
- Store bottles at room temperature and protect from light.
- Bring your study tables and this diary to every clinic visit. You will take ruxolitinib with a nurse (not at home) on the days you come in for appointments.
- Do not throw away any study capsule bottles. Your doctor or nurse will collect them.
- If you think you are having any side effects, feel sick, or have any other questions about your capsules, please call your doctor/nurse at the number above.
- Take your doses this cycle as your doctor has written them in the special instructions below.
- Several drugs and supplements interact with ruxolitinib and need to be avoided while you are taking it. Your doctor/nurse will give you a handout with complete information about what drugs and supplements to avoid that you should refer to while taking ruxolitinib.

Special instructions: ***[Note to Investigators: Please include instructions for when to take dose, as appropriate to each patient at each visit.]***

RUXOLITINIB INTAKE CALENDAR (page 1 of 3)

Date mm/dd/yy	DAY	Was Dose Taken?	Total # of Capsules Taken?	What Time?	Comments
__/ /__	**1 first dose**	□ Yes □ No		: am/pm	
	1 second dose	□ Yes □ No		: am/pm	
__/ /__	**2 first dose**	□ Yes □ No		: am/pm	
	2 second dose	□ Yes □ No		: am/pm	
__/ /__	**3 first dose**	□ Yes □ No		: am/pm	
	3 second dose	□ Yes □ No		: am/pm	
__/ /__	**4 first dose**	□ Yes □ No		: am/pm	
	4 second dose	□ Yes □ No		: am/pm	
__/ /__	**5 first dose**	□ Yes □ No		: am/pm	
	5 second dose	□ Yes □ No		: am/pm	
__/ /__	**6 first dose**	□ Yes □ No		: am/pm	
	6 second dose	□ Yes □ No		: am/pm	
__/ /__	**7 first dose**	□ Yes □ No		: am/pm	
	7 second dose	□ Yes □ No		: am/pm	
__/ /__	**8 first dose**	□ Yes □ No		: am/pm	
	8 second dose	□ Yes □ No		: am/pm	
__/ /__	**9 first dose**	□ Yes □ No		: am/pm	
	9 second dose	□ Yes □ No		: am/pm	
__/ /__	**10 first dose**	□ Yes □ No		: am/pm	
	10 second dose	□ Yes □ No		: am/pm	
Additional Comments:					
Clinician Review – date and initials					

RUXOLITINIB INTAKE CALENDAR (page 2 of 3)

Date mm/dd/yy	DAY	Was Dose Taken?	Total # of Capsules Taken?	What Time?	Comments
__/ /__	**11 first dose**	□ Yes □ No		: am/pm	
	11 second dose	□ Yes □ No		: am/pm	
__/ /__	**12 first dose**	□ Yes □ No		: am/pm	
	12 second dose	□ Yes □ No		: am/pm	
__/ /__	**13 first dose**	□ Yes □ No		: am/pm	
	13 second dose	□ Yes □ No		: am/pm	
__/ /__	**14 first dose**	□ Yes □ No		: am/pm	
	14 second dose	□ Yes □ No		: am/pm	
__/ /__	**15 first dose**	□ Yes □ No		: am/pm	
	15 second dose	□ Yes □ No		: am/pm	
__/ /__	**16 first dose**	□ Yes □ No		: am/pm	
	16 second dose	□ Yes □ No		: am/pm	
__/ /__	**17 first dose**	□ Yes □ No		: am/pm	
	17 second dose	□ Yes □ No		: am/pm	
__/ /__	**18 first dose**	□ Yes □ No		: am/pm	
	18 second dose	□ Yes □ No		: am/pm	
__/ /__	**19 first dose**	□ Yes □ No		: am/pm	
	19 second dose	□ Yes □ No		: am/pm	
__/ /__	**20 first dose**	□ Yes □ No		: am/pm	
	20 second dose	□ Yes □ No		: am/pm	
Additional Comments:					
Clinician Review – date and initials					

RUXOLITINIB INTAKE CALENDAR (page 3 of 3)

Date mm/dd/yy	DAY	Was Dose Taken?	Total # of Capsules Taken?	What Time?	Comments
__/ /__	**21 first dose**	□ Yes □ No		: am/pm	
	21 second dose	□ Yes □ No		: am/pm	
__/ /__	**22 first dose**	□ Yes □ No		: am/pm	
	22 second dose	□ Yes □ No		: am/pm	
__/ /__	**23 first dose**	□ Yes □ No		: am/pm	
	23 second dose	□ Yes □ No		: am/pm	
__/ /__	**24 first dose**	□ Yes □ No		: am/pm	
	24 second dose	□ Yes □ No		: am/pm	
__/ /__	**25 first dose**	□ Yes □ No		: am/pm	
	25 second dose	□ Yes □ No		: am/pm	
__/ /__	**26 first dose**	□ Yes □ No		: am/pm	
	26 second dose	□ Yes □ No		: am/pm	
__/ /__	**27 first dose**	□ Yes □ No		: am/pm	
	27 second dose	□ Yes □ No		: am/pm	
__/ /__	**28 first dose**	□ Yes □ No		: am/pm	
	28 second dose	□ Yes □ No		: am/pm	
__/ /__	**29 first dose**	□ Yes □ No		: am/pm	
	29 second dose	□ Yes □ No		: am/pm	
__/ /__	**30 first dose**	□ Yes □ No		: am/pm	
	30 second dose	□ Yes □ No		: am/pm	
Additional Comments:					
Clinician Review – date and initials					

RUXOLITINIB END OF CYCLE (90-DAY) INVENTORY – *FOR CLINIC USE*

Cycle _____ Tablet bottle(s) returned? Yes / No (circle one) # of tablets returned (to be completed by RN or MD) FINAL REVIEW AND COLLECTION NOTES:
Patient Signature:_____Date: / / _ MD/RN Signature:_____Date: / /

[Note to investigators: Cycles of ruxolitinib are longer than 30 days, so please distribute additional calendar pages with adjusted calendar days to be as patient-friendly as possible. Please ensure that patients understand the length of the cycle that they are to take.]

18.6 Specimen Banking Instructions for the SWOG Biospecimen Bank

Specimen Receipt, Processing, and Storage
Upon receipt, the SWOG Biospecimen Bank will process peripheral blood. At pre-registration, the whole blood will be processed for plasma and peripheral blood mononuclear cells (PBMCs) using a ficoll-hypaque gradient. At all other time points, the whole blood will be processed for plasma and white blood cells using a red blood cell lysing technique. Plasma will be stored in 1-mL aliquots in a -80°C freezer. PBMCs and white blood cells are aliquoted in 1×10^7 cells per vial with freezing media, and stored in a liquid nitrogen freezer in vapor phase until distribution.

The Central BCR-ABL specimens for translational medicine, at the six months after off protocol treatment timepoint, will not be banked.

At the end of the study, the SWOG Statistics and Data Management Center will notify the Bank to distribute specimens. Frozen cell vials will be distributed for BCR-ABL in one batch to:

Radich Laboratory
Fred Hutchinson Cancer Research
Center 1100 Fairview Avenue N, D4-385
Seattle, WA 98109
E-mail: jradich@fredhutch.org

18.7 Drugs Known to be Metabolized by CYP450 Isoenzyme 3A4

CYP3A3/4	
Substrates	
Acetaminophen	Chlorpromazine
Aifentanil	Cimetidine
Alosetron	Cisapride
Alprazolam	Citałopram
Amiodarone	Clarithromycin
Amitriptyline (minor)	Clindamycin
Amlodipine	Clomipramine
Anastrozole	Clonazepam
Androsterone	Clozapine
Antipyrine	Cocaine
Astemizole	Codeine (demethylation)
Atorvastatin	Cortisol
Benzphetamine	Cortisone
Bepridil	Cyclobenzaprine (demethylation)
Bexarotene	Cyclophosphamide
Bromazepam	Cyclosporine
Bromocriptine	Dapsone
Budesonide	Dehydroepiandrostendione
Bupropion (minor)	Delavirdine
Buspirone	Desmethyldiazepam
Busutfan	Dexamethasone
Caffeine	Dextromethorphan (minor, N-demethylation)
Cannabinoids	
Carbamazepine	Diazepam (minor; hydroxylation, N-demethylation)
Cevimeline	
Cerivastatin	
Digitoxin	Nefazodone
Diltiazem	Nelfinavir
Disopyramide	Nevirapine
Docetaxel	Nicardipine
Dolasetron	Nifedipine
Donepezil	Niludipine
Doxorubicin	Nimodipine
Doxycycline	Nisoldipine
Dronabinol	Nitrendipine
Enalapril	Omeprazole (sulfonation)
Erylhromycin	Ondansetron
Estradiol	Oral contraceptives
Ethinyl estradiol	Orphenadrine
Ethosuximide	Paclitaxel
Etoposide	Pantoprazole
Exemestene	Pimozide
Dofetilide (minor)	Pioglitazone
Felodipine	Pravastatin
Fentanyl	Prednisone
Fexotenadine	Progesterone
Finaxteride	Proguanil
Fluoxetine	Propafenone

FLUTAMIDE	
Substrates	
Glyburide	Quercetin
Granisetron	Quetiapine
Halofantrine	Quinidine
Hydrocortixone	Quinine
Hydroxyarginine	Repaglinide
Ifosfamide	Retinoic acid
Imipramine	Rifampin
Indinavir	Risperidone
Isradipine	Ritonavir
Itraconazole	Salmeterol
Ketoconazole	Saquinavir
Lansoprazole (minor)	Sertindole
Letrozole	Sertraline
Levobupivicaine	Sibutramine
Lidocaine	Sildenafil citrate
Loratadine	Simvastatin
Losartan	Sirolimus
Lovastatin	Sufentanil
Methadone	Tacrolimus
Mibefradil	Tamoxifen
Miconazole	Temazepam
Midazolam	Teniposide
Mifepristone	Terfenadine
Mirtazapine (N-demethylation)	Testosterone
Montelukast	Tetrahydrocannabinol
Navelbine	Theophylline
	Tiagabine
Toremifene	Tolterodine
Trazodone	Vincristine
Tretinoin	Warfarin (R-warfarin)
Triazolam	Yohimbine
Troglitazone	Zaleplon (minor pathway)
Troleandomycin	Zatoestron
Venlafaxine (N-demethylation)	Zileuton
Verapamil	**Ziprasidone**
Vinblastine	Zolpidem
	Zonisamide
INDUCERS	
Carbamazepine	Phenytoin
Dexamethasone	Primidone
Ethosuximide	Progesterone
Glucocorticoids	Rifabutin
Griseofulvin	Rifampin
Nafcillin	Rofecoxib (mild)
Nelfinavir	St John's wort
Nevirapine	Sulfadimidine
Oxcarbazepine	Sulfinpyrazone
Phenobarbital	Troglitazone
Phenylbutazone	
INHIBITORS	

Amiodarone	Ketoconazole
Anastrozole	Metronidazole
Azithromycin	Mibefradil
Cannabinoids	Miconazole (moderate)
Cimetidine	Nefazodone
Clarithromycin	Nelfinavir
Clotrimazole	Nevirapine
Cyclosporine	Norfloxacin
Danazol	Norfluoxetine
Delavirdine	Omeprazole (weak)
Dexamethasone	Oxiconazole
Diethyldithiocarbamate	Paroxetine (weak)
Diltiazem Dirithromycin	Propoxyphene
Disulfiram	Quinidine
Entacapone (high dose)	Quinine
Erythromycin	Quinupristin and dalfopristin
Ethinyl estradiol	Ranitidine
Fluconazole (weak)	Ritonavir
Fluoxetine	Saquinavir
Fluvoxamine	Sertindole
Gestodene	Sertraline
Grapefruit juice	Troglitazone
Indinavir	Troleandomycin
Isoniazid	Valproic acid (weak)
Itraconazole	Verapamil
	Zafirlukast
	Zileuton

(Adapted from Cytochrome P-450 Enzymes and Drug metabolism. In : Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 8th ed. Hudson, OH; LexiComp Inc. 2000: 1364-1371)