SWOG CANCER RESEARCH NETWORK

Version Date: August 16, 2021

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS; CTSU

FROM: SWOG Operations Office (Email: protocols@swog.org)

RE: **S1318**, "A Phase II Study of Blinatumomab (NSC-765986) and POMP (Prednisone, Vincristine, Methotrexate 6-Mercaptopurine) for Patients ≥ 65yYears of Age with Newly Diagnosed Philadelphia-Chromosome Negative (Ph-) Acute Lymphoblastic Leukemia (ALL) and of Dasatinib (NSC-732517), Prednisone and Blinatumomab for Patients ≥ 65 Years of Age with Newly Diagnosed Philadelphia-Chromosome Positive (Ph+) ALL and Philadelphia-Chromosome-Like Signature (Ph-like) ALL (Newly Diagnosed or Relapsed/Refractory) With Known or Presumed Activating Dasatinib-Sensitive Mutations or Kinase Fusions (DSMKF)."

Study Chairs: Drs. Anjali Advani, Kristen O'Dwyer, and Brent Wood

REVISION #15

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IRB Review Requirements
(√) Expedited review allowed

Protocol changes
(√) Other: Study Calendar Clarifications

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of the CIRB posting of this notice.

Sites not using the NCI CIRB: Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice.

REVISION #15

The above referenced protocol has been revised as follows:

1. The Version Date has been revised in the Protocol and the Model Consent Form. No additional changes were made to the Model Consent Form.

2. Section 9.4: The timing of assessments/treatment on the calendar was updated from Days 8-15 to Days 8-14, from Days 16-21 to Days 15-21, and from Days 67-70 to Days 64-70.

3. Section 9.6: On the calendar an 'X' was added to the Serum for Immunogenicity procedure during the Pre TX timepoint.

4. Section 15.2a.3: This specimen submission time point was updated to clarify that it is "within 30 days *after* last dose of blinatumomab."

This study has been reviewed and approved by the NCI's Central Institutional Review Board (CIRB).

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL AND INFORMATION OFFICE
Diane Feldman – Alliance
Sally Vanture – ECOG-ACRIN
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PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY

Activated January 12, 2015

SWOG

A PHASE II STUDY OF BLINATUMOMAB (NSC-765986) AND POMP (PREDNISONE, VINCRISTINE, METHOTREXATE, 6-MERCAPTOPURINE) FOR PATIENTS ≥ 65 YEARS OF AGE WITH NEWLY DIAGNOSED PHILADELPHIA-CHROMOSOME NEGATIVE (PH-) ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) AND OF DASATINIB (NSC-732517), PREDNISONE AND BLINATUMOMAB FOR PATIENTS ≥ 65 YEARS OF AGE WITH NEWLY DIAGNOSED PHILADELPHIA-CHROMOSOME POSITIVE (PH+) ALL, RELAPSED/REFRACTORY PHILADELPHIA-CHROMOSOME POSITIVE (PH+) ALL, AND PHILADELPHIA-CHROMOSOME-LIKE SIGNATURE (PH-LIKE) ALL (NEWLY DIAGNOSED OR RELAPSED/REFRACTORY) WITH KNOWN OR PRESUMED ACTIVATING DASATINIB-SENSITIVE MUTATIONS OR KINASE FUSIONS (DSMKF)

NCT #02143414

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AGENTS:

IND-Exempt Agents:

6-Mercaptopurine (NSC-755)
Dexamethasone (Decadron)(NSC-34521)
Methotrexate (NSC-740)
Prednisone (NSC-10023)
Vincristine (Oncovin) (NSC-67574)

NCI Supplied Investigational Agents

Blinatumomab (NSC-765986)
Dasatinib (BMS-354825) (NSC-732517)

(NCI Sponsored Clinical Trial)

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NRG/NRG Oncology
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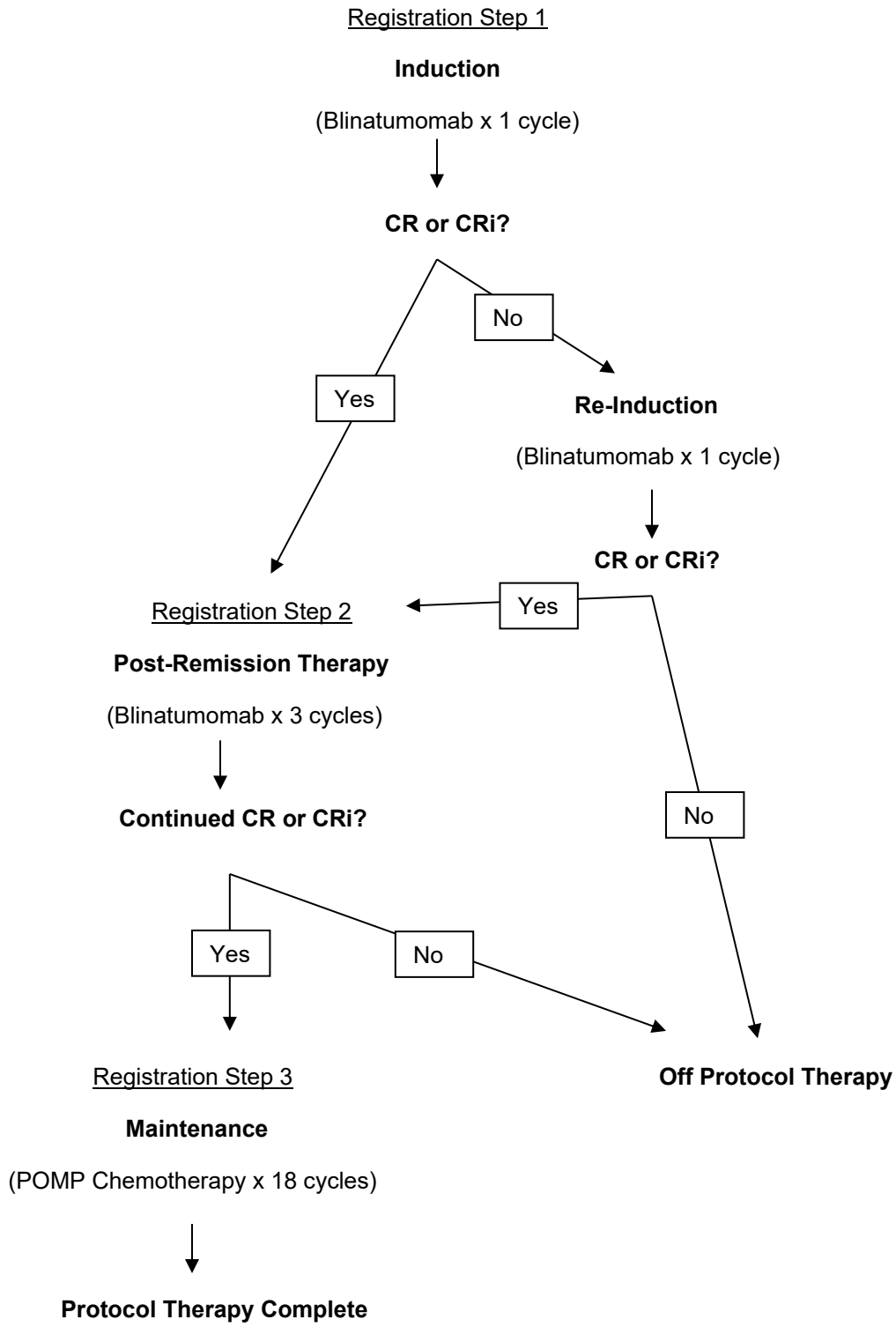
CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

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 Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 866-651-2878 to receive further information and support. Contact the CTSU Regulatory Help Desk at 866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which 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 Other Tools and Reports: Institutions participating through the CTSU continue to have access to other tools and reports available on the SWOG Workbench via the SWOG website (www.swog.org).
The most current version of the study protocol and all related forms and 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. Sites must use the current form version and adhere to the instructions and submission schedule outlined in the protocol. CTSU sites should follow procedures outlined in the protocol for Site registration, Patient Enrollment, Adverse Event Reporting, Data Submission (including ancillary studies), and Drug Procurement.		
For patient eligibility 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 at S1318SC@swog.org.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU HelpDesk 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.		
For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website: https://www.ctsu.org		
The CTSU Web site is located at https://www.ctsu.org		

SCHEMA

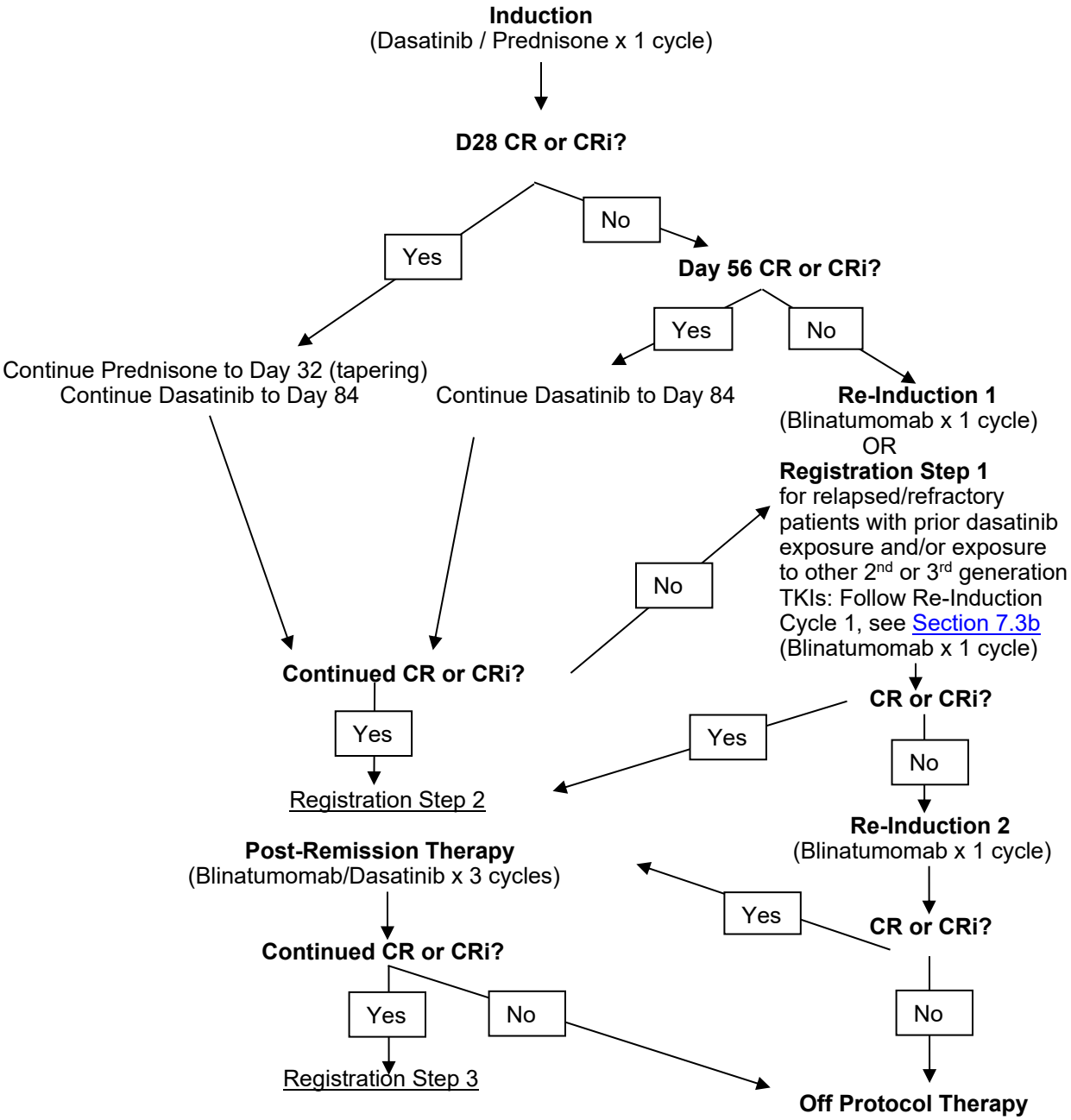
Cohort 1 – Philadelphia Chromosome Negative (Ph-) Patients:



Cohort 2 – Philadelphia Chromosome Positive (Ph+) Patients, Relapsed/Refractory Ph+ Patients, and Ph-like DSMKF Patients:

Registration Step 1

(Newly-diagnosed patients and relapsed/refractory patients who are naive to both dasatinib and other 2nd/3rd generation TKIs)



1.0 OBJECTIVES

1.1 Primary Objectives

a. To evaluate the 3-year overall survival rate in elderly patients with newly diagnosed Ph-negative ALL treated with blinatumomab followed by POMP maintenance.

b. To evaluate in a preliminary manner (feasibility study) the safety of dasatinib-steroid based induction followed by blinatumomab treatment in combination with dasatinib followed by dasatinib-based maintenance in patients with newly diagnosed, Ph-positive ALL, relapsed/refractory Ph-positive ALL, and Ph-like DSMKF ALL (newly-diagnosed relapsed or refractory).

1.2 Secondary Objectives

a. To evaluate toxicities in these patient populations treated with these regimens.

b. To estimate the rates of complete response (CR), complete remission with incomplete count recovery (CRi) and disease-free survival in Ph-negative patients.

c. To estimate disease-free and overall survival in Ph-positive ALL and Ph-like DSMKF ALL.

d. To estimate in each cohort the rate of minimal residual disease (MRD) negativity, and the time to achieve MRD negativity (exploratory analysis).

To determine whether anti-idiotype antibodies directed against blinatumomab develop with blinatumomab treatment in this study.

1.3 Additional Translational Medicine Objectives

a. To estimate the incidence of the Ph-like signature in elderly patients (≥ 65 years of age) with newly diagnosed Philadelphia-chromosome negative ALL (see Appendix 18.15).

b. To estimate the incidence of the various tyrosine-kinase fusions, making up the Ph-like signature in elderly patients with newly diagnosed Philadelphia-chromosome negative ALL (see Appendix 18.15).

c. To evaluate outcomes (EFS and OS) in patients with the Ph-like signature versus those without the Ph-like signature in Ph-negative ALL (see Appendix 18.15).

2.0 BACKGROUND

Intensive combination chemotherapy remains the standard of care for adult patients with acute lymphoblastic leukemia (ALL). Older adults with ALL (defined as patients aged > 60 years) have been difficult to treat with this conventional chemotherapy, however, and the five-year survival rate is estimated at 6-12%. (1*)* During the past decade, multiple clinical trials have attempted to improve upon the survival of adults with ALL with early dose intensification of myelosuppressive agents, but despite very intensive therapies, none have resulted in improvement in overall survival in the elderly cohort. *(2,3,4,5,6,7,8)* Thus, the incorporation of new agents to ALL therapy for older patients is a priority. The **S1318** protocol proposes to improve the overall survival of older patients with de novo ALL by utilizing a novel chemo-immunotherapy regimen. The hypothesis is that targeting the B-cell surface antigen CD19 with blinatumomab will result in increased leukemia cytotoxicity with limited nonspecific toxicity, and thus will lead to improvement in overall survival in older adult patients with ALL.

Rationale for Study Design

An early trial of dose intensification for adult patients with ALL was the Cancer and Leukemia Group B's **CALGB-8811**. *(9)* This study evaluated an intensive five-drug regimen for adults with newly diagnosed ALL, similar to the five-drug induction regimen used by the Children's Cancer Group study for high-risk childhood ALL. *(10)* In this study, 197 patients were enrolled, of whom 18 were aged ≥ 60 years. The induction treatment regimen was intensified by adding a single dose of cyclophosphamide (1,200 mg/m^2) on Day 1 to three days of daunorubicin, weekly vincristine, bi-weekly L-asparaginase and three weeks of prednisone. Patients who entered remission proceeded to consolidation treatment, which was modified by increasing the dose of cyclophosphamide from 600 to 1000 mg/m^2 and adding 2 weeks of vincristine and L asparaginase. Early intensification (Course II) included two months of treatment with cyclophosphamide, subcutaneous cytarabine, oral 6-mercaptopurine (6-MP), vincristine, L-asparaginase and intrathecal methotrexate (MTX). Course III included central nervous system prophylaxis with cranial irradiation, five weekly doses of intrathecal MTX, and daily 6-MP, followed by interim maintenance with daily oral 6-MP and weekly oral MTX. Late intensification (Course IV) included 8 weeks of doxorubicin, vincristine, dexamethasone, cyclophosphamide, 6-thioguanine and subcutaneous cytarabine. Prolonged maintenance (Course V) continued until 24 months from the time of diagnosis and included daily 6-MP, weekly oral methotrexate, and monthly pulses of vincristine and prednisone ("POMP").

Initially, per the terms of the study, no dose reductions or treatment delays were permitted for myelosuppression alone, but after one year of accrual to the study, dose reductions (one-third dose reduction for cyclophosphamide and daunorubicin, and prednisone therapy was shortened to 1 week) were implemented for patients older than 60 years due to treatment related mortality in induction of 50%, compared to a TRM of 8% for patients 30 to 59 years of age, and 1% for patients less than 30 years of age. Remission induction was achieved in 39% of patients 60 years and older, 85% of patients between the ages of 30 and 59 years, and 94% of patients less than 30 years old. After a median follow-up of 43 months, the estimates of the proportion surviving at 3 years were significantly associated with age, with 69% surviving for patients <30 years of age, 39% for patients 30-59 years of age, and only 17% for patients ≥ 60 years. Overall, this intensive chemotherapy regimen produced a high-remission rate, and durable remissions in younger adults, but older adults continued to experience significant morbidity and mortality, mostly due to infection.

The CALGB study **CALGB-9111** investigated whether filgrastim (granulocyte colony stimulating factor [G-CSF]) could reduce the infectious complications of the intense induction chemotherapy developed in **CALGB-8811**. *(11)* This trial randomized 198 adults with ALL, of whom 41 were aged ≥ 60 years, to receive G-CSF (5 mcg/kg/d) or placebo beginning on Day 4 of the induction regimen developed in **CALGB-8811** and continuing until the absolute neutrophil count >1000/mcL for 2 days. *(12)* The patients who received G-CSF in induction continued with G-CSF during the two monthly courses of consolidation chemotherapy. The remission induction rate was 77% for patients ≥ 60 years and 87% for patients < 60 years. For the 21 patients ≥ 60 years assigned to G-CSF treatment, the remission rate was 81%, and the TRM was 10%. For the 20 patients ≥ 60 years assigned to placebo, the remission rate was 55%, and the TRM was 25%. For patients < 60 years of age, the remission rate was 89% with G-CSF and 83% with placebo, and the TRM was 4% and 8% respectively. The remission rate for the older adults is improved in **CALGB-9111** as compared to **CALGB-8811**, and likely reflects fewer total induction deaths due to the introduction of dose reductions of cyclophosphamide, daunorubicin and prednisone in this age group. The estimates of the proportion surviving at 3 years were still significantly associated with age when compared to **CALGB-8811**, with 57% surviving for patients < 30 years of age, 40% for patients 30-59 years of age, and only 17% for patients ≥ 60 years. Overall, the use of G-CSF did not decrease overall toxicity and there was no significant difference in disease-free survival or overall survival for the patients assigned to G-CSF as compared to placebo.

Data from the most recent CALGB Phase II study (**CALGB-19802)** evaluated whether dose intensification of daunorubicin during induction and cytarabine during consolidation could improve disease-free survival for adult patients with ALL. *(13)* This CALGB trial enrolled 161 patients, of whom 33 were aged ≥ 60 years. The treatment consisted of 6 monthly courses of therapy that alternated vincristine, prednisone, cyclophosphamide, daunorubicin and L-asparaginase with high-

doses of cytarabine and methotrexate, and intrathecal chemotherapy, followed by 18 months of "POMP" maintenance chemotherapy. *(14)* The dose intensification of daunorubicin for the patients aged > 60 years was 60 mg/m^2 for 3 daily doses (prior daunorubicin doses for older patients enrolled in **CALGB-8811** and **CALGB-9111** was 30 mg/m^2 for 3 daily doses), while cyclophosphamide was omitted. Remission induction was achieved in 61% of patients, but 5-year disease free survival (DFS) was 10%, and the 5-year overall survival was 6% in the older cohort. Further, the reported treatment related mortality (TRM) for the entire cohort of **CALGB-19802** was 13%, but for patients older than 60 years, the treatment-related death was 21%. *(15)* This study concluded that adults older than 60 years of age showed no benefit to dose intensification of daunorubicin, and the overall survival remained very poor at 6%.

The international MRC UKALL XII/**ECOG-2993** study analyzed a cohort of 100 older adults (defined as age 55-65 years) and compared their outcomes to the 1,814 younger patients. *(16)* All patients were treated with a two-stage 4-drug induction therapy and 3 cycles of intensification with high-dose methotrexate and L-asparaginase. Patients were then randomized to post-remission consolidation consisting of 4 cycles combining cytarabine, etoposide, vincristine and dexamethasone, followed by POMP maintenance, or autologous transplantation. Remission induction was achieved in 73% of older adults, as compared to 93% of adults <55 years. *(17)* Significantly more infections were reported in the older group during induction chemotherapy 81% versus 70%. There were many more dose reductions in the older patients 14% versus younger patients 5%. In addition, there were more dose omissions, with asparaginase being the drug that was most commonly omitted, and treatment delays in the older group. *(18)* The TRM was 18% in this older age group and 4% in the younger age group. Overall outcomes were worse in the older group as well. The 5-year overall survival was 21% in the older adults versus 41% in the younger adults. *(19)* Five-year overall survival for those patients who achieved CR was also inferior in the older group versus the younger adults, 30% versus 44%, respectively. It is worth noting that in this study, older patients were defined as those between 55 and 65 years, whereas in the CALGB series the older patients included patients up to age 82. It is very likely that the treatment related toxicities and outcomes are more pronounced in a cohort > 65 years, and thus, in part, may explain the inferior outcome observed in the CALGB series.

The University of Texas - MD Anderson Cancer Center (MDACC) reported the outcomes of 122 patients aged ≥ 60 years with newly diagnosed ALL that received alternating Hyper-CVAD and high dose cytarabine and methotrexate. *(20)* This cohort was compared to 34 older patients who received less intense ALL regimens (prehyper-CVAD) and 409 younger patients (≤ 60 years) who received hyper-CVAD. Remission induction was achieved in 84% of older patients receiving hyper-CVAD, 59% in older patients receiving prehyper-CVAD, and 92% of younger patients receiving hyper-CVAD. The treatment related mortality rates were 10%, 12%, and 2%, respectively. Nearly all of the deaths that occurred during induction were related to infection. *(21)* The intensity of the therapy was effective, however, with the incidence of disease resistance during induction only 5% in the older group treated with hyper-CVAD as compared to 27% of the older patients who received prehyper-CVAD. For all patients who achieved a CR, death in CR occurred in 34% of older patients treated with hyper-CVAD, 15% of patients treated with prehyper-CVAD, and 7% of younger patients treated with hyper-CVAD. Among the deaths that occurred in the older patients treated with hyper-CVAD, the majority (63%) were caused by infections. *(22)* The 5-year survival for older patients on hyper-CVAD improved to 20% compared to 9% for older patients treated with prehyper-CVAD. The 5-year survival for younger patients was 48%. So although the outcome in the elderly cohort improved with the dose-intensification of Hyper-CVAD, the investigators observed that the incidence of death in CR from myelosuppression-associated infections increased, and thus concluded that the ultimate cause of treatment failure changed from disease recurrence to death in CR because of myelosuppression associated complications.

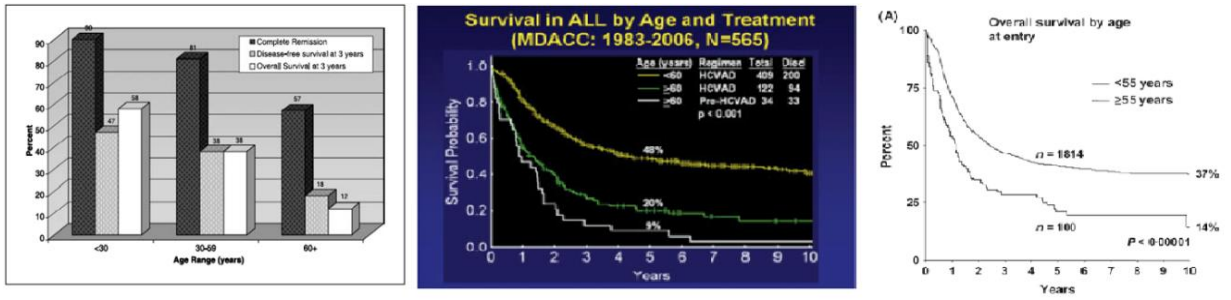


Figure 1: Outcome for older and younger patients with ALL showing (A) Treatment outcome by age for 759 adults with ALL enrolled on CALGB studies between 1988 and 2002; (B) Survival by age and treatment for patients treated at MDACC; and (C) Overall survival of patients by age enrolled in MRC UKALL XII/**ECOG2003** trial. *(23,24,25)*

Taken together, these data from CALGB, MRC/ECOG and MDACC, as well as multiple retrospective analysis and population-based studies (see Section 18.10) underscore the limitation of intensive chemotherapy in older adults and the need to develop novel regimens with selective anti leukemia activity in older adults with de novo ALL.

The development of antibody-based therapy that target B cell specific antigens, such as anti-CD20 monoclonal antibody (Rituximab), and the anti-CD22 monoclonal antibody (Epratuzumab), have been incorporated into ALL therapy, both as initial therapy and in salvage regimens. *(26,27,28)* A novel antibody drug conjugate, Inotuzumab ozogamicin, which is an anti-CD22 monoclonal antibody bound to calicheamicin, has been used as a single agent in the relapsed/refractory disease settings, and a large international Phase III study in adults is ongoing (NCT01564784). *(29)*

More recently, the CD19 antigen, which is expressed on the surface of virtually all B-ALL cells, has been emerging as a new therapeutic target. Blinatumomab is a bi-specific antibody that engages the T cell and the malignant B cell by binding to both CD19 and CD3 (BiTE). The BiTE is hypothesized to cause interaction between the malignant B lymphoblasts and native T cells, resulting in cell-mediated cytotoxicity.

Blinatumomab has demonstrated impressive clinical results in patients with minimal residual disease (MRD) positive ALL and in relapsed/refractory ALL. Topp et al. demonstrated an 80% rate of complete molecular remission in patients with relapsed or persistent MRD positive ALL. *(30)* A subsequent Phase II trial in adult patients demonstrated a 69% rate of complete remission or complete remission with partial hematologic recovery in patients with relapsed or refractory ALL. (17) The most recent international multicenter Phase 2 study in adult patients with relapsed or refractory ALL demonstrated significant clinical activity with 43% of patients achieving a complete response (CR) or CR with partial hematologic recovery (CRh). (31) Overall, blinatumomab has been well tolerated with the most significant treatment-related adverse events being neurologic toxicities in 50% of patients and the Cytokine Release Syndrome (CRS) in 11% of patients Grade 3 or higher neurologic toxicities occurred in 15% of patients and included seizures, encephalopathy, and cerebellar toxicity (balance and coordination disorders). Grade 3 or higher CRS occurred in 1% of patients. The most frequent treatment-related adverse reactions (>20%) were pyrexia (62%), headache (36%), peripheral edema (25%), febrile neutropenia (25%), nausea (25%), hypokalemia (23%), rash (21%), and constipation (20%). The toxicity profile and response rate associated with blinatumomab in relapsed B-ALL patients suggest that this agent could improve outcomes in previously untreated B-ALL patients who are older than 65 years of age.

This Phase II study will test the hypothesis that outcomes in older adults, defined as 65 years of age or older, with de novo Philadelphia chromosome negative ALL will be superior with the blinatumomab and low-dose POMP maintenance chemotherapy as compared to historical experience of standard multi-agent chemotherapy. Given the dismal outcome and the significant

toxicity seen with standard chemotherapy regimens in the elderly population, the investigators believe that a single arm Phase II study is a reasonable approach to evaluate blinatumomab in combination with low-dose chemotherapy and will provide sufficient information as to whether blinatumomab should be further studied.

The goals of our proposed study are to (1) improve the CR rate, disease-free survival, and overall survival of elderly patients with Philadelphia-chromosome negative B-ALL by using an induction treatment regimen of blinatumomab and intrathecal chemotherapy followed by low dose POMP maintenance chemotherapy (prednisone, vincristine, methotrexate, 6-mercaptopurine). POMP maintenance chemotherapy for 2-3 years is a standard part of ALL therapeutic regimens, and omission of maintenance therapy has been associated with shorter disease-free survival rates. *(32,33);* And (2) to improve the disease-free survival and overall survival of older patients with Philadelphia-chromosome positive ALL by using a treatment induction regimen of dasatinib/prednisone, followed by post-remission therapy with blinatumomab/dasatinib, and maintenance therapy with dasatinib/prednisone. CNS prophylaxis with intrathecal chemotherapy is included in each cycle of therapy.

Accrual will be limited to patients 65 years of age or older, in order to avoid competing with patients being considered for **E1910** (randomized Phase III ECOG study of Philadelphia chromosome negative ALL patients up to age 70 years). There is an industry-sponsored (Talon Pharmaceutical) Phase III study of standard ALL chemotherapy with either vincristine or liposomal vincristine (Marqibo) for previously untreated, older ALL patients. This proposed study would not compete with that Phase III study since the Phase III study of Marqibo will target patients eligible to receive intensive ALL chemotherapy regimens.

Rationale for Cohort 2 (Ph+ Patients and Ph-like DSMKF Patients)

Cohort 2 (the Ph+ / Ph-like DSMKF cohort) will have a maximum of 20 evaluable patients. Therefore, the rationale is best explained as a feasibility Phase II, rather than one of estimating outcome. This cohort will be studied as a Phase II feasibility to inform whether inclusion of this group would be advisable in late stage Phase II and III trials of Ph+ ALL using blinatumomab and the tyrosine kinase inhibitor, dasatinib. The study will be limited to a maximum of 6 patients with early stopping rules, and based on favorable safety evaluation, the study will allow for an additional expansion of the cohort to 14 more evaluable patients. The objective is to evaluate the safety of blinatumomab in combination with dasatinib and dexamethasone, and a study of 20 patients can provide that information for subsequent study design, but will not provide the kind of outcome data that will inform practice.

Patients with Philadelphia chromosome positive ALL represent a distinct cohort of patients, with biological and clinical features that set it apart from other subtypes of ALL and require specific treatment. Historically, the diagnosis of Ph-positive ALL denoted an inferior prognosis than other forms of B-ALL. With the addition of tyrosine kinase inhibitors, several approaches have been studied, including a chemotherapy-free treatment based on TKI and steroids with complete response rates that are close to 100% and a 5-year overall survival approaching 40%. *(34,35)* Moreover, the most recent studies have shown improvement in survival rates > 60%. *(36)* However, due to the frequent occurrence of mutations bearing resistance to TKIs and a high incidence of relapse, allogeneic hematopoietic stem cell transplant remains the standard of care for these patients. Relapsed/refractory Ph-positive ALL also remains a significant clinical problem, and the outcomes are extremely poor with reported 5-year overall survival rate of 7%. *(37)* These patients are difficult to salvage because most have chemotherapy-refractory disease. For that reason, one benefit of CD19 directed therapy using blinatumomab is the potential to overcome chemotherapy resistance. Therefore, inclusion of CD19 directed therapy in combination with TKIs for patients with relapsed disease may represent an effective salvage regimen.

There is limited data for the use of blinatumomab in Ph+ALL, however; only two patients with Ph+ALL were included in the first Phase II trial of blinatumomab, and no patients with Ph-positive ALL were enrolled in the larger Phase II study. *(38,39)* The MD Anderson Cancer Center recently reported a retrospective analysis of 12 patients with relapsed/refractory Ph+ ALL who received

blinatumomab and dasatinib and concluded that the combination was safe and generally well-tolerated. *(40)* Currently, in the United States, the only other open clinical trial evaluating the use of frontline treatment of blinatumomab with TKI in Ph-positive ALL is at MD Anderson Cancer Center. The relapsed/refractory Ph-positive ALL patient population has been included to provide additional data to inform whether blinatumomab and dasatinib combinatorial therapy should be further studied in this patient population.

Likewise, since the incidence of ALL is rare, patients with Ph-like dasatinib-sensitive kinase mutations or kinase fusions have also been included to provide additional options and data to better inform future decisions regarding further study of this combinatorial therapy in this population. Moreover, the addition of both populations is anticipated to increase the overall accrual rate for this cohort.

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.

Ethnic Category	Females	Males	Total
Hispanic or Latino	3	4	7
Not Hispanic or Latino	25	26	51
Total Ethnic	28	30	58
Racial Category			
American Indian or Alaskan Native	1	2	3
Asian	2	1	3
Black or African American	3	4	7
Native Hawaiian or other Pacific Islander	1	1	2
White	21	22	43
Racial Category: Total of all Subjects	28	30	58

Note that gender accrual distribution is based on SWOG's historical accrual data and may not be indicative of the current/actual accrual to this study, as there is no known data indicating that ALL is more common in males than in females.

3.0 DRUG INFORMATION

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

For this study, 6-mercaptopurine, methotrexate, prednisone and vincristine are commercially available; therefore, Investigator Brochures are not applicable to these drugs. Information about commercial drugs is publicly available in the Physician's Desk Reference (PDR), prescribing information and other resources.

For this study, blinatumomab and dasatinib are investigational and are being provided under INDs held by the National Cancer Institute. The current versions of the Investigator Brochures for the agents will be accessible to site investigators and research staff through the PMB Online Agent Ordering Processing (OAOP) application (http://ctep.cancer.gov/branches/pmb/agent_order_processing.htm). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB coordinator via e-mail (ibcoordinator@mail.nih.gov).

3.1 6-Mercaptopurine (NSC-755)

a. PHARMACOLOGY

Mechanism of Action

6-Mecaptopurine (6MP) is an antimetabolite chemically known as 1,7-dihydro-6H-purine-6-thione monohydrate, an analogue of the purine bases, adenine and hypoxanthine. 6MP competes with hypoxanthine and guanine for the enzyme, hypoxanthine-guanine phosphoribosyltransferase (HGPRT). 6MP is converted to thioinosinic acid (TIMP) by HGPRT. The conversion to TIMP inhibits inosinic acid conversion to xanthylic acid and adenylic acid. TIMP also inhibits glutamine-5-phosphoribosylpyrophosphate amidotransferase, the first enzyme unique to the de novo pathway for purine ribonucleotide synthesis.

b. PHARMACOKINETICS

Absorption: Variable and incomplete (~50%)

Distribution: CNS penetration is poor

Metabolism: Hepatic and in GI mucosa; hepatically via xanthine oxidase and methylation via TPMT to sulfate conjugates, 6-thiouric acid, and other inactive compounds

Elimination: Elimination half-life is 2 hours

c. ADVERSE EFFECTS

1. Possible Side Effects of 6-Mercaptopurine:

Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions. The most frequently reported adverse reactions occurring in greater than 20% of patients are hepatotoxicity, rash, anorexia, and malaise. Adverse effects reported in 4 to 20 % of patients include pain, intestinal ulceration, drug fever, infection, myelosuppression, leukopenia, anemia, thrombocytopenia, and oligospermia. Rare but serious events occurring in less than or equal to 3% of patients include pancreatitis, hepatic encephalopathy, pulmonary fibrosis, and secondary malignancies.

2. Pregnancy and Lactation:

Pregnancy Category D. It is not known whether 6-Mercaptopurine is excreted in human breast milk.

3. Drug Interactions:

Due to potential drug interactions, a complete patient medication list, including 6-Mercaptopurine, should be screened prior to initiation of and during treatment with 6-Mercaptopurine. See Section 8.0 Toxicities to be Monitored and Dosage Modifications.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

e. HOW SUPPLIED

6-Mercaptopurine is commercially available and will not be supplied. Refer to the current FDA-approved package insert for the most comprehensive and up to date information.

f. STORAGE, PREPARATION & STABILITY

Refer to the current FDA-approved package insert.

3.2 Blinatumomab (AMG103, MT103) (NSC-765986)

a. PHARMACOLOGY

Blinatumomab is classified as a bispecific T-cell engaging antibody with a molecular weight of ~ 55 kDa.

Mechanism of Action: Through CD3 binding, blinatumomab recruits and engages T cells for redirected lysis of CD19-positive B cells, including those expressed with B-cell malignancies. T cells are bound by its anti-CD3 moiety, whereas B cells are bound by the anti-CD19 moiety. The subsequent serial lysis of multiple malignant cells by a single blinatumomab-activated T cell closely resembles a natural cytotoxic T cell reaction. Treatment with blinatumomab is associated with a rapid depletion of peripheral B cells, accompanied by T cell activation and a transient increase in cytokine.

Description: Blinatumomab is a fusion protein composed of two single-chain antibodies (scFv), murine anti-CD19 scFv and murine anti-CD3 scFv.

b. ADVERSE EFFECTS

1. Adverse Events: 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* 996 *patients.* Below is the CAEPR for Blinatumomab (AMG 103).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.5, September 4, 2019[1]

Adverse Events with Possible Relationship to Blinatumomab (AMG 103) (CTCAE 5.0 Term) [n= 1276]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 2)***
	Blood and lymphatic system disorders - Other (coagulopathy)[2]		***Blood and lymphatic system disorders - Other (coagulopathy)[2] (Gr 2)***
		Blood and lymphatic system disorders - Other (hematophagic histiocytosis)	
		Blood and lymphatic system disorders - Other (lymphadenitis)	
		Blood and lymphatic system disorders - Other (lymphadenopathy)	
		Blood and lymphatic system disorders - Other (pancytopenia)	
	Disseminated intravascular coagulation[2,3]		***Disseminated intravascular coagulation[2,3] (Gr 2)***
	Febrile neutropenia		***Febrile neutropenia (Gr 3)***
CARDIAC DISORDERS			
	Sinus tachycardia		***Sinus tachycardia (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 2)***
		Gastric hemorrhage	
		Gastrointestinal disorders - Other (pneumoperitoneum)	
	Mucositis oral		

Adverse Events with Possible Relationship to Blinatumomab (AMG 103) (CTCAE 5.0 Term) [n= 1276]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Nausea			***Nausea (Gr 2)***
		Oral hemorrhage	
		Pancreatitis	
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills[3]		***Chills[3] (Gr 2)***
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue[3]			***Fatigue[3] (Gr 2)***
Fever[3]			***Fever[3] (Gr 2)***
	Generalized edema		
	Non-cardiac chest pain		
	Pain		
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (hepatic function abnormal)[4]		***Hepatobiliary disorders - Other (hepatic function abnormal)[4] (Gr 2)***
IMMUNE SYSTEM DISORDERS			
		Allergic reaction[3]	
	Cytokine release syndrome[3]		***Cytokine release syndrome[3] (Gr 3)***
	Immune system disorders - Other (immunodeficiency [immunoglobulin decreased])[5]		***Immune system disorders - Other (immunodeficiency [immunoglobulin decreased])[5] (Gr 2)***
INFECTIONS AND INFESTATIONS			
Infection[6]			***Infection[6] (Gr 4)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction		
		Injury, poisoning and procedural complications - Other (overdose)[7]	
INVESTIGATIONS			
		Activated partial thromboplastin time prolonged[2]	
	Alanine aminotransferase increased[4]		***Alanine aminotransferase increased[4] (Gr 3)***

Adverse Events with Possible Relationship to Blinatumomab (AMG 103) (CTCAE 5.0 Term) [n= 1276]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Alkaline phosphatase increased[4]		***Alkaline phosphatase increased[4] (Gr 2)***
	Aspartate aminotransferase increased[4]		***Aspartate aminotransferase increased[4] (Gr 4)***
	Blood bilirubin increased[4]		***Blood bilirubin increased[4] (Gr 2)***
	Blood lactate dehydrogenase increased		
		Creatinine increased[8]	
	GGT increased[4]		***GGT increased[4] (Gr 2)***
		Investigations - Other (blood fibrinogen increased)[2]	
	Investigations - Other (C-reactive protein increased)		***Investigations - Other (C-reactive protein increased) (Gr 2)***
	Investigations - Other (fibrin D dimer increased)[2]		
Lymphocyte count decreased			***Lymphocyte count decreased (Gr 4)***
Neutrophil count decreased			***Neutrophil count decreased (Gr 4)***
Platelet count decreased[2]			***Platelet count decreased[2] (Gr 2)***
	Weight gain		***Weight gain (Gr 2)***
	Weight loss		
	White blood cell decreased		***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Hyperglycemia		***Hyperglycemia (Gr 2)***
	Hyperuricemia		
	Hypoalbuminemia		
	Hypocalcemia		
Hypokalemia			***Hypokalemia (Gr 2)***
	Hypomagnesemia		
	Hypophosphatemia		
		Tumor lysis syndrome[9]	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		

Adverse Events with Possible Relationship to Blinatumomab (AMG 103) (CTCAE 5.0 Term) [n= 1276]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Back pain		***Back pain (Gr 2)***
	Bone pain		
	Generalized muscle weakness		
	Myalgia		
	Pain in extremity		***Pain in extremity (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Ataxia[10]		
	Cognitive disturbance[10]		
	Dizziness[10]		***Dizziness[10] (Gr 2)***
		Dysarthria[10]	
	Dysphasia[10]		
	Encephalopathy[10]		
		Facial nerve disorder[10]	
Headache[10]			***Headache[10] (Gr 2)***
		Intracranial hemorrhage	
		Leukoencephalopathy	
	Memory impairment[10]		
	Nervous system disorders - Other (apraxia)		
	Nervous system disorders - Other (cerebellar syndrome)[10]		
		Nervous system disorders - Other[10]	
	Paresthesia[10]		
		Reversible posterior leukoencephalopathy syndrome	
	Seizure[10]		
	Somnolence[10]		
		Transient ischemic attacks[10]	
	Tremor[10]		***Tremor[10] (Gr 2)***
PSYCHIATRIC DISORDERS			
		Agitation[10]	
	Anxiety[10]		
	Confusion[10]		

Adverse Events with Possible Relationship to Blinatumomab (AMG 103) (CTCAE 5.0 Term) [n= 1276]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Hallucinations[10]	
	Insomnia		***Insomnia (Gr 2)***
		Personality change[10]	
		Psychosis[10]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		
	Epistaxis		
		Hypoxia	
	Oropharyngeal pain		
		Pneumonitis	
	Voice alteration[10]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Hyperhidrosis		
	Pruritus		
	Skin and subcutaneous tissue disorders - Other (rash)[11]		***Skin and subcutaneous tissue disorders - Other (rash)[11] (Gr 2)***
VASCULAR DISORDERS			
		Capillary leak syndrome[3]	
	Flushing[3]		
	Hypertension[3]		***Hypertension[3] (Gr 2)***
	Hypotension[3]		***Hypotension[3] (Gr 2)***
	Thromboembolic event[2]		***Thromboembolic event[2] (Gr 2)***

[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]Blinatumomab (AMG 103) is known to cause a variety of adverse events associated with coagulopathy which may include: Activated partial thromboplastin time prolonged, Disseminated intravascular coagulation, Fibrinogen decreased, INR increased, Investigations - Other (blood fibrinogen increased), Investigations - Other (fibrin D dimer increased), Investigations - Other (activated partial thromboplastin time shortened), Investigations - Other (antithrombin III decreased), Investigations - Other (coagulation factor XII level decreased), Investigations - Other (coagulation factor XIII level increased), Investigations - Other (haptoglobin decreased), Investigations - Other (protein S decreased), Platelet count decreased, and Thromboembolic events.

[3]Symptoms of cytokine release syndrome (CRS) and/or allergic reaction may include chills, fever, fatigue, flushing, bronchospasm, and hypotension. In some cases, disseminated intravascular coagulation (DIC), capillary leak syndrome (CLS), and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) have been reported in the setting of CRS.

[4]Symptoms of hepatic dysfunction may include Alanine aminotransferase increased, Alkaline phosphatase increased, Aspartate aminotransferase increased, Blood bilirubin increased, and GGT increased under the INVESTIGATIONS SOC.

[5]Immunodeficiency (immunoglobulin decreased) includes immunoglobulins decreased, blood immunoglobulin G decreased, blood immunoglobulin M decreased, and blood immunoglobulin A decreased.

[6]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[7]Overdoses have been observed. Overdoses resulted in adverse reactions, which were consistent with the reactions observed at the recommended therapeutic dose and included fever, tremors, and headache. In the event of overdose, interrupt the infusion, monitor the patient for signs of toxicity, and provide supportive care. Consider re-initiation of blinatumomab at the correct therapeutic dose when all toxicities have resolved and no earlier than 12 hours after interruption of the infusion.

[8]Acute kidney injury (acute renal failure) is associated with increased creatinine levels.

[9]Tumor lysis syndrome is defined as a massive overload of potassium, phosphate, uric acid, plus hypocalcemia, potentially causing lethal cardiac arrhythmias and/or renal failure.

[10]Blinatumomab (AMG103) is known to cause a variety of nervous system disorders which may include: Ataxia, Cognitive disturbance, Concentration impairment, Depressed level of consciousness, Dizziness, Dysphagia, Dysarthria, Dysesthesia, Dysphasia, Encephalopathy, Facial nerve disorder, Headache, Lethargy, Memory impairment, Paresthesia, Peripheral sensory neuropathy, Seizure, Somnolence, Syncope, Transient ischemic attacks, Tremor, Voice alteration, Nervous system disorders - Other (allodynia), Nervous Systems disorders - Other (cerebellar syndrome), Nervous system disorders - Other (dysgraphia), Nervous system disorders - Other (epilepsy), Nervous system disorders - Other (facial palsy), Nervous system disorders - Other (hemiparesis), Nervous system disorders - Other (hypertonia), Nervous system disorders - Other (hypotonia), Nervous system disorders - Other (pleocytosis), and Nervous system disorders - Other (polyneuropathy). Additionally, symptoms of some nervous system disorders are adverse events under the PSYCHIATRIC DISORDERS SOC and may include: Agitation, Anxiety, Confusion, Hallucinations, Personality change, and Psychosis.

[11]Rash includes rash, rash maculo-papular, erythema, local erythema, erythematous rash, generalized rash, exanthema, allergic dermatitis, and palmar-plantar erythrodysesthesia syndrome.

Adverse events reported on blinatumomab (AMG 103) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that blinatumomab (AMG 103) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Pericardial effusion; Sinus bradycardia; Supraventricular tachycardia
CONGENITAL, FAMILIAL AND GENETIC DISORDERS - Congenital, familial and genetic disorders - Other (aplasia)
EAR AND LABYRINTH DISORDERS - Vertigo
EYE DISORDERS - Blurred vision; Optic nerve disorder; Papilledema; Periorbital edema; Photophobia
GASTROINTESTINAL DISORDERS - Abdominal distension; Anal mucositis; Dyspepsia; Dysphagia
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Gait disturbance; General disorders and administration site conditions - Other (thrombosis in device); Hypothermia; Malaise; Multi-organ failure
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Vascular access complication
INVESTIGATIONS - Cardiac troponin I increased; Electrocardiogram QT corrected interval prolonged; INR increased; Investigations - Other (hypoproteinemia); Investigations - Other (lipase decreased); Lipase increased; Lymphocyte count increased
METABOLISM AND NUTRITION DISORDERS - Acidosis; Dehydration; Hypercalcemia; Hyperkalemia; Hyperphosphatemia; Hyponatremia; Metabolism and nutrition disorders - Other (fluid overload)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Muscle cramp; Neck pain
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Leukemia secondary to oncology chemotherapy; Treatment related secondary malignancy
NERVOUS SYSTEM DISORDERS - Amnesia; Facial muscle weakness; Muscle weakness left-sided; Nervous system disorders - Other (difficulty following commands); Neuralgia
PSYCHIATRIC DISORDERS - Delirium; Depression; Psychiatric disorders - Other (altered mental status); Psychiatric disorders - Other (sleep disorder); Restlessness
RENAL AND URINARY DISORDERS - Acute kidney injury[7]; Hematuria; Proteinuria; Urinary incontinence
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Genital edema
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Bronchospasm[3]; Pleural effusion; Productive cough; Pulmonary edema; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (chronic obstructive pulmonary disease)

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Purpura; Skin and subcutaneous tissue disorders - Other (skin irritation)
VASCULAR DISORDERS - Hematoma

Note: Blinatumomab (AMG 103) 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: Formal drug interaction studies have not been conducted with blinatumomab.

3. Patient Care Implications: The effect of blinatumomab on fertility has not been evaluated. Blinatumomab is not recommended in pregnant women and in women of childbearing potential not using contraception. It is not known whether blinatumomab or its metabolites are excreted in human milk. Women are not allowed to breastfeed while receiving blinatumomab. Monitor patients for cytokine release syndrome, tumor lysis syndrome, and infusion reaction. Refer to protocol for specific recommendation. Monitor patients for psychiatric events such as confusion, disorientation, and cognitive attention disturbances. Patients should not drive or operate dangerous machinery while receiving blinatumomab.

c. DOSING & ADMINISTRATION

1. See Section 7.0 Treatment Plan

2. Use a central line to administer the final blinatumomab prepared IV solution as a continuous infusion. **Do not flush the IV line** as it will create an IV bolus to be administered into the patient.

3. All infusion interruptions must be recorded. Technical or logistical interruption must be as minimal as possible and re-start the infusion as soon as possible. If an interruption is longer than four hours, the re-start of the infusion must take place in the hospital under supervision of the investigator. Monitor patients for potential adverse events as described in Section 3.2 of this protocol.

d. HOW SUPPLIED

1. Blinatumomab and IV solution stabilizer for blinatumomab will be supplied free of charge by Amgen and distributed by NCI/DCTD.

2. Blinatumomab is available as a **38.5 mcg** preservative-free, white to off-white lyophilized powder for injection in 4 mL single-use vial. The agent is formulated with 3.68 mg citric acid monohydrate, 105 mg trehalose dihydrate, and 25.55 mg lysine hydrochloride, and 0.70 mg polysorbate 80, pH 7. The stopper of the vial is **latex free**.

3. IV solution stabilizer for blinatumomab (NSC 773150) is not for reconstitution of blinatumomab. The solution is available as a 10 mL single-use vial, preservative-free, clear, colorless-to-slightly yellow liquid solution. Each solution consists of 25 mM citric acid monohydrate, 1.25 M L-lysine hydrochloride, and 0.1% (w/v) polysorbate 80, pH 7. The stopper of the vial is latex free.

e. STORAGE, PREPARATION & STABILITY

1. Store intact vials of blinatumomab and IV solution stabilizer of blinatumomab refrigerated at 2-8°C (36°-46°F) and protect from light.

2. Only trained staff may prepare blinatumomab IV solution. Sites' standard procedure for compounding blinatumomab must be in compliance with the USP <797> guidelines (ISO Class 5 or better). Use aseptic technique and prepare blinatumomab IV solution under a qualified laminar flow hood.

IV Bags / IV Infusion Sets:
- IV bags: Polyolefin/polyethylene, ethylene vinyl acetate (EVA) or PVC non-DEHP
- IV Infusion sets: PVC Non-DEHP with 0.2 µm inline filter

Infusion Pump:
- Use programmable pump that is approved by the appropriate regulatory authority for the country in which the subject is undergoing treatment.
- Pump alarm must be visual and auditory.
- Pump must be lockable.
- **Elastomeric pumps are NOT allowed.**
- CADD Infusion pumps are allowed.

Reconstitute blinatumomab lyophilized powder to a final concentration of 12.5 mcg/mL.

To reconstitute blinatumomab lyophilized powder (38.5 mcg/vial):

a) Add 3 mL of Sterile Water for Injection (SWI) to the vial to yield 3.08 mL of blinatumomab at a final concentration of **12.5 mcg/mL**.

b) Rotate the vial to dissolve all powder. Do not shake.

c) The stability of the reconstituted vial is 4 hours at room temperature (22°-27°C) or 24 hours refrigerated at 2° to 8°C.

Following the reconstitution of the vial, blinatumomab needs to be further diluted prior to administration. The final IV solution must be prepared in the following order:

(1) First, add 0.9% NaCl to the IV bag;

(2) next, add the IV solution stabilizer for blinatumomab;

(3) last, add the calculated dose (mL) of blinatumomab to the solution.

The total volume of blinatumomab IV solution will account for the volume of the IV infusion set for the inpatient or outpatient setting.

INPATIENT: (24-hour IV bag): Infusion rate = 10 mL/hr over 24 hrs		
	Volume to be prepared	Volume to be infused
24-hour IV bag	1. Add calculated volume of 0.9% NaCl(mL)[1] into approved IV bag 2. Add **5.4 mL** IV solution **stabilizer** for blinatumomab [2] 3. Add blinatumomab calculated dose volume per 270 mL bag(mL)[3]	240 mL
	270 mL total volume[4]	

[1] 0.9% NaCl (mL) = total volume to be prepared (270 mL) – stabilizer solution volume (5.4 mL) – blinatumomab calculated dose volume (mL) per 270 mL bag

[2] stabilizer solution (5.4 mL) = 0.02 x total volume to be prepared (270 mL)

[3] blinatumomab calculated dose volume per 270 mL bag (mL) = daily dose (mcg) ÷ volume (240 mL) to be infused x total volume to be prepared (270 mL) ÷ 12.5 mcg/mL of blinatumomab vial concentration

[4] total volume (270 mL) = Volume to be infused (240 mL) + 30 mL f for inpatient IV infusion volume

OUTPATIENT (24-hour infusion): Infusion rate = 10 mL/hr over 24 hours		
	Volume to be prepared	Volume to be infused
24-hour IV bag	1. Add calculated volume of 0.9% NaCl(mL)[1] into approved IV bag 2. Add **5.4 mL** IV solution stabilizer for blinatumomab[2] 3. Add blinatumomab calculated dose volume per 270 mL bag(mL)[3]	**240 mL**
	270 mL total volume [4]	

[1] 0.9% NaCl (mL) = total volume to be prepared (270 mL) – stabilizer solution volume (5.4 mL) – blinatumomab calculated dose volume (mL) per 270 mL bag

[2] stabilizer solution (5.4 mL) = 0.02 x total volume to be prepared (270 mL)

[3] blinatumomab calculated dose volume per 270 mL bag (mL) = 24 hour dose (mcg) ÷ volume to be infused (240 mL) x total volume to be prepared (270 mL) ÷ 12.5 mcg/mL of blinatumomab vial concentration

[4] total volume (270 mL) = Volume to be infused (240 mL) + 30 mL for outpatient IV infusion volume

OUTPATIENT (48-hour infusion): Infusion rate = 5 mL/hr over 48 hours		
	Volume to be prepared	Volume to be infused
48-hour IV bag	1. Add calculated volume of 0.9% NaCl(mL)[1] into approved IV bag 2. Add **5 mL** IV solution **stabilizer** for blinatumomab[2] 3. Add blinatumomab calculated dose volume per 250 mL bag(mL)[3]	**240 mL**
	250 mL total volume[4]	

[1] 0.9% NaCl (mL) = total volume to be prepared (250 mL) – stabilizer solution volume (5 mL) – blinatumomab calculated dose volume (mL) per 250 mL bag
[2] stabilizer solution (5 mL) = 0.02 x total volume to be prepared (250 mL)
[3] blinatumomab calculated dose volume per 250 mL bag (mL) = 48 hour dose (mcg) ÷ volume to be infused (240 mL) x total volume to be prepared (250 mL) ÷ 12.5 mcg/mL of blinatumomab vial concentration
[4] total volume (250 mL) = Volume to be infused (240 mL) + 10 mL for outpatient IV infusion volume

OUTPATIENT (72-hour infusion): Infusion rate = 3.3 mL/hr over 72 hrs		
	Volume to be prepared	Volume to be infused
72-hour IV bag	1. Add calculated volume of 0.9% NaCl(mL)[1] into approved IV bag 2. Add **5 mL** IV solution **stabilizer** for blinatumomab[2] 3. Add blinatumomab calculated dose volume per 250 mL bag(mL)[3]	**237.6 mL**
	250 mL total volume[4]	

[1] 0.9% NaCl (mL) = total volume to be prepared (250 mL) – stabilizer solution volume (5 mL) – blinatumomab calculated dose volume (mL) per 250 mL bag
[2] stabilizer solution (5 mL) = 0.02 x total volume to be prepared (250 mL)
[3] blinatumomab calculated dose volume per 250 mL bag (mL) = 72 hour dose (mcg) ÷ volume to be infused (238 mL) x total volume to be prepared (250 mL) ÷ 12.5 mcg/mL of blinatumomab vial concentration
[4] total volume to be made is 250 mL of which patient will receive 237.6 mL at 3.3 mL/hour and 12.4 mL will remain in the IV-line set.

OUTPATIENT (96-hour infusion): Infusion rate 2.5 mL/hr over 96 hrs		
	Volume to be prepared	Volume to be infused
96-hour IV bag	1. Add calculated volume of 0.9% NaCl(mL)[1] into approved IV bag 2. Add **5 mL** IV solution **stabilizer** for blinatumomab[2] into the normal saline IV bag 3. Add blinatumomab calculated dose volume per 250 mL bag (mL)[3]	**240 mL**
	250 mL total volume[4]	

[1] 0.9% NaCl (mL) = total volume to be prepared (250 mL) – stabilizer solution volume (5 mL) – blinatumomab calculated dose volume (mL) per 250 mL bag

[2] stabilizer solution (5 mL) = 0.02 x total volume to be prepared (250 mL)

[3] blinatumomab calculated dose volume per 250 mL bag (mL) = 96 hour dose (mcg) ÷ volume to be infused (240 mL) x total volume to be prepared (250 mL) ÷ 12.5 mcg/mL of blinatumomab vial concentration

[4] total volume (250 mL) = Volume to be infused (240 mL) + 10 mL*(will remain in the IV line set) for outpatient IV infusion volume over 96 hours at 2.5mL/hour infusion rate.

Volume for the dead space of the IV line may be adjusted according to the size of the infusion IV line being used at each institution

Rotate IV bag to thoroughly mix the solution. Do not shake. Avoid foaming the IV bag.

Visually inspect for floating particles or discoloration of the IV solution. If present, do not use the prepared solution.

Prime the IV line with the prepared IV solution prior to administering it to the patient.

Infusion bags should be changed in accordance with local pharmacy standards for infusion of compounded sterile products. All infusion bags may be changed at least **every 4th day** (not to exceed 96 hours) in the US and in the foreign sites. Shorter time intervals of 24, 48 or 72 hours may also be utilized for convenience of patient scheduling as needed.

Label the final product with the following information:
- Patient name and number
- Name of the drug
- Dose (mcg/day and volume/day)
- Infusion rate

- Expiration date and time
- CAUTION: NEW DRUG – Limited by United States law to investigational use.
- Bag number

Additional information may be provided on the label in accordance with state, local, and country pharmacy regulations.

3. Stability: Shelf life stability studies of the intact vials of blinatumomab and stabilizer solution are on-going. The stability of the prepared IV solution is 8 days when stored refrigerated at 2° - 8°C. The total storage and administration time must not exceed 8 days. Once at room temperature, discard the IV bag after 96 hours.

4. See Section 18.7 "Clinical Site Management of Out-Patient Treatment Using CTEP-Supplied Blinatumomab" for additional administration information.

f. DRUG ORDERING & ACCOUNTABILITY

1. Drug ordering: NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP assigned protocol number (**S1318**) must be used for ordering all CTEP supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form and a Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

2. Sites may order initial agent supplies after a subject has been assigned to an arm on the study.

   Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

3. Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator in this protocol.

   Useful Links and Contacts
   - CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
   - NCI CTEP Investigator Registration (RCR) Help Desk: RCRHelpDesk@nih.gov
   - PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm

- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/index.jsp
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB IB Coordinator: IBCoordinator@mail.nih.gov
- PMB e-mail: PMBAfterHours@mail.nih.gov

PMB phone and hours of service: 240/276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) and hours of service: 240/276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

3.3 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 slightly soluble in ethanol (USP), methanol, polyethylene glycol 400, and propylene glycol. It is very slightly soluble in acetone and acetonitrile, practically insoluble in corn oil, and insoluble in water.

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. 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 via CTEP-AERS (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 2937 patients.* Below is the CAEPR for dasatinib (BMS-354825).

NOTE: Report AEs on the SPEER ONLY IF they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE

listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.7, September 10, 2018

Adverse Events with Possible Relationship to Dasatinib (BMS-354825, Sprycel) (CTCAE 5.0 Term) [n= 2937]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)** (formerly known as ASAEL)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 3)***
	Febrile neutropenia		
CARDIAC DISORDERS			
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction	
	Pericardial effusion		
GASTROINTESTINAL DISORDERS			
	Abdominal distension		***Abdominal pain (Gr 3)***
	Abdominal pain		
	Anal mucositis		
	Constipation		
Diarrhea			***Diarrhea (Gr 3)***
	Dyspepsia		
	Gastrointestinal hemorrhage[2]		
	Mucositis oral		
Nausea			***Nausea (Gr 3)***
	Rectal mucositis		
	Small intestinal mucositis		
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	General disorders and administration		***General disorders and administration site conditions - Other***

Adverse Events with Possible Relationship to Dasatinib (BMS-354825, Sprycel) (CTCAE 5.0 Term) [n= 2937]			Specific Protocol Exceptions to Expedited Reporting (SPEER) (formerly known as ASAEL)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	site conditions - Other (superficial edema)		***(superficial edema) (Gr 2)***
	Generalized edema		
	Non-cardiac chest pain		
	Pain		
INFECTIONS AND INFESTATIONS			
	Infection[3]		***Infection[3] (Gr 3)***
INVESTIGATIONS			
	Alanine aminotransfer-ase increased		
	Aspartate aminotransfer-ase increased		
		Electrocardiogram QT corrected interval prolonged	
Neutrophil count decreased			***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	Weight gain		
	Weight loss		
	White blood cell decreased		***White blood cell decreased Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Hypocalcemia		
	Hypokalemia		***Hypophosphatemia (Gr 3)***
	Hypophos-phatemia		
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
		Growth suppression[4]	
		Musculoskeletal and connective	

Adverse Events with Possible Relationship to Dasatinib (BMS-354825, Sprycel) (CTCAE 5.0 Term) [n= 2937]			Specific Protocol Exceptions to Expedited Reporting (SPEER) (formerly known as ASAEL)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		tissue disorder – Other (epiphyses delayed fusion)[4]	
		Musculoskeletal and connective tissue disorder – Other (osteopenia)[4]	
Myalgia			***Myalgia (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		
Headache			***Headache (Gr 3)***
		Intracranial hemorrhage	
		Leuko-encephalopathy	
		Reversible posterior leukoencephalopathy syndrome	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
		Gynecomastia[4]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
Dyspnea			***Dyspnea (Gr 3)***
	Laryngeal mucositis		
	Pharyngeal mucositis		
Pleural effusion			***Pleural effusion (Gr 3)***
	Pneumonitis		
		Pulmonary hypertension	
	Tracheal mucositis		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
		Erythema multiforme	
	Pruritus		
	Rash acneiform		

Adverse Events with Possible Relationship to Dasatinib (BMS-354825, Sprycel) (CTCAE 5.0 Term) [n= 2937]			Specific Protocol Exceptions to Expedited Reporting (SPEER) (formerly known as ASAEL)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Rash maculo-papular			***Rash maculo-papular (Gr 2)***
		Stevens-Johnson syndrome	
		Toxic Epidermal necrolysis	
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[5]; 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.

d. DOSING AND ADMINISTRATION

1. 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 H_2 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

1. Dasatinib will be supplied free of charge by Bristol-Myers Squibb and distributed by NCI/DCTD.

2. How Supplied: BMS-354825 is available in the following tablet/bottle sizes:

   - 20 mg biconvex round, white to off-white film-coated tablets containing 30 tablets per bottle. The tablet is debossed with “20” on one side and “527” on the other side (or BMS on one side and 527 on the other side)
   - 50 mg biconvex oval, white to off-white film-coated tablets containing 30 tablets per bottle. The tablet is debossed with “50” on one side and “528” on the other side (or BMS on one side and 528 on the other side).

   Inactive ingredients include lactose, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The film-coating contains hypromellulose, titanium trioxide, and polyethylene glycol (in the 20 mg tablets and 50 mg tablets).

f. STORAGE, PREPARATION & STABILITY

1. The intact bottles should be stored at controlled room temperature (15°C-25°C) and protected from light. Excursions are permitted up to 30° C. Stability studies are ongoing.

2. **Special handling: BMS-354825 tablets consist of a core tablet (containing the active drug) surrounded by a film coating to prevent exposure to the active drug substance. If tablets are accidentally crushed or broken, caregivers should wear disposable chemotherapy gloves. Pregnant women should avoid exposure to crushed and/or broken tablets.**

g. DRUG ORDERING & ACCOUNTABILITY

1. NCI-supplied agents may be requested by the eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP assigned protocol number (**S1318**) must be used for ordering all CTEP supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and a Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

   Sites may order initial agent supplies after a subject has been assigned to an arm on the study.

   Order Processing (OAOP) application: Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an “active” account status, a “current” password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB’s website for specific policies and guidelines related to agent management.

   Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator in this protocol.

   Useful Links and Contacts
   - CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
   - NCI CTEP Investigator Registration (RCR) Help Desk: RCRHelpDesk@nih.gov
   - PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
   - PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
   - CTEP Identity and Access Management (IAM) account:

https://ctepcore.nci.nih.gov/iam/index.jsp
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB IB Coordinator: IBCoordinator@mail.nih.gov
- PMB e-mail: PMBAfterHours@mail.nih.gov

PMB phone and hours of service: 240/276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET).

3.4 Dexamethasone (Decadron) (NSC-34521)

a. PHARMACOLOGY

Mechanism of Action: Dexamethasone is a synthetic adrenocortical steroid with potent anti-inflammatory effects in disorders of many organ systems, however, it lacks the sodium-retaining property of hydrocortisone.

b. PHARMACOKINETICS

1. Absorptions:

a. Bioavailability: 61-86% after oral administration

b. T_{max}: 10-60 minutes (oral elixir), 1-2 hours (oral tablet), 5-10 minutes (IV), 30-120 minutes (IM)

2. Distribution: V_D 2 L/kg

3. Elimination:

a. Half-life: 4 hours (oral) and 1-5 hours (IV).

b. Approximately 10 % of drug is excreted in urine.

c. ADVERSE EFFECTS

1. Possible Side Effects of Dexamethasone

The most common adverse effects occurring in >20% people receiving dexamethasone include: fluid and electrolyte disturbances, congestive heart failure in susceptible persons, hypertension, euphoria, personality changes, insomnia, exacerbation of infection (e.g., tuberculosis), hyperglycemia, psychosis, muscle weakness, osteoporosis, , pancreatitis, esophagitis, , dermatologic disturbances (e.g. acne, rash and skin atrophy), convulsions, vertigo and headache, endocrine abnormalities, glaucoma, conjunctival hemorrhage, metabolic changes (e.g. decreased body growth, Cushing's syndrome), peripheral edema, fatigue, bruising, abdominal pain, increase appetite and weight gain.

Adverse effects occurring in 4–20% patients: cataract, non-healing wound, heartburn, kidney stones

Rare and Serious (< 3%): blurred vision, peptic ulcer, vertebral compression fractures

Some patients have experienced itching and other allergic, anaphylactic or other hypersensitivity reactions. Withdrawal from prolonged therapy

may result in symptoms including fever, myalgia and arthralgia. Phenytoin phenobarbital and ephedrine enhance metabolic clearance of corticosteroids.

Corticosteroids should be used cautiously in patients with hypothyroidism, cirrhosis, ocular herpes simplex, existing emotional instability or psychotic tendencies, nonspecific ulcerative colitis, diverticulitis, fresh intestinal anastomoses, peptic ulcer, renal insufficiency, hypertension, osteoporosis and myasthenia gravis. Immunization procedures (especially smallpox vaccination) should not be undertaken in patients on corticosteroids.

Refer to the FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

2. Pregnancy and Lactation: Pregnancy Category C. When systemic corticosteroids are needed in pregnancy, it is generally recommended to use the lowest effective dose for the shortest duration of time, avoiding high doses during the first trimester. Corticosteroids are excreted in human milk; information specific to dexamethasone is unknown.

3. Drug Interactions: Dexamethasone is a substrate of CYP3A4 (major) and P-glycoprotein. It is an inducer of several cytochrome P450 isoenzymes including CYP3A4 (strong), CYP2A6 (weak/moderate), CYP2B6 (weak/moderate), CYP2C9 (weak/moderate). Dexamethasone is an inducer and inhibitor and P-glycoprotein.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

e. HOW SUPPLIED

Dexamethasone is commercially available and will not be supplied. Refer to the current FDA-approved package insert for the most comprehensive and up to date information.

3.5 Methotrexate (Methotrexate Sodium) (NSC-740)

a. PHARMACOLOGY

Mechanism of Action: Methotrexate, an antimetabolite, inhibits dihydrofolic acid reductase. Dihydrofolates must be reduced to tetrahydrofolates by this enzyme before they can be utilized as carriers of 1-carbon groups in the synthesis of purine nucleotides and thymidylate. Therefore, methotrexate interferes with DNA synthesis, repair, and cellular replication. Actively proliferating tissues such as malignant cells, bone marrow, fetal cells, buccal and intestinal mucosa, and cells of the urinary bladder are in general more sensitive to this effect of methotrexate. When cellular proliferation in malignant tissues is greater than in most normal tissues, methotrexate may impair malignant growth without irreversible damage to healthy tissues.

b. PHARMACOKINETICS

1. Absorption: Methotrexate is generally completely absorbed from parenteral routes of injection. After intramuscular injection, peak serum concentrations occur in 30 to 60 minutes.

2. Distribution: After intravenous administration, the initial volume of distribution is approximately 0.18 L/kg (18% of body weight) and steady-state volume of distribution is approximately 0.4 to 0.8 L/kg (40% to 80% of body weight). Methotrexate competes with reduced folates for active transport across cell membranes by means of a single carrier-mediated active transport process. At serum concentrations greater than 100 micromolar, passive diffusion becomes a major pathway by which effective intracellular concentrations can be achieved. Methotrexate in serum is approximately 50% protein bound. Laboratory studies demonstrate that it may be displaced from plasma albumin by various compounds including sulfonamides, salicylates, tetracyclines, chloramphenicol, and phenytoin.

   Methotrexate does not penetrate the blood-cerebrospinal fluid (CSF) barrier in therapeutic amounts when given orally or parenterally. High CSF concentrations of the drug may be attained by intrathecal administration.

3. Metabolism: Methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms which can be converted back to methotrexate by hydrolase enzymes. These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate synthetase. Small amounts of methotrexate polyglutamates may remain in tissues for extended periods. The retention and prolonged drug action of these active metabolites vary among different cells, tissues and tumors. A small amount of metabolism to 7-hydroxymethotrexate may occur at doses commonly prescribed. Accumulation of this metabolite may become significant at the high doses used in osteogenic sarcoma. The aqueous solubility of 7-hydroxymethotrexate is 3- to 5-fold lower than the parent compound.

4. Elimination: Renal excretion is the primary route of elimination and is dependent upon dosage and route of administration. With IV administration, 80% to 90% of the administered dose is excreted unchanged in the urine within 24 hours. There is limited biliary excretion amounting to 10% or less of the administered dose. Enterohepatic recirculation of methotrexate has been proposed.

   Renal excretion occurs by glomerular filtration and active tubular secretion. Nonlinear elimination due to saturation of renal tubular reabsorption has been observed in psoriatic patients at doses between 7.5 and 30 mg. Impaired renal function, as well as concurrent use of drugs such as weak organic acids that also undergo tubular secretion, can markedly increase methotrexate serum levels. Excellent correlation has been reported between methotrexate clearance and endogenous creatinine clearance.
   Methotrexate clearance rates vary widely and are generally decreased at higher doses. Delayed drug clearance has been identified as one of the major factors responsible for methotrexate toxicity. It has been postulated that the toxicity of methotrexate for normal tissues is more dependent upon the duration of exposure to the drug rather than the peak level achieved. When a patient has delayed drug elimination due to compromised renal function, a third-space effusion, or other causes, methotrexate serum concentrations may remain elevated for prolonged periods.

   The terminal half-life reported for methotrexate is approximately 3 to 10 hours for patients receiving treatment for psoriasis, or rheumatoid arthritis or low-dose antineoplastic therapy (less than 30 mg/m2). For patients receiving high doses of methotrexate, the terminal half-life is 8 to 15 hours.

c. ADVERSE EFFECTS

1. Possible Side Effects of Methotrexate: Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions. In general, the incidence and severity of acute side effects are related to dose and frequency of administration. The most frequently reported adverse reactions occurring in greater than 20% of patients are photosensitivity and rash, Adverse effects reported in 4 to 20 % of patients include pneumonitis, pericarditis, pericardial effusion, internal hemorrhage, nausea, vomiting, diarrhea, ulcerative stomatitis, mucositis, gingivitis, cirrhosis, hepatic fibrosis, hepatitis, elevated transaminases, alopecia, thrombocytopenia, bone marrow depression (nadir: 7-10 days), leukopenia, infection, anemia, secondary cancer, confusion, seizure, renal failure, dermatologic reactions including toxic epidermal necrolysis, Stevens-Johnson Syndrome, exfoliative dermatitis, skin necrosis, and erythema multiforme, thromboembolic events. Rare but serious events occurring in less than or equal to 3% or patients include neurotoxicity, encephalopathy and leukoencephalopathy.

2. Pregnancy and Lactation: Category X. Methotrexate causes embryotoxicity, abortion, and fetal defects in humans. Pregnancy should be avoided if either partner is receiving methotrexate; during and for a minimum of 3 months after therapy for male patients, and during and for at least 1 ovulatory cycle after therapy for female patients.

   Because of the potential for serious adverse reactions from methotrexate in breastfed infants, it is contraindicated in nursing mothers.

3. Drug Interactions: Nonsteroidal anti-inflammatory drugs (NSAIDs) should not be administered prior to or concomitantly with the high doses of methotrexate, such as used in the treatment of osteosarcoma. Concomitant administration of some NSAIDs with high dose methotrexate therapy has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe hematologic and gastrointestinal toxicity.

   Caution should be used when NSAIDs and salicylates are administered concomitantly with lower doses of methotrexate. These drugs have been reported to reduce the tubular secretion of methotrexate in an animal model and may enhance its toxicity.

   Methotrexate is partially bound to serum albumin, and toxicity may be increased because of displacement by certain drugs, such as salicylates, phenylbutazone, phenytoin, and sulfonamides. Renal tubular transport is also diminished by probenecid; use of methotrexate with this drug should be carefully monitored.

   In the treatment of patients with osteosarcoma, caution must be exercised if high-dose methotrexate is administered in combination with a potentially nephrotoxic chemotherapeutic agent (e.g., cisplatin).

   Methotrexate increases the plasma levels of mercaptopurine. The combination of methotrexate and mercaptopurine may therefore require dose adjustment.

   Oral antibiotics such as tetracycline, chloramphenicol, and nonabsorbable broad spectrum antibiotics, may decrease intestinal absorption of

methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria.

Penicillins may reduce the renal clearance of methotrexate; increased serum concentrations of methotrexate with concomitant hematologic and gastrointestinal toxicity have been observed with high and low dose methotrexate. Use of methotrexate with penicillins should be carefully monitored.

The potential for increased hepatotoxicity when methotrexate is administered with other hepatotoxic agents has not been evaluated. However, hepatotoxicity has been reported in such cases. Therefore, patients receiving concomitant therapy with methotrexate and other potential hepatotoxins (e.g., azathioprine, retinoids, sulfasalazine) should be closely monitored for possible increased risk of hepatotoxicity.

Methotrexate may decrease the clearance of theophylline; theophylline levels should be monitored when used concurrently with methotrexate.

Vitamin preparations containing folic acid or its derivatives may decrease responses to systemically administered methotrexate. Preliminary animal and human studies have shown that small quantities of intravenously administered leucovorin enter the CSF primarily as 5methyltetrahydrofolate and, in humans, remain 1 to 3 orders of magnitude lower than the usual methotrexate concentrations following intrathecal administration. However, high doses of leucovorin may reduce the efficacy of intrathecally administered methotrexate.

Folate deficiency states may increase methotrexate toxicity. Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by decreased tubular secretion and/or an additive antifolate effect.

d. DOSING & ADMINISTRATION

Dosing – See Section 7.0 Treatment Plan.

e. HOW SUPPLIED

Methotrexate is commercially available and will not be supplied. Refer to the current FDA-approved package insert for the most comprehensive and up to date information.

3.6 Prednisone (NSC-10023)

a. PHARMACOLOGY

Prednisone decreases inflammation by inhibiting the migration of polymorphonuclear leukocytes; at high doses it suppresses adrenal function. The antitumor effects may be due to inhibition of glucose transport, phosphorylation, or induction of cell death of immature lymphocytes.

b. PHARMACOKINETICS

1. Absorption: 50-90% after oral administration. T_{max}: 2 hours (oral regular-release), 6-6.5 hours (oral delayed-release)

2. Distribution: 70% protein binding, V_D: 0.4 to 1 L/kg

3. Metabolism: Converted from prednisone to prednisolone (active drug) hepatically.

4. Elimination: Half-life (normal renal function): 3.5 hours

c. ADVERSE EFFECTS

Possible Side Effects of Prednisone: The most common adverse effects occurring in > 20% of people receiving prednisone include: increase in absolute granulocyte count, decrease in lymphocyte and monocyte count, hypertension, GI disorder, infection, oropharyngeal candidiasis, hypernatremia, fluid retention, growth retardation, osteoporosis, depression, euphoria, skin atrophy, acne, impaired skin healing.

Adverse effects occurring in ≤ 20% of people receiving prednisone include: hypokalemia, hyperuricemia, hyperglycemia, myopathy, petechiae, ecchymosis, dermatitis, facial erythema, hirsutism, increased sweating, healing wound, kidney stones, and heartburn.

Rare (< 3%) but potentially serious adverse effects include: leukemoid reaction, cataracts, glaucoma, gastrointestinal perforation and ulceration, pancreatitis, pulmonary tuberculosis, Cushing's syndrome, primary adrenocortical insufficiency, diabetes mellitus, aseptic necrosis of bone, pseudotumor cerebri, mental status changes, personality changes, mania, hallucinations, Kaposi's sarcoma.

Adverse events occurring in < 1%, postmarketing, and/or case reports: staphylococcal scalded skin syndrome, disseminated varicella-zoster virus, hyperthyroidism, porphyria, abnormal lipids, extrapyramidal sign, lung abscess, aspergillosis, interstitial pneumonia, pulmonary nocardiosis, decreases in cardiac function.

Refer to package insert or manufacturer website for the most complete and up to date information on contraindications, warnings and precautions, and adverse reactions.

Pregnancy and Lactation: Pregnancy Category C. Adverse events have been observed with corticosteroids in animal reproduction studies. Prednisone and prednisolone cross the human placenta. Prednisone enters breast milk. American Academy of Pediatrics rates it as compatible.

Drug Interactions: Prednisone is a minor substrate of CYP3A4 and induces both CYP2C19 and CYP3A4 weakly/moderately. Refer to the current FDA-approved package insert for additional information. Due to potential drug interactions, a complete patient medication list, including prednisone, should be screened prior to initiation of prednisone.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

e. HOW SUPPLIED

Prednisone is commercially available and will not be supplied. Please refer to the current FDA-approved package insert for most comprehensive and up to date information.

3.7 Vincristine (Oncovin) (NSC-67574)

a. PHARMACOLOGY

Mechanism of Action: Vincristine is a vinca alkaloid. The mechanism of action of vincristine is thought to be due to inhibition of microtubule formation in the mitotic spindle. This leads to arrest of dividing cells during the metaphase stage.

b. PHARMACOKINETICS

1. Distribution: Within 15-30 minutes of injection, 90% of the drug is distributed from the blood into tissues where it is tightly bound.

2. Metabolism: Extensively metabolized by the liver via cytochrome P450 isoenzymes in the 3A subfamily (CYP3A).

3. Elimination: Terminal half-life: 85 hours (range, 19-155 hours); 80% excreted in feces, 10-20% excreted in urine.

c. ADVERSE EFFECTS

Possible Side Effects of Vincristine: Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions. Adverse effects reported in more than 20% of patients include constipation, alopecia, injection site reaction, peripheral neuropathy, headache, jaw pain and/or myalgia, weakness, gait instability and difficulty walking, and edema. Anemia, ptosis, and hoarseness is reported in 4 to 20% of patients and seizures are reported in 3% or less patients.

1. Pregnancy and Lactation: Pregnancy Category D. It is not known whether vincristine is excreted in human breast milk.

Drug Interactions: Due to potential drug interactions, a complete patient medication list, including vincristine, should be screened prior to initiation of vincristine and during treatment with vincristine. See Section 8.0 Toxicities to be Monitored and Dosage Modifications. Of note, vincristine is a CYP3A subfamily and P-glycoprotein (P-gp) substrate. Caution should be used in patients concurrently taking drugs known to inhibit drug metabolism by the CYP3A subfamily or in patients taking potent P-gp inhibitors.

d. DOSING & ADMINISTRATION

1. Dosing – See Section 7.0 Treatment Plan.

2. To reduce the potential for fatal medication errors due to incorrect route of administration, vincristine injection should be diluted in a flexible plastic container and prominently labeled to indicate that it is for intravenous use only. Syringes containing vincristine must be labeled with an auxiliary label stating “FOR INTRAVENOUS USE ONLY – FATAL IF GIVEN BY OTHER ROUTES.”

3. Vincristine must be administered via an intact, free-flowing intravenous needle or catheter. The needle or catheter must be secured within the vein to avoid extravasation during administration. The solution may be injected either directly into a vein or into the tubing of a running intravenous infusion.

e. HOW SUPPLIED

Vincristine is commercially available and will not be supplied. Refer to the current FDA-approved package insert for the most comprehensive and up to date information.

4.0 STAGING CRITERIA

4.1 Diagnostic Criteria

a. Definitions:

1. Bone marrow cellularity: The volume of hematopoietic nucleated cells, expressed as a percentage of marrow volume minus the volume of fibrosis.

2. Blasts: Blasts characteristic of L1, L2, or L3 are included in the calculation of blast percentages. *(41,42)*

3. Marrow Blast Percentage: Bone marrow blast percentage is calculated as the percentage of blasts among all nucleated marrow cells except mature lymphocytes and plasma cells.

b. WHO Classification of ALL, with the following additions and classifications *(43,44,45)*

	ICD-O Code Equivalent	FAB
Precursor B-cell neoplasm Precursor B lymphoblastic Leukemia	9836/3	L1, L2
Precursor T-cell neoplasms Precursor T lymphoblastic leukemia	9837/3	L1, L2

4.2 Staging Criteria

Staging criteria are not applicable to this protocol.

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 registration in OPEN. Use the spaces provided to confirm a patient's eligibility. Section 5.0 may be printed and used by the site but is not to be uploaded in RAVE (unless specially stated). 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 (SDMC) in Seattle at 206/652-2267 prior to registration. 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 14 or 28 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 Registration Step 1 – Induction/Re-Induction

Disease Related Criteria

a. Patients must have a new morphologic diagnosis of precursor B cell acute lymphoblastic leukemia (ALL) (non T cell) based on WHO criteria as defined in Section 4.1b. Patients with Burkitts (L3) are excluded. Patients with Ph-positive or Ph-like ALL with dasatinib-sensitive mutations or kinase fusions may have relapsed or refractory diagnoses.

NOTE: Relapsed/Refractory Ph-positive patients or Ph-like patients with dasatinib-sensitive mutations or kinase fusions who have previous exposure to either dasatinib or another 2nd or 3rd generation TKI will begin protocol therapy with Cohort 2: Re-Induction Cycle 1 (see Section 7.3b).

b. Patients must have a diagnosis of Philadelphia chromosome negative ALL or Ph chromosome positive ALL by cytogenetics, FISH or polymerase chain reaction (PCR). Patients will be registered to receive treatment in either Cohort 1 (Ph-) or Cohort 2 (Ph+ or Ph-like DSMKF) based on these results. Diagnostic specimens must be submitted to the site's local CLIA-approved cytogenetics laboratory and results of tests (cytogenetics, FISH or PCR) must confirm Ph status prior to registration. If not already known, BCR-ABL status (p190 or p210) must be evaluated in Ph-positive patients by PCR.

For Cohort 2, Ph-like testing is not required specifically for this study. However, to be registered to Cohort 2 under the Ph-like DSMKF criterion, the patient must have a known or presumed activating Ph-like signature and dasatinib-sensitive mutation or kinase fusion, such as: ABL1, ABL2, CSF1R, PDGFRB, PDGFRA, or FGFRs that was otherwise identified as part of normal standard of care. Prior to registering any patients with a known or presumed activating Ph-like signature and dasatinib-sensitive mutations or kinase fusions (DSMKF) treating physicians must confirm eligibility with the study chairs via email to S1318SC@swog.org. The study chairs must respond via email with confirmation of patient eligibility prior to patient registration.

c. All newly diagnosed patients must have evidence of ALL in their marrow or peripheral blood with at least 20% lymphoblasts present in blood or bone marrow collected within 28 days prior to registration. All relapsed/refractory patients (Cohort 2) must have at least 5% lymphoblasts present in blood or bone marrow collected within 28 days prior to registration. For relapsed/refractory patients, pathology and cytogenetics reports (both from time of original diagnosis) must be submitted at time of registration. See Section 14.4a.

If a bone marrow aspirate cannot be obtained despite an attempt (dry tap), appropriate IHC testing, including CD19, must be performed on the bone marrow biopsy to determine lineage.

For ALL in marrow or peripheral blood, immunophenotyping of the blood or marrow lymphoblasts must be performed to determine lineage (B cell, T cell or mixed B/T cell). Appropriate marker studies including C D19 (B cell), must be performed. Co-expression of myeloid antigens (CD13 and CD33) will not exclude patients. If possible, the lineage specific markers (myeloid cells) should be determined. The blood/bone marrow sample for these assays must be obtained within 28 days prior to registration.

Patients with only extramedullary disease in the absence of bone marrow or blood involvement are not eligible.

Clinical/Laboratory Criteria

d. Patient must not have a history or presence of clinically relevant CNS pathology such as epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, psychosis, active ALL in the CNS confirmed by CSF analysis, or other significant CNS abnormalities.

e. Patients must have a lumbar puncture to determine CNS involvement of ALL within 14 days prior to registration. Categories of CNS involvement are outlined in Section 18.5. Patients with CNS3 are excluded from the trial; patients with CNS1 or CNS2 will be eligible, but will be monitored for CNS involvement. Note that intrathecal methotrexate administered during the pre-study lumbar puncture may count as the first dose of intrathecal therapy required as part of the study (see Section 7.1a).

f. **Cohort 1, Ph- Patients Only:**

Patients must not have received any prior chemotherapy, radiation therapy, or other therapy for the treatment of ALL (other than those noted below) and must not be receiving any immunosuppressive therapy. Patients may not have received any prior investigational therapy within 28 days prior to registration. Patients must not have received any monoclonal antibody therapy within 42 days of registration.

1. Patients may have received the following within any time prior to registration: low dose chemotherapy-including: cyclophosphamide 1 g/m^2, oral 6-mercaptopurine, or oral methotrexate (Other low dose chemotherapy may be allowable, however any other options not listed here should be confirmed with the study chairs), TKI therapy, steroids, hydroxyurea, leukapheresis, intrathecal chemotherapy or vincristine.

2. In the event that the patient's bone marrow blast count is ≥ 50% blasts, patients may be registered but should receive steroids for 3-5 days in order to reduce tumor burden prior to blinatumomab administration, as follows.

   a. Prephase treatment with dexamethasone (10-20 mg/m^2) for 3-5 days is required for patients with bone marrow blasts ≥ 50%, peripheral blood blasts 15,000/uL or higher, or elevated LDH suggesting rapidly progressive disease per investigator opinion.

      1. Pre-treatment should conclude at least 24 hours prior to the first dose of blinatumomab (although additional dexamethasone is automatically given as a pre-med prior to the first dose). At the time of first infusion of blinatumomab, the absolute peripheral blast count should be < 25,000/uL.

      2. Note: For the purposes of the study, Day 1 of the cycle will be the first day of blinatumomab administration.

3. It is preferred, but not required, that corticosteroids and hydroxyurea should start only after all diagnostic samples have been obtained. However, if the patient was previously on corticosteroids and/or hydroxyurea, this is allowable provided that the patient still has measurable disease at time of the bone marrow aspirate.

a. Corticosteroids and/or hydroxyurea, as well as any of the other therapies mentioned (with the exception of IV cyclophosphamide), may continue to be administered, at physician discretion, until 1 day prior to blinatumomab administration.

b. IV cyclophosphamide must be discontinued at least 7 days prior to blinatumomab administration.

g. **Cohort 2, Ph+ and Ph-like DSMKF Patients Only:**

Patients must NOT have received a prior autologous or allogeneic hematopoietic stem cell transplant at any time. Patients must NOT have received any chemotherapy, investigational agents, or undergone major surgery within 14 days prior to registration, with the following exceptions:

1. Monoclonal antibodies must not have been received for 1 week prior to registration.

2. Chimeric antigen receptor (CAR) T-cells must not have been received for 28 days prior to registration.

3. Steroids, hydroxyurea, vincristine, 6-mercaptopurine, methotrexate, thioguanine and intrathecal chemotherapy are permitted within any timeframe prior to registration. FDA-approved TKIs may also be administered until 1 day prior to start of study therapy (C1, D1). IV cyclophosphamide may be administered at doses of 1 g/m^2 or less until up to 7 days prior to registration.

h. Patients must be ≥ 65 years of age. For patients 65-69 years of age, patient must be deemed not suitable for standard intensive Induction chemotherapy at the discretion of the local investigator, or must have refused standard intensive chemotherapy.

i. **Cohort 1, Ph- Patients Only:**

Patients must not be candidates for allogeneic hematopoietic stem cell transplant. NOTE: Subjects up to age 70 years who are considered fit for allogeneic hematopoietic stem cell transplant, should be considered for enrollment on E1910, in order to avoid competing with that study. If a patient is considered unfit for intensive chemotherapy at the time of initial diagnosis, but subsequently achieves a CR, then it will be left to the treating physician's discretion to consider HSCT.

j. Patients must have complete history and physical examination within 28 days prior to registration.

k. Patients must have a Zubrod Performance Status of 0-2 (see Section 10.10).

l. Patients must have serum creatinine ≤ 1.5 mg/dl within 14 days prior to registration.

m. Patients must have AST and ALT ≤ 3.0 x Institutional Upper Limit of Normal (IULN) within 14 days prior to registration.

n. Patients must have total bilirubin ≤ 2.0 x IULN within 14 days prior to registration.

o. Patients must have alkaline phosphatase ≤ 2.5 x IULN within 14 days prior to registration.

p. Patients must not have systemic fungal, bacterial, viral or other infection that is not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment).

q. Patients must not have CTCAE ≥ Grade 2 neuropathy (cranial, motor or sensory) within 14 days prior to registration.

r. Patients known to be positive for HIV (the human immunodeficiency virus) may be eligible, providing they meet the following additional criteria within 28 days prior to registration:

- No history of AIDS-defining conditions
- CD4 cells > 350 cells/mm^3
- If on antiretroviral agents, must not include zidovudine or stavudine
- Viral load ≤ 50 copies HIV mRNA/mm^3 if on cART or ≤ 25,000 copies HIV mRNA/mm^3 if not on cART.
- HAART regimens are acceptable providing they have only weak P450A4 interactions.

s. Patients must not have any known autoimmune disease.

t. Patients must not have testicular involvement. If clinical or ultrasound findings are equivocal, biopsy must be performed. All tests for establishing testicular involvement must be completed within 14 days prior to registration.

u. Patients with evidence of extramedullary disease at diagnosis will have CT scan or MRI of the chest, abdomen and pelvis to obtain baseline values within 28 days prior to registration. See Section 7.1b for additional CT/MRI time points during treatment.

v. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for five years.

w. Patients must have the following tests within 28 days prior to registration to obtain baseline measurements:

- PT/PTT/INR/fibrinogen (all patients)

Cohort 1, Ph- Patients Only
- Neurologic assessment (see Section 7.1c.2)

x. **Cohort 2, Ph+ and Ph-like DSMKF Patients Only:**

Patients must not have active pericardial effusion, ascites or pleural effusion of any grade based on chest x-ray and echocardiogram within 28 days prior to registration. Exception: If the effusion is suspected to be related to the leukemia, the patient may have pericardial effusion ≤ Grade 2 or pleural effusion ≤ Grade 1.

y. **Cohort 2, Ph+ and Ph-like DSMKF Patients Only:**

Patients must have ejection fraction ≥ 45% based on echocardiogram performed within 28 days prior to registration.

z. **Cohort 2, Ph+ and Ph-like DSMKF Patients Only:**

Patients must have QTcF (by Fridericia calculation) < 480/msec based on EKG performed within 28 days prior to registration.

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

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

aa. **Cohort 2, Ph+ and Ph-like DSMKF Patients Only:**

Patients must not be receiving any proton pump inhibitors at the time of registration.

Specimen Submission Criteria

bb. Pretreatment cytogenetics must be performed on all patients. Collection of pretreatment specimens must be completed up to 28 days prior to registration to **S1318**. Specimens must be submitted to the site's preferred CLIA-approved cytogenetics laboratory. BCR-ABL status must be verified in Ph-positive patients by FISH, cytogenetics, and/or PCR prior to enrollment. If a patient is Ph-positive, PCR for both p190 and p210 must be sent. If PH status cannot be determined, see Section 15.4d for instructions on obtaining a SWOG patient ID for specimen submission prior to registration.

cc. Patients must be offered participation in specimen submission for future research. With patient's consent, specimens must be submitted as outlined in Section 15.3 and Section 15.4.

dd. **Cohort 1, Ph-negative patients only:** Patients must have specimens submitted for blinatumomab immunogenicity assessment. Collection of pretreatment specimens must be completed up to 28 days prior to registration to **S1318**. Specimens must be submitted to LabConnect as outlined in Section 15.2.

Cohort 2, Ph-positive and Ph-like DSMKF patients only: Patients must agree to have specimens submitted for blinatumomab immunogenicity testing if subsequently moved to a blinatumomab containing treatment regimen on protocol.

Regulatory Criteria

ee. Patients or their legally authorized representative must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

ff. As a part of the OPEN registration process (see Section 13.5 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.

5.2 Registration Step 2 – Post-Remission Therapy

a. **Cohort 1, Ph-negative Patients Only**: Patients must have achieved CR or CRi within 2 cycles of Induction/Re-Induction with blinatumomab.

NOTE: For Cohort 1: Day 1 of Post-Remission = Day 43 of the preceding cycle (+/- 3 days)

Cohort 2, Ph-positive and Ph-like DSMKF Patients Only: Newly diagnosed Ph+, Newly-diagnosed Ph-like DSMKF, and relapsed/refractory Ph+ patients without prior dasatinib or other 2nd or 3rd generation TKI therapy, must have achieved CR or CRi within 1 cycle of Induction with dasatinib/prednisone, or within 2 cycles of Re-Induction with blinatumomab. Relapsed/refractory Ph+ or Ph-like DSMKF patients with prior dasatinib or other 2nd or 3rd generation TKI therapy must have achieved CR or CRi within 2 cycles of Re-Induction therapy with blinatumomab.

NOTE: For Cohort 2: Day 1 of Post-Remission = Day 85 of the preceding Induction cycle (+/- 3 days), or Day 43 of the preceding Re-Induction cycle (+/- 3 days) as applicable.

See Section 7.3 for additional information regarding timing of Post-Remission Day 1.

b. Patients must have serum creatinine ≤ 1.5 mg/dl within 14 days prior to registration.

c. Patients must have AST and ALT ≤ 3.0 x Institutional Upper Limit of Normal (IULN) within 14 days prior to registration.

d. Patients must have total bilirubin ≤ 2.0 x IULN within 14 days prior to registration.

e. Patients must have adequate marrow function as evidenced by ANC ≥ 750/mcL and platelets ≥ 50,000/mcL within 28 days prior to registration.

f. Patients must be registered to Step 2 within 28 days after count recovery. (Note: there is no maximum allotted time period for count recovery, providing patient remains in CR or CRi.)

g. All non-hematologic treatment related toxicities that are deemed clinically significant by the treating investigator must have resolved to ≤ Grade 2.

5.3 Registration Step 3 – Maintenance

a. Patients must have documented CR or CRi within 28 days prior to registration. Note that bone marrow examination is only required if there are clinical signs/symptoms of progression. If progression is a concern due to the length of the time for count recovery, a bone marrow examination is recommended.

b. Patients must have serum creatinine ≤ 1.5 mg/dl within 14 days prior to registration.

c. Patients must have AST and ALT ≤ 3.0 x Institutional Upper Limit of Normal (IULN) within 14 days prior to registration.

d. Patients must have total bilirubin < 2.0 x Institutional Upper Limit of Normal (IULN) within 14 days prior to registration.

e. Patients must have adequate marrow function as evidenced by ANC ≥ 750/mcL and platelets ≥ 75,000/mcL within 28 days prior to registration.

f. All non-hematologic treatment related toxicities that are deemed clinically significant by the treating investigator must have resolved to ≤ Grade 2.

6.0 STRATIFICATION FACTORS

Patients will be stratified by Registration Cohort (1 and 2).

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Dr. Anjali Advani 216/445-9354 or Dr. Kristen O'Dwyer at 585/275-4099. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at https://www.swog.org/sites/default/files/docs/2017-11/Policy38.pdf.

7.1 General Considerations, Prophylactic Therapy and Pre-Medication

a. IT Methotrexate and Lumbar Punctures

1. IT Methotrexate Administration

All patients, regardless of Ph-status, will receive prophylactic intrathecal (IT) chemotherapy with methotrexate (12 mg) every 4-6 weeks for at least 8 doses. Subsequent doses may be administered at physician discretion.

IT methotrexate must not be given on the same days as blinatumomab, but should be given 2 days apart from blinatumomab administration (Day -2 or Day +31). Note: The first dose of IT methotrexate must be given within 5 weeks of initiation of blinatumomab therapy. During Maintenance, IT methotrexate may be delayed by up to 2 weeks if toxicities are thought to be attributable to IT methotrexate administration.

2. Substitutions/Alternative IT Methotrexate Administration

If a patient is intolerant to IT methotrexate, it may be substituted with 70 mg intrathecal cytarabine.

Alternatively, IT chemotherapy may be administered by Ommaya reservoir.

3. Additional Instructions

Patients should remain in a horizontal position for at least 30 minutes following the administration of IT chemotherapy to enhance drug delivery to the head.

Concomitant medication of hydrocortisone (50 mg) with either IT methotrexate or cytarabine is allowable at treating physician discretion. Hydrocortisone should not be administered through an Ommaya reservoir.

4. Lumbar Puncture for CNS Involvement Monitoring

A lumbar puncture to monitor for CNS involvement is performed every 4-6 weeks with IT methotrexate administration during administration of IT chemotherapy. If IT methotrexate is delayed per the allowance in Section 7.1a.1, LP may also be delayed up to 2 weeks to correspond.

b. Patients with evidence of extramedullary disease at diagnosis will have CT scan or MRI of the chest, abdomen and pelvis within 28 days prior to registration, then

every 3 months for 2 years, then every 6 months until 5 years after initial registration.

c. For the prevention of acute reaction, patients must receive dexamethasone 20 mg IV within 1 hour prior to the start of treatment (or re-start of treatment) in each cycle of blinatumomab. For patients with ≥ 5% blasts, dexamethasone 20 mg IV must be given within 1 hour prior to start of blinatumomab infusion at 9 mcg/day on Day 1 and repeat at same dose (dexamethasone 20 mg IV) within 1 hour prior to start of blinatumomab infusion at 28 mcg/day on Day 8.

During treatment with blinatumomab patients must:

1. Receive adequate hydration according to institutional guidelines.

2. Perform a writing test (see Section 18.3) at the time of visits for blinatumomab infusion bag changes or weekly clinical visits (or weekly for patients receiving inpatient therapy or home-health infusions). The test will be evaluated immediately by medical staff for evidence of early signs of neurologic toxicity. If changes are noted, patients should be monitored and graded for signs of neurologic toxicity. See Section 8.3a for timing of writing test for patients experiencing neurologic toxicities. The writing test samples should be kept in the patient chart; they are not submitted centrally.

3. Avoid non-steroidal anti-inflammatory drugs (NSAIDs) if possible because they are a potential cause of endothelial stress.

4. Be hospitalized per FDA recommendation. If patients have not achieved CR, Cohort 1 (Ph-negative) patients should be hospitalized for the first 9 days of Induction Cycle 1. Similarly, Cohort 2 (Ph-positive) patients with ≥ 5% blasts should be hospitalized for the first 9 days of re-induction Cycle 1. If patients have achieved CR, it is recommended that patients be hospitalized for at least the first 3 days (72 hours) of the first cycle of blinatumomab, and the first 2 days (48 hours) of subsequent cycles.

5. Have blinatumomab bag changed every 24-96 hours.

Note: Home health care for blinatumomab administration and bag changes is acceptable, providing it is in accordance with local policies and procedures and the patient continues to make minimum weekly clinic visits. The Study Chair must be contacted to discuss prior to allowing the patient to receive home health care for blinatumomab.

IMPORTANT NOTE: Please see Section 18.7: Clinical Site Management of Out-Patient Treatment Using CTEP-Supplied Blinatumomab, Section 18.13: Shipment of Blinatumomab IV Bag from Site/Pharmacy to Patient's Home, and the "Manual for Blinatumomab Outpatient Administration". All participating investigators must also complete the Outpatient Administration Investigator Statement of Verification, accessible from the SWOG protocol abstract page (www.swog.org), certifying that these materials have been reviewed, that the "Manual for Blinatumomab Outpatient Administration" has been provided to any/all applicable Outpatient Administration Facilities or Organizations that are being utilized at the Investigator's site, and that a communication plan has been established with these same Outpatient Administration Facilities or Organizations.

d. Note that specimens must be submitted to the local CLIA-approved laboratory for cytogenetics every time a marrow/blood is collected for response assessment.

e. Cardiopulmonary Considerations **(Cohort 2, Ph+ and Ph-like DSMKF Patients Only)**

Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating dasatinib and during dasatinib treatment.

Symptoms of pulmonary arterial hypertension (PAH) include dyspnea, fatigue, hypoxia, and edema. Since other medical conditions may also cause these symptoms, non-invasive procedures (including echocardiogram) should be done first to rule out more the common etiologies of these symptoms, such as pleural effusion, pulmonary edema, anemia, and lung infiltration.

Right heart catheterization can confirm the diagnosis of PAH. Hypertension is "pre-capillary" and not a consequence of left heart failure or chronic lung disease if there is normal pulmonary capillary wedge pressure (< 15 mm Hg) but elevated pulmonary artery pressure (mean pulmonary artery pressure > 25 mm Hg). Since PAH may be reversible upon discontinuation of dasatinib, a diagnostic approach of interruption of dasatinib treatment may be considered at the discretion of the treating physician; however, if PAH is confirmed, dasatinib should be permanently discontinued.

f. **Cohort 1, Ph- Patients:** Patients should have baseline PT, PTT, INR and fibrinogen testing performed at baseline (during screening or prior to beginning treatment) to establish baseline measurements. These tests will then be repeated weekly during Days 1-28 of Induction and Re-Induction.

g. **Considerations for Ph-like DSMKF patients**: In the event that a patient is registered to Cohort 1 for Ph-negative patients, and the investigator subsequently receives result indication that the patient is not Ph-negative (that is, the patient is determined to be Ph-like DSMKF), the participating investigator must notify the study chair and SWOG Statistics and Data Management Center (leukemia@crab.org). NOTE: Due to differences in schema, transfer between cohorts will not be allowed.

7.2 Cohort 1 – Philadelphia Chromosome Negative (Ph-) Patients (Permanently closed to accrual 6/29/17)

a. Registration Step 1 – Induction/Re-Induction – Blinatumomab

Induction

Agent	Dose	Route	Day	Schedule [a]
Blinatumomab [b, c]	9 mcg/day	continuous IV	1-7	One Induction cycle
	28 mcg/day	continuous IV	8-28	One Induction cycle
IT Methotrexate	12 mg	Intrathecal	See Section 7.1a	
Dexamethasone	20 mg	IV	See Section 7.1c	

[a] Note: One cycle = 42 days
[b] See Section 7.1c for blinatumomab premedication and administration requirements.
[c] Patients should be given a blinatumomab medication guide prior to beginning blinatumomab therapy (see Section 18.12).

Blinatumomab Induction/Re-Induction consists of 28 day continuous IV infusion, **followed by 14 days of no treatment**, for a total of a 42 day cycle.

Response will be assessed at Day 35 (± 2 days) of the Induction cycle. Patients achieving CR or CRi will be registered to Step 2 and receive up to 3 Post-Remission cycles of blinatumomab therapy as outlined in Section 7.2b, after completion of the first Induction cycle. Patients may proceed to Step 2 Registration as soon as CR or CRi is documented and the 14 day treatment free period is completed. Cycle 1, Day 1 of Post-Remission = Day 43 of the preceding Induction Cycle (+/- 3 days).

Patients not achieving CR or CRi will receive a second cycle of blinatumomab Induction (Re-Induction) as outlined below, after completion of the first Induction cycle.

IMPORTANT NOTE: Please see Section 18.7: Clinical Site Management of Out-Patient Treatment Using CTEP-Supplied Blinatumomab, Section 18.13: Shipment of Blinatumomab IV Bag from Site/Pharmacy to Patient's Home, and the "Manual for Blinatumomab Outpatient Administration". All participating investigators must also complete the Outpatient Administration Investigator Statement of Verification, accessible from the SWOG protocol abstract page (www.swog.org), certifying that these materials have been reviewed, that the "Manual for Blinatumomab Outpatient Administration" has been provided to any/all applicable Outpatient Administration Facilities or Organizations that are being utilized at the Investigator's site, and that a communication plan has been established with these same Outpatient Administration Facilities or Organizations.

Re-Induction

Agent	Dose	Route	Day	Schedule [a]
Blinatumomab [b]	28 mcg/day	continuous IV	1-28	One Re-Induction cycle
IT Methotrexate	12 mg	Intrathecal	See Section 7.1a	
Dexamethasone	20 mg	IV	See Section 7.1c	

[a] Note: One cycle = 42 days
[b] Patients should be given a blinatumomab medication guide prior to beginning blinatumomab therapy (see Section 18.12).

Response will then be assessed again on Day 35 (± 2 days) of the Re-Induction Cycle. Patients achieving CR or CRi will be registered to Step 2 and receive up to 3 Post-Remission cycles of blinatumomab therapy as outlined in Section 7.2b. Patients may proceed to Step 2 Registration as soon as CR or CRi is documented and the **14 day treatment free period** is completed. Cycle 1, Day 1 of Post-Remission = Day 43 of the preceding Re-Induction Cycle (+/- 3 days).

Patients not achieving CR or CRi after a second Induction cycle will be removed from protocol therapy.

b. Registration Step 2 – Post-Remission – Blinatumomab[c]

Patients must be registered to Step 2 prior to beginning Post-Remission therapy.

Agent	Dose	Route	Day	Schedule[a]
Blinatumomab[b]	28 mcg/day	continuous IV	1-28	every Post-Remission cycle
IT Methotrexate	12 mg	Intrathecal	See Section 7.1a	
Dexamethasone	20 mg	IV	See Section 7.1c	

[a] Note: One cycle = 42 days
[b] Patients should be given a blinatumomab medication guide prior to beginning blinatumomab therapy (see Section 18.12).
[c] Note: Cycle 1, Day 1 of Post-Remission should begin on Day 43 of the preceding Induction or Re-Induction cycle, as applicable (+/- 3 days)

Patients will receive 3 cycles of Post-Remission therapy with blinatumomab. Patients remaining in CR or CRi will proceed to Maintenance as outlined in Section 7.2c. Patients not remaining in CR or CRi will be removed from protocol therapy.

c. Registration Step 3 – Maintenance – POMP Chemotherapy[e]

Patients must be registered to Step 3 prior to beginning Maintenance therapy.

Agent	Dose	Route	Day	Schedule[a]
Prednisone	60 mg/m^2/day (max 120 mg/day)	PO	1-5	every Maintenance cycle for up to 18 cycles
Vincristine[b]	1.4 mg/m^2 (max 2 mg)	IV	1	every Maintenance cycle
6-mercaptopurine[d]	60 mg/m^2/day	PO	1-28	every Maintenance cycle
Methotrexate[c]	20 mg/m^2/day	PO	1, 8, 15, 22	every Maintenance cycle
IT Methotrexate	12 mg	Intrathecal		See Section 7.1a

[a] Note: One cycle = 28 days
[b] Patients should not receive azoles (except for fluconazole) within ± 2 days of vincristine administration.
[c] Patients should not receive NSAIDS, penicillins, proton pump inhibitors or Bactrim (sulfamethoxazole and trimethoprim) on the same day as methotrexate (see Section 3.5 for potential drug interactions).
[d] Doses should be taken without milk or citrus products, and at least one hour after the evening meal. Adjust dose using 50 mg tablets and different doses on alternating days to achieve cumulative weekly dose as close to 420 mg/m^2 as possible (see Section 18.8).
[e] Note: Cycle 1, Day 1 of Maintenance should begin on Day 43 of the preceding Post-remission cycle (+/- 7 days).

Patients will receive POMP chemotherapy for 18 cycles, or until one of the criteria in Section 7.6 has been met.

7.3 Cohort 2 – Philadelphia Chromosome Positive (Ph+) Patients and Ph-like DSMKF Patients

a. Registration Step 1 – Induction – Dasatinib/Prednisone

1. Newly-diagnosed Ph-positive Patients, Newly-diagnosed Ph-like DSMKF Patients, and Relapsed/Refractory Ph-positive Patients who are both dasatinib and other 2nd/3rd generation TKI-naive.

Induction – Dasatinib/Prednisone[a]

Agent	Dose	Route	Day	Schedule[b]
Dasatinib[e]	140 mg/day	PO	1-84[d]	one Induction cycle
Prednisone[c]	60 mg/m^2/day (max 120 mg/day)	PO	1-24	one Induction cycle
Prednisone[c]	tapering	PO	25-32	one Induction cycle
IT Methotrexate	12 mg	Intrathecal		See Section 7.1a

[a] Ph+ and Ph-like DSMKF patients who received dasatinib or another 2nd or 3rd generation TKI prior to Registration will begin protocol therapy with Re-Induction Cycle 1 (see Section 7.3b).
[b] Note: One cycle = 84 days
[c] Prednisone dose will taper starting on Day 25 and stop at Day 32, with the last tapered dose administered on Day 32. It is recommended that dose be tapered by 15%/day for 7 days, but local institutional standards for dose tapering may be used instead.
[d] Patients not achieving CR or CRi by Day 56 will not receive dasatinib on Days 57-84, but will proceed directly to Re-Induction as outlined in Section 7.3b.
[e] Patients should be given a dasatinib handout/wallet card prior to beginning dasatinib therapy (see Section 18.11).

Response will be assessed on Day 28 (± 2 days). Patients not achieving Day 28 response (CR or CRi) will be re-evaluated at Day 56 (± 2 days). Patients achieving CR or CRi (Day 28 or Day 56) and with continued hematologic remission after Day 84 will then receive up to 3 cycles of post-remission blinatumomab/dasatinib as outlined in Section 7.3c. Patients not achieving CR or CRi by Day 56 will not receive dasatinib on Days 57-84, but will proceed directly to Re-Induction as outlined in Section 7.3b. Patients who do not have continued hematologic remission after Day 84 will proceed to Re-Induction as outlined in Section 7.3b.

Dasatinib may be taken with or without meals. The dosing time may be adjusted as required (for once daily dosing, recommend skipping doses that are missed by more than 12 hours). If doses are missed for toxicity, they should not be replaced. If vomiting occurs within 30 minutes of intake, that dose may be repeated. Crushing or cutting dasatinib tablets is prohibited.

2. Relapsed/Refractory Ph-positive and Ph-like DSMKF Patients who have received prior therapy with either dasatinib or another 2nd/3rd generation TKI.

   Ph+ and Ph-like DSMKF patients who received dasatinib or another 2nd or 3rd generation TKI prior to Registration will begin protocol therapy with Re-Induction Cycle 1 (see Section 7.3b below).

b. Re-Induction – Blinatumomab

Agent	Dose	Route	Day	Schedule [a]
Blinatumomab [b]	9 mcg/day 28 mcg/day	continuous IV continuous IV	1-7 8-28	Re-Induction Cycle 1 Re-Induction Cycle 1
Blinatumomab	28 mcg/day	continuous IV	1-28 [c]	Re-Induction Cycle 2
IT Methotrexate	12 mg	Intrathecal	See Section 7.1a	
Dexamethasone	20 mg	IV	See Section 7.1c	

[a] Note: One cycle = 42 days
[b] Patients should be given a blinatumomab medication guide prior to beginning blinatumomab therapy (see Section 18.12).
[c] Blinatumomab Re-Induction consists of a 28-day continuous IV infusion, followed by 14 days of no treatment, for a total of a 42 day cycle.

Response will be assessed at Day 35 (± 2 days) of Cycle 1. Patients achieving CR or CRi will proceed to blinatumomab/dasatinib therapy as outlined in Section 7.3c. Patients not achieving CR or CRi will receive a second cycle of blinatumomab re-Induction. Response will then be assessed again on Day 35 (± 2 days) of Cycle 2. Patients achieving CR or CRi will proceed to blinatumomab/dasatinib therapy as outlined in Section 7.3c. Patients not achieving CR or CRi will be removed from protocol therapy. Patients may proceed to Step 2 Registration as soon as CR or CRi is documented and the 14 day treatment free period is completed.

c. Registration Step 2 – Post-Remission – Blinatumomab/Dasatinib (see Section 7.3e) [d]

Patients must be registered to Step 2 prior to beginning Post-Remission therapy.

Agent	Dose	Route	Day	Schedule [a]
Blinatumomab [b c]	28 mcg/day	continuous IV	1-28	Post-Remission Cycles 1-3
Dasatinib [c]	70 mg/day	PO	1-42	Post-Remission Cycles 1-3
IT Methotrexate	12 mg	Intrathecal	See Section 7.1a	
Dexamethasone	20 mg	IV	See Section 7.1c	

[a] Note: One cycle = 42 days

[b] Blinatumomab dosing frequency is 28 days on-treatment and 14 days off-treatment in a 42-day cycle.
[c] Patients should be given a blinatumomab medication guide prior to beginning blinatumomab therapy (see Section 18.12).
[d] Patients should be given a dasatinib handout/wallet card prior to beginning dasatinib therapy (see Section 18.11).
[e] Note: Day 1, Cycle 1 of Post-Remission should begin on Day 43 of the preceding Induction cycle (+/- 3 days) or Day 85 of the preceding Re-Induction cycle (+/- 3 days), as applicable.

Patients will receive 3 post-remission cycles of blinatumomab/dasatinib therapy. Patients remaining in CR or CRi will proceed to Maintenance as outlined in Section 7.3d. Patients not remaining in CR or CRi will be removed from protocol therapy.

Dasatinib may be taken with or without meals. The dosing time may be adjusted as required (for once daily dosing, recommend skipping doses that are missed by more than 12 hours). If doses are missed for toxicity, they should not be replaced. If vomiting occurs within 30 minutes of intake, that dose may be repeated. Crushing or cutting dasatinib tablets is prohibited.

d. Registration Step 3 – Maintenance – Dasatinib/Prednisone[c]

Patients must be registered to Step 3 prior to beginning Maintenance therapy.

Agent	Dose	Route	Day	Schedule[a]
Dasatinib[b]	140 mg/day	PO	1-28	each Maintenance cycle
Prednisone	60 mg/m^2/day (max 120 mg/day)	PO	1-5	each Maintenance cycle for up to 18 cycles
IT Methotrexate	12 mg	Intrathecal		See Section 7.1a

[a] Note: One cycle = 28 days
[b] Patients should be given a dasatinib handout/wallet card prior to beginning dasatinib therapy (see Section 18.11).
[c] Note: Cycle 1, Day 1 of Maintenance should begin on Day 43 of the preceding Post-remission cycle (+/- 7 days).

Dasatinib may be taken with or without meals. The dosing time may be adjusted as required (for once daily dosing, recommend skipping doses that are missed by more than 12 hours). If doses are missed for toxicity, they should not be replaced. If vomiting occurs within 30 minutes of intake, that dose may be repeated.

Patients will receive Maintenance until one of the criteria in Section 7.6 has been met.

e. Dose Limiting Toxicities and Feasibility

For Cohort 2 only, a feasibility study will be conducted for the dasatinib/blinatumomab portion of the trial. After the first 9 patients who receive post-remission therapy are accrued, the trial will be evaluated in a run-in phase. Although there will not be a dose escalation, the regimen will not be considered feasible if 3 or more of the first 9 patients have dose limiting toxicities (DLT). Dose-limiting toxicity (DLT) will be defined as any of the following events occurring during the first cycle of post-remission treatment that are possibly, probably, or definitely attributable to blinatumomab or dasatinib: (1) Grade 3 or higher non-hematologic

toxicities, with the exception of nausea, vomiting, or diarrhea (if manageable with supportive care measures and does not require hospitalization, TPN, or tube feeding); and (2) Grade 4 neutropenia that lasts > 42 days. Section 11.2 contains further details of this design.

Adverse events and accrual monitoring are done routinely by the Study Chairs and Study Statisticians. A mandatory conference call for study teams with active patients will take place twice a month (see Section 15.6).

7.4 Drug Compliance Documentation

Drug compliance of oral drugs will be recorded by patients in the Intake Calendar (see Section 18.1). Institutional CRAs will review and ascertain patient adherence with oral protocol therapy at the end of treatment for each applicable cycle. The calendar should be kept in the patient's clinic 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.

7.5 Full CDUS Reporting Requirement

Because this study contains an investigational drug for which CTEP holds the IND, it falls under CTEP requirements for full reporting. This involves required submission of cycle-specific toxicity and dose information (see Section 14.4d, the **S1318** Treatment Form, and the **S1318** Adverse Event Form). Cycle definitions are as follows:

a. Cohort 1 – Ph-Negative Patients

1. Induction/Re-Induction – Blinatumomab: 35-42 days

2. Post-Remission – Blinatumomab: 35-42 days

3. Maintenance – POMP Chemotherapy: 28 days

b. Cohort 2 – Ph-Positive and Ph-like DSMKF Patients

1. Induction – Dasatinib/Prednisone: 56-84 days (for newly diagnosed patients and relapsed/refractory patients without prior dasatinib or another 2nd or 3rd generation TKI)

2. Re-Induction – Blinatumomab: 35-42 days

3. Post-Remission – Blinatumomab/Dasatinib: 42 days

4. Maintenance – Dasatinib/Prednisone: 28 days

7.6 Criteria for Removal from Protocol Treatment

a. Relapse (as defined in Section 10.5).

b. Failure to achieve remission (CR or CRi) after completion of Induction/Re-Induction therapy.

c. Failure to remain in remission (CR or CRi) following Post-Remission Therapy.

d. **Ph- patients**: Completion of 18 cycles of POMP chemotherapy.

e. **Ph+ and Ph-like DSMKF patients**: Completion of 10 years of protocol therapy (from time of initial registration).

f. Unacceptable toxicity. See Section 8.3 for allowable treatment interruption timeframes due to toxicity.

g. The patient may withdraw from the study at any time for any reason.

h. Treatment delay for any reason > 42 days.

7.7 Discontinuation of Treatment

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

7.8 Follow-Up Period

All patients will be followed until death or 10 years after initial registration, whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

Two different versions of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be used on this study.

a. Serious Adverse Event (SAE) reporting

The CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 will be utilized **for SAE reporting only**. The CTCAE Version 5.0 can be downloaded from the CTEP home page (https://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0.

b. Routine toxicity reporting

This study will utilize the CTCAE Version 4.0 for routine toxicity reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (https://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

8.2 General Considerations

a. Dose modifications will be made only as outlined below.

b. Missed doses should be made up as soon as possible, unless otherwise noted below.

c. If multiple toxicities are experienced, dose modifications will be based on the toxicity requiring the largest dose reduction. Doses will not be reduced for alopecia.

d. Reductions are based on the dose given in the preceding cycle and are based on toxicities observed since the prior toxicity evaluation.

e. If a drug must be permanently discontinued, the patient may continue on protocol treatment with the remaining drug(s). Exceptions: If blinatumomab is permanently discontinued in either cohort or dasatinib is permanently discontinued in Cohort 2 (Ph+/Ph-like DSMKF), patients must be removed from protocol therapy.

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

8.3 Dose Modifications

a. Blinatumomab

Pretreatment as outlined in Section 7.1 is required prior to re-starting blinatumomab infusion. Re-start of the infusion should be performed in the hospital under supervision of the principal investigator. The table below outlines treatment cycle duration following treatment interruption for adverse events:

Length of Interruption	Length of Treatment Prior to Interruption	Re-Starting Infusion
≤ 7 days	Any	Continue same cycle of blinatumomab for total treatment duration 28 days on blinatumomab.
8-14 days	≤ 14 days	Same Cycle of treatment will be re-started as if a new cycle and continue for an additional 28 days total.
8-14 days	> 14 days	The cycle of treatment will be terminated and will not be repeated. The next cycle will begin as scheduled.
> 14 days (+5 days for logistical issues – see below)	Any	Blinatumomab is permanently discontinued; patient is removed from protocol therapy.

Note that if the adverse events resolve to a level allowing resumption of blinatumomab in < 14 days, but logistical difficulties arise, re-start of treatment can be postponed for up to 5 additional days without resulting in permanent treatment discontinuation.

Dose modifications for adverse events thought to be related to blinatumomab are listed in the table below:

Adverse Event	Toxicity Grade	Action
Events within the "Nervous System Disorders" or "Psychiatric Disorders" "System Organ Class (SOC) (other than seizures)" [1]	Grade 1	Continue at same dose level.
	Grade 2	Dexamethasone should be administered at a dose of at least 24 mg per day (8 mg every 8 hours orally or IV) for up to three days. The dexamethasone dose will then be reduced step-wise over up to four days.
	Grade 3	Infusion of the blinatumomab must be stopped immediately. Dexamethasone should be administered at a dose of at least 24 mg per day (8 mg every 8 hours orally or IV) for up to three days. The dexamethasone dose will then be reduced step-wise over up to four days. Hold blinatumomab until toxicity resolves to Grade ≤ 1, and for at least 3 days, then resume blinatumomab at 9 mcg/day. Escalate to 28 mcg/day after

Adverse Event	Toxicity Grade	Action
Events within the "Nervous System Disorders" or "Psychiatric Disorders" "System Organ Class (SOC) (other than seizures)" 1 (contd.)	Grade 3 (contd.)	7 days if the toxicity does not recur. If the toxicity occurred at 9 mcg/day or if the toxicity takes more than 7 days to resolve, discontinue blinatumomab permanently. Subsequent cycles of blinatumomab will be started at 9 mcg/day and then escalated to 28 mcg/day after 7 days if the toxicity does not recur. Infusion should be re-started in the hospital, under supervision of the investigator and the patient should remain hospitalized for at least two days. Within one hour prior to re-start of treatment and within one hour prior to any dose increases, patients must receive 20 mg of dexamethasone intravenously. At first three days after re-start, vital sign measurements and writing tests should be performed on study Days 1-3. If patient has already been dose reduced to 9 mcg/day dose for any reason and Grade 3 event occurs, blinatumomab is discontinued permanently and the patient is removed from protocol therapy.
	Grade 4	Infusion of the blinatumomab must be stopped immediately. Dexamethasone should be administered at a dose of at least 24 mg per day (8 mg every 8 hours orally or IV) for up to three days. The dexamethasone dose will then be reduced step-wise over up to four days. Blinatumomab is discontinued permanently and the patient is removed from protocol therapy.
Seizure	Grade 1-2	Discontinue blinatumomab permanently if more than 1 seizure occurs. As per Grade 3 Nervous System/Psychiatric Disorders (above). Appropriate prophylactic therapeutic doses of anticonvulsant treatment (e.g. phenytoin or levetiracetam) will be administered during subsequent infusions of blinatumomab.

Adverse Event	Toxicity Grade	Action
Seizure (contd.)	Grade 3	Discontinue blinatumomab permanently if more than 1 seizure occurs. Withhold blinatumomab until no more than Grade 1 (mild) and for at least 3 days, then restart blinatumomab at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. If the toxicity occurred at 9 mcg/day, or if the toxicity takes more than 7 days to resolve, discontinue blinatumomab permanently.
	Grade 4	Discontinue blinatumomab permanently.
All other events under “Nervous System Disorders” or “Psychiatric Disorders” “System Organ Class (SOC)”	Grade 1-4	Continue therapy with supportive care as per local institutional guidelines
Cytokine Release Syndrome (CRS), Allergic Reactions, Anaphylaxis, or Infusion Related Reaction	Grade 1	Continue therapy with supportive care, as per institutional guidelines.
	Grade 2	The infusion of the blinatumomab must be stopped immediately. Supportive care, as per institutional guidelines. If the interruption is longer than four hours, re-start of the infusion should be performed in the hospital, under supervision of the investigator. Within one hour prior to re-start of treatment and within one hour prior to any dose increases, patients must receive 20 mg of dexamethasone intravenously.
	Grade 3	The infusion of the blinatumomab must be stopped immediately. Dexamethasone should be administered at a dose of at least 24 mg per day (8 mg every 8 hours orally or IV) for up to three days. The dexamethasone dose will then be reduced step-wise over up to four days. Hold blinatumomab until toxicity resolves to Grade ≤ 1, then resume drug at 9 mcg/day for one week. If toxicity remains Grade ≤ 1, increase dose to 28 mcg/day to complete 28 day cycle of therapy.

Adverse Event	Toxicity Grade	Action
Cytokine Release Syndrome (CRS), Allergic Reactions, Anaphylaxis, or Infusion Related Reaction (contd.)	Grade 3 (contd.)	Within one hour prior to re-start of treatment and within one hour prior to any dose increases, patients must receive 20 mg of dexamethasone intravenously. If Grade 3 recurs after blinatumomab is resumed, stop drug permanently; patient is removed from protocol therapy. If the initial adverse event lasts for ≥ 2 weeks without improvement, then blinatumomab is discontinued permanently and the patient is removed from protocol therapy.
	Grade 4	Blinatumomab is discontinued permanently; patient is removed from protocol therapy.
Sepsis, bacteremia, device or catheter-related infection	Grade 1-2	Continue therapy with supportive care as per local institutional guidelines
	Grade 3-4	Monitor for recurrence. Per Section 11.5, SWOG will evaluate overall infection rate for all patients receiving 72-96 hour IV bags.
Aspartate Aminotransferase (AST) Increased, Alanine Aminotransferase (ALT) Increased	Grade 1-2	Continue at same dose level.
	Grade 3-4	Hold blinatumomab until toxicity resolves to Grade ≤ 1, then resume drug at 9 mcg/day for one week. If toxicity remains Grade ≤ 1, increase dose to 28 mcg/day to complete 28 day cycle of therapy. If Grade 3-4 toxicity recurs, stop drug permanently; patient is removed from protocol therapy. Within one hour prior to re-start of treatment and within one hour prior to any dose increases, patients must receive 20 mg of dexamethasone intravenously.
Blood Bilirubin Increased	Grade 1-2	Continue at same dose level.
	Grade 3-4	Hold blinatumomab until toxicity resolves to Grade ≤ 1, then resume drug at 9 mcg/day for one week. If toxicity remains Grade ≤ 1, increase dose to 28 mcg/day to complete 28 day cycle of therapy. If Grade 3-4 toxicity recurs, stop drug permanently; patient is removed from protocol therapy.

Adverse Event	Toxicity Grade	Action
Blood Bilirubin Increased (contd.)	Grade 3-4 (Contd.)	Within one hour prior to re-start of treatment and within one hour prior to any dose increases, patients must receive 20 mg of dexamethasone intravenously.
Disseminated Intravascular Coagulation	Grade 1-2	Continue at same dose level.
	Grade 3-4	Hold blinatumomab until resolves to Grade ≤ 2, then resume drug at 9 mcg/day for one week. If toxicity remains Grade ≤ 1, increase dose to 28 mcg/day to complete 28 day cycle of therapy. If Grade 3-4 toxicity recurs, stop drug permanently. If the initial adverse event lasts for ≥ 2 weeks without improvement, then blinatumomab will be permanently discontinued; patient is removed from protocol therapy. Within one hour prior to re-start of treatment and within one hour prior to any dose increases, patients must receive 20 mg of dexamethasone intravenously.
Thromboembolic Events	Grade 1	Continue at same dose level.
	Grade 2-4	Hold blinatumomab until clot and clinical situation stabilized, then resume drug at 9 mcg/day for one week. If no progression of thrombus, increase dose to 28 mcg/day to complete 28 day cycle of therapy. If progression of existing thrombosis or new thrombosis or Grade 4 initially, stop drug permanently; patient is removed from protocol therapy. Within one hour prior to re-start of treatment and within one hour prior to any dose increases, patients must receive 20 mg of dexamethasone intravenously.
Lymphocyte Count Decreased	Grade 1-4	Continue at same dose level.
Neutrophil Count Decreased	Grade 1-2	Continue at same dose level.
	Grade 3-4	Hold blinatumomab until toxicity resolves to Grade ≤ 1, then resume drug at 9 mcg/day for one week. If toxicity remains Grade ≤ 1, increase dose to 28 mcg/day to complete 28 day cycle of therapy. If Grade 3 recurs, reduce dose to 9 mcg/day and if after one week toxicity is Grade ≤ 2, continue at 9 mcg/day. If Grade 4

Adverse Event	Toxicity Grade	Action
Neutrophil Count Decreased (contd.)	Grade 3-4 (contd.)	toxicity recurs, stop drug permanently; patient is removed from protocol therapy. Within one hour prior to re-start of treatment and within one hour prior to any dose increases, patients must receive 20 mg of dexamethasone intravenously.
Platelet Count Decreased	Grade 1-3	Continue at same dose level.
	Grade 4	Hold blinatumomab until resolves to Grade ≤ 2, then resume drug at 9 mcg/day for one week. If toxicity remains Grade ≤ 3, increase dose to 28 mcg/day to complete 28 day cycle of therapy. If Grade 4 toxicity recurs, reduce dose to 9 mcg/day and if after one week toxicity is Grade ≤ 2, continue at 9 mcg/day. If Grade 4 toxicity recurs, stop drug permanently; patient is removed from protocol therapy. Within one hour prior to re-start of treatment and within one hour prior to any dose increases, patients must receive 20 mg of dexamethasone intravenously.
All Other AEs within the "Investigation" SOC and "Metabolism and Nutrition Disorders" SOC	Grade 1-4	Continue at same dose level, provided toxicity is not medically consequential and has been readily corrected. If abnormality is medically consequential, refer to guidelines for other non-hematologic events. Patients who develop Grade 3 or 4 electrolyte laboratory abnormalities may continue study treatment without interruption but should receive appropriate medical therapy.
Other Non-Hematologic AEs	Grade 1-2	Continue at same dose level.
	Grade 3-4	Hold blinatumomab until resolves to Grade ≤ 1, then resume drug at 9 mcg/day for one week. If toxicity remains Grade ≤ 1, increase dose to 28 mcg/day to complete 28 day cycle of therapy. If Grade 3 recurs, reduce dose to 9 mcg/day and if after one week toxicity is Grade ≤ 2, continue at 9 mcg/day. If Grade 4 toxicity recurs, stop drug permanently; patient is removed from protocol therapy.

Adverse Event	Toxicity Grade	Action
Other Non-Hematologic AEs (contd.)	Grade 3-4 (contd.)	Within one hour prior to re-start of treatment and within one hour prior to any dose increases, patients must receive 20 mg of dexamethasone intravenously.

[1] For the purposes of blinatumomab dose modification, neurological toxicity does not include: CNS infections, CNS bleeding events, or CNS events due to leukemic involvement.

If a patient experiences one or more of the AEs listed in the table above, and the AE(s) is/are determined by the investigator to be possibly, probably, or definitely related to blinatumomab, follow the dose management guidelines for nervous system or psychiatric disorders specified at the top of the table above. Note that Seizure (an AE under the "Nervous System Disorders" SOC) also has a possible, probable, or definite link to blinatumomab but has a separate set of management guidelines as outlined in the table.

b. Dasatinib

1. Induction:

For Grade 3-4 non-hematologic toxicity, hold dasatinib until toxicity resolves to ≤ Grade 1. Dose may be reduced to 70 mg once daily for Grade 3 or 4 non-hematologic toxicity. Consider discontinuing if Grade 3 or Grade 4 non-hematologic toxicity recurs. Further dose reductions should be discussed with the Study Chair.

2. Post-Remission:

a. For Grade 3-4 non-hematologic toxicity, hold dasatinib until toxicity resolves to ≤ Grade 1. Upon resumption of protocol therapy, the dose may be reduced to 40 mg once daily.

b. For ANC < 500/ mcL or platelets < 30,000/ mcL, hold dasatinib until ANC ≥ 1000/mcL and platelets ≥ 50,000/mcL. If recovery occurs in ≤ 2 weeks, resume at previous dose. If recovery occurs in > 2 weeks, resume at 40 mg/day.

c. Further dose reductions should be discussed with the Study Chair.

3. Maintenance

a. For Grade 3-4 non-hematologic toxicity, hold dasatinib until toxicity resolves to ≤ Grade 1. Upon resumption of protocol therapy, the dose may be reduced to 70 mg once daily.

b. For ANC < 500/mcL or platelets < 30,000/mcL, hold until ANC > 1,000/mcL and platelets > 50,000/mcL. If recovery occurs in ≤ 2 weeks, resume at same dose. If recovery occurs in > 2 weeks, resume at 70 mg once daily.

c. Further dose reductions should be discussed with the Study Chair.

c. Prednisone

Any dose reductions or omissions of prednisone while on any portion of the trial must be discussed with the Study Chair and documentation of this discussion must be kept in the patient's clinical chart.

d. POMP Chemotherapy

1. Recommendations for Thiopurine Monitoring and Dosage Adjustments for Myelosuppression (6-Mercaptopurine as part of POMP Chemotherapy)

a. It is recommended that patients have their Thiopurine Methyltransferase (TPMT) status and/or their thiopurine metabolite concentrations evaluated, so that the dose of 6-mercaptopurine can be reduced in patients with a TPMT defect. Patients with the rare homozygous deficient TPMT phenotype may tolerate only 1/10th to 1/20th the average 6- mercaptopurine dose. Heterozygotes may need a 30-50% dose reduction of 6-mercaptopurine. TPMT testing and thiopurine metabolite measurements are commercially available.

When myelosuppression has led to significant delays in therapy (> 2 weeks) or is disproportionate to the therapy, thiopurine testing should be performed (If not already done).

For patients who have received full dose thiopurine during the 2 weeks immediately preceding the test, RBC thiopurine metabolites will likely predict the TPMT status and actual thiopurine exposure.

In the absence of RBC transfusions for 3 months prior, TPMT activity will accurately reflect TPMT status.

TPMT genotyping will be informative in all patients, if at least one mutant allele is identified. If not, and myelosuppression continues, send samples for TPMT activity and/or metabolites since TPMT genotyping will miss 5-10% of mutants.

For patients with TPMT mutation, 6-mercaptopurine dose will not be re-escalated if reduced.

NOTE: Genotyping can be done despite recent transfusions.

b. Dose Adjustments for Patients with Unacceptable Myelosuppression

- **If the patient is homozygous deficient for TPMT**, the thiopurine dose should be reduced to 10-20 mg/m^2/day given 3 days per week.
- **If the patient is heterozygous for TPMT and has experienced significant myelosuppression**, the thiopurine dose should be reduced by 30-50%. Do not increase the dose in response to a high ANC for four weeks to allow for achievement of steady state. All other myelosuppressive medications should be delivered at full dose, and the thiopurine dose should be titrated based on blood counts. Further thiopurine pharmacologic measures are often not necessary.

- **If the patient is homozygous wild-type (high activity) for TPMT**, then discontinue cotrimoxazole (if used) and use pentamidine or dapsone. Should ANC fall again below 500/mcL on two or more occasions, decrease dose of 6-MP or MTX by 25% on an alternating basis upon resumption of therapy.

2. Oral Methotrexate and 6-Mercaptopurine

a. Cytopenias

ANC < 500/mcL	1st Instance: Hold 6-MP and PO MTX until ANC ≥ 750/mcl then resume at full dose. 2nd Instance: Discontinue 6-MP and PO MTX until ANC ≥ 750/mcL. Restart 6-MP and/or MTX at 50% of the original dose on the same day the counts recover. Increase to 75% and then 100% of the original dose in 2-4 week intervals provided ANC ≥ 750/mcL. Consider discontinuing cotrimoxazole and switching patient to dapsone or pentamidine. Subsequent Instances: If ANC < 500/mcL on ≥ 2 occasions, perform thiopurine pharmacology testing (see Section 8.3d.1). Should therapy be withheld for myelosuppression, do not "make up" that week. Resume therapy at the correct point chronologically.
Platelets < 75,000/mcL	1st Instance: Hold 6-MP and PO MTX. Resume at full dose once platelets ≥ 75,000/mcL. 2nd Instance: Discontinue 6-MP until platelets ≥ 75,000/mcL. Restart 6-MP and/or MTX at 50% of the original dose on the same day the counts recover. Increase to 75% and then 100% of the original dose at 2-4 week intervals provided platelets ≥ 75,000/mcL. Consider discontinuing cotrimoxazole and switching patient to dapsone or pentamidine. Subsequent Instances: If platelets < 75,000/mcL on ≥ 2 occasions, perform thiopurine pharmacology testing (see Section 8.3d.1). Should therapy be withheld for myelosuppression, do not "make up" that week. Resume therapy at the current point chronologically.

b. Oral MTX and 6-MP Dose Escalation During Maintenance Therapy

For ANC ≥ 1500/mcL, on 3 CBCs done over 6 weeks or 2 successive monthly CBCs, first increase the dose of either PO

MTX or 6-MP by 25%. Then increase the dose of the other drug by 25%. If there is no fall in ANC after both PO MTX and 6-MP have been increased once, consider noncompliance is a possibility. Consider observing the administration of an oral dose of MTX and checking plasma MTX concentration 2-4 hours later. This will document whether or not poor absorption contributes to lack of response and may facilitate discussions about noncompliance. **If oral MTX dose is escalated to 40 mg/m^2, contact the Study Chair before further escalation.**

c. Oral MTX Dose Modifications for Maintenance Therapy for Elevated Transaminases

ALT or AST > 5 x ULN[a]	Obtain total bilirubin. Monitor ALT or AST and total bilirubin every week during Maintenance Therapy as long as transaminases remain > 5 x ULN.
ALT or AST > 8 x ULN on two determinations at least one week apart or total bilirubin > 2 mg/dL	Hold MTX and monitor labs weekly. When ALT or AST is < 5 x ULN and direct bilirubin is within normal, then resume at the previous dose.

[a] The investigator may reduce the dose of methotrexate for AST or ALT >8x ULN at their discretion in elderly patients.

Exclude infectious hepatitis (A, B, C) for persistent (> 1 month) elevations in ALT or AST.

d. Oral MTX Dose Modifications for Mucositis During Maintenance Therapy

Grade 3	PO MTX should be given at 50% of the previous dose.
Grade 4	PO MTX should be temporarily held. Once toxicity resolves, then resume PO MTX at 50% of the previous dose. PO MTX should then be escalated as tolerated. Consider culturing lesions for herpes simplex if mucositis persists or recurs.

e. Oral MTX Dose Modifications for Diarrhea and Vomiting During Maintenance Therapy

If either severe diarrhea or vomiting (≥ Grade 3) develops after PO MTX administration, PO MTX should be temporarily held. After resolution of symptoms (i.e., < Grade 2) for a period of one week, resume PO MTX at 50% of the previous dose. PO MTX should then be escalated as tolerated. If symptoms recur, adjust the dose to the maximum tolerated to prevent recurrent symptoms. The patient should be evaluated for infectious as well as other causes of diarrhea and vomiting.

f. Oral MTX for Bilirubin

If direct bilirubin > 2.0 mg/dl, then hold methotrexate. Monitor labs weekly until bilirubin ≤ 2.0 mg/dl, then resume at previous dose.

g. Dose Modifications for Renal/Genitourinary Toxicity During Maintenance Therapy

- For ≥ Grade 2 creatinine, hold PO MTX until toxicity resolves to ≤ Grade 2. Once toxicity has resolved to this level, then PO MTX may be resumed at the previous dose.
- For ≥ Grade 2 creatinine, hold 6-MP until toxicity resolves to ≤ Grade 1. Once toxicity has resolved to this level, then 6-MP may be resumed at the previous dose.

3. Vincristine

Obtain bilirubin within ± 2 days of vincristine administration. Hold vincristine for direct bilirubin ≥ 2.

Hold vincristine for neuropathy ≥ Grade 2.

If toxicity (bilirubin or neuropathy) resolves to ≤ Grade 1 within 1 week dose may be made up; otherwise dose is skipped.

8.4 Supportive Care and Concomitant Medications

a. General Instructions for Blinatumomab

Fluid Intake/Output Monitoring

Close monitoring of fluid status by intake and output should be undertaken for the first week of blinatumomab infusion. Efforts to keep patients balanced between intake and output should be maintained, even if diuretic therapy (furosemide or similar) is needed to do this. Careful attention to fluid status may prevent deterioration from capillary leak, however even with meticulous attention, some patients will experience pulmonary edema and require more aggressive respiratory support. Treating physicians should use their clinical judgment and institutional standards for whatever supportive care measures are needed during this period of time.

Monitoring of Disseminated Intravascular Coagulation (DIC)

In the first days of treatment, transient disseminated intravascular coagulation (DIC)-like pictures may develop. Because patients are at risk for capillary leak syndrome and cytokine release syndrome, appropriate supportive care with dexamethasone (see dose modification table in Section 8.3a), blood products and factors (packed red cells, platelets, cryoprecipitate, fresh frozen plasma), vitamin K, and/or albumin should be considered according to institutional standards of care. Particularly in the first week of infusion, when the risk of capillary leak and cytokine release is more prominent, appropriate use of blood products and factors is preferred if laboratory indications suggest the need for replacement, as large volumes of crystalloid fluids tend to exacerbate the capillary leak. See Section 8.3a for guidelines regarding blinatumomab dose modifications and AE management.

Cytokine Release Syndrome (CNS) Risk Mitigation Plan

Manifestations of cytokine release syndrome include fever, headache, nausea, asthenia, hypotension, increased alanine aminotransferase, increased aspartate aminotransferase, increased total bilirubin, and disseminated intravascular coagulation (DIC).

Monitor patients for signs or symptoms of these symptoms:

- In patients treated for MRD-positive B-cell precursor ALL, hospitalization is recommended for the first 3 days of the first cycle and the first 2 days of the second cycle.
- In patients treated for relapsed or refractory B-cell precursor ALL, hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle.

Administer corticosteroids for severe or life-threatening cytokine release syndrome.

Hematological Monitoring

In the first days of treatment, a rapid transient drop in platelets, neutrophils and/or hemoglobin may be observed. These effects are not necessarily cytokine-mediated. Counts typically recover to baseline during treatment, and usually within two weeks of starting blinatumomab. Transfusion of blood and platelets should be performed according to appropriate institutional standards. Blinatumomab dose modification and AE management guidelines for decreases in neutrophils, lymphocytes, and platelets can be found in Section 8.3a.

Monitoring of Blood ALT/AST levels

In the first days of treatment, transient increases in transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) up to over 1000 U/L may develop. These have generally returned to baseline in the first week of treatment. Blinatumomab dose modification and AE management guidelines for Grade 3 and 4 increases in ALT or AST can be found in Section 8.3a.

b. Supportive care regarding adequate hydration and use of antiemetics for nausea and vomiting should be administered according to institutional guidelines.

c. G-CSF/GM-CSF Guidelines

G-CSF/GM-CSF may be used at the discretion of the treating investigator and in accordance with ASCO guidelines.

Growth factors should not be administered on the same day as methotrexate or 6-mercaptopurine, or during any cycles of blinatumomab treatment.

The use of G-CSF/GM-CSF must be documented on the **S1318** Treatment Form. Any toxicities associated with G-CSF must also be documented on the **S1318** Adverse Event Form.

d. Patients should not take antacids, but if they are absolutely necessary they must be taken at least 2 hours before or 2 hours after dosing of dasatinib.

e. For Cohort 2 (Ph+/Ph-like DSMKF cohort) during dasatinib treatment: Patients currently taking drugs that are generally accepted to have a risk of causing Torsades de Pointes (including: quinidine, procainamide, disopyramide, amiodarone, sotalol, ibutilide, dofetilide, erythromycins, clarithromycin, chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide, cisapride, bepridil, droperidol, methadone, arsenic, chloroquine, domperidone, halofantrine, levomethadyl, pentamidine, sparfloxacin, lidofazine) should change these to acceptable alternatives.

f. For Cohort 2 (Ph+/Ph-like DSMKF cohort) during dasatinib treatment: Medications that inhibit platelet function (i.e., aspirin, dipyridamole, epoprostenol, eptifibatide, clopidogrel, cilostazol, abciximab, ticlopidine, and any non-steroidal anti-inflammatory drug) or anticoagulants (warfarin, heparin/low molecular weight heparin [e.g., danaparoid, dalteparin, tinzaparin, enoxaparin]) should be avoided as much as possible.

Exceptions include low-dose warfarin for prophylaxis to prevent catheter thrombosis, and for heparin-flushes for IV lines. If patients develop deep vein thrombosis during the course of therapy or are receiving anticoagulation for indications such as recent thrombosis or artificial heart valves these drugs may be continued with close monitoring of the patients.

g. Dasatinib should not be used concomitantly with strong CYP3A4 inhibitors, such as ketoconazole, itraconazole, voriconazole, and posaconazole. Dasatinib may be used with moderate CYP3A4 inhibitors such as isavuconzole or fluconazole when necessary for oral antifungal prophylaxis. (A list of CYP3A4 inhibitors can be found in Section 18.3). Dose reduction while administering oral antifungal agents is not necessary.

h. Recommended medications for fever management are paracetamol/ acetaminophen and/or dexamethasone. The dexamethasone dose should be reduced step-wise as soon as the fever resolves. If these medications are not sufficiently effective, pethidine/meperidine is recommended. For pethidine/meperidine, adequate anti-emetic prophylaxis should be administered.

i. During POMP Chemotherapy, it is recommended that patients receive prophylaxis with Sulfamethoxazole/trimethoprim 800/160 mg (Bactrim DS), one tablet oral daily on Monday, Wednesday, and Friday continuing throughout and for 6 months after the completion of POMP chemotherapy. For patients allergic to or experiencing excessive myelosuppression with cotrimoxazole, alternative prophylactic regimens include dapsone or aerosolized pentamide (300 mg once every 4 weeks via nebulizer). In some settings IV pentamidine may be considered.

Allopurinol must be stopped during administration of 6-Mercaptopurine. Concurrent use can result in excess toxicity. Allopurinol inhibits xanthine oxidase, which metabolizes mercaptopurine. When administered with allopurinol, the dose of 6-Mercaptopurine must be reduced to 25-30% of the usual dose.

Avoid use of itraconazole, voriconazole or posaconazole with vincristine therapy (Echinocandin or amphotericin may be considered, in accordance with local institutional guidelines).

j. Other supportive measures and prophylactic antibiotics, antivirals and/or antifungals may be used at the discretion of the treating physician.

8.5 Dose Modifications Contacts

For treatment or dose modification questions, please contact the Study Chairs at S1318SC@swog.org (email preferred) or via phone Dr. Anjali Advani at 216/445-9354 or Dr. Kristen O'Dwyer at 585/275-4099.

8.6 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of the protocol must be reported to the Operations Office, Study Chair and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

9.1 Cohort 1 – Ph-Negative Patients – Induction/Re-Induction – Blinatumomab (Permanently closed to accrual 6/29/17)

	Pre-Treatment	Days 1-7	Days 8-14	Days 15-21	Days 22-28	Days 29-35	Days 36-42	Off Protocol Therapy	Follow Up Ω #
REQUIRED STUDIES									
PHYSICAL									
History and Physical Exam £	X	X	X	X	X	X	X		X
Weight and Performance Status	X								
Toxicity Notation £	X	X	X	X	X	X	X		
LABORATORY									
CBC, Differential, Platelets £	X	X	X	X	X	X	X		X
Comprehensive Metabolic Panel £ β	X	X	X	X	X	X	X		X
PT/PTT/INR/Fibrinogen ^	X	X	X	X	X				
Bone Marrow Aspirate and Biopsy #	X					X %		X	
Biopsy for Testicular Involvement €	X								
Lumbar Puncture ∑	X	X ∑							
FISH and/or PCR µ	X								
Neurologic Assessment &	X	X	X	X	X	X	X		
CD4/Viral Load ϖ	X								
X-RAYS AND SCANS									
Chest X-Ray ¥	X								
CT or MRI $	X	X						X	X
ECHO ¥	X								
EKG	X								
SPECIMEN SUBMISSION									
BM Aspirate/Biopsy - TM (MRD) *ƒ*	X					X%			
BM/PB for Cytogenetics ®	X					X%		X	
Serum for Immunogenicity ∝	X						X	X	
BMA Banking & Future Research π	X					X			
TREATMENT Φ									
Blinatumomab		X	X	X	X				
IT Methotrexate		X ∑							

Note: Forms accessible from protocol page at www.swog.org. Form submission schedule is listed in Section 14.0.
Click here for footnotes.

Footnotes for Calendar 9.1.

£ Pre-study, then weekly during Induction and Re-Induction. All Grade 3 or higher relevant infections will be evaluated every 6 months (see Section 11.5).
β Institutional standard metabolic panel is sufficient, providing it includes total bilirubin, AST and ALT, serum creatinine & alkaline phosphatase.
& See Section 7.1c.2.
$ Only if there is evidence of extramedullary disease at diagnosis, CT scan or MRI of the chest, abdomen & pelvis will be performed pre-study, then every 3 months until CT/MRI is negative for extramedullary disease. Once negative, CT/MRI will be performed every 3 months for 2 years, then every 6 months until 5 years after initial registration. CT/MRI is also required at the time the patient is removed from protocol therapy for any reason.
^ Performed at pre-study, then weekly during Days 1-28.
¥ Results do not determine eligibility.
® See Section 15.1. Note: Bone marrow aspirate or (if dry tap) peripheral blood should be submitted for cytogenetic (and FISH, if possible) any time a bone marrow biopsy is performed for disease assessment.
∝ See Sections 15.2 and 18.9.
ƒ See Sections 15.3 and 18.4.
π See Section 15.4 and 15.5. Note: The banked samples will be used for the translational medicine portion detailed in Section 18.15.
% Day 35 (± 2 days) of Induction and Day 35 (± 2 days) of Re-Induction (if needed).
€ Required only if clinical or ultrasound findings are equivocal.
µ Cytogenetics (& FISH, if possible) analyses must be done up to 28 days prior to registration, then subsequently at any time a bone marrow biopsy is performed for disease assessment (see Sections 5.1b & 15.1).
∑ See Section 7.1a.
Ω F/U visits/labs will be performed every 3 months for the first 2 years, then every 6 months for the next 2 years, then annually until 10 years from initial registration.
Φ See Section 7.2a for treatment days and details.
ϖ Required for patients known to be HIV+ only (see Section 5.1r).
After CR or CRi, marrows will be obtained at the discretion of the treating physician.

NOTE: 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.

9.2 Cohort 1 – Ph-Negative Patients – Post-Remission – Blinatumomab

	Pre-Treatment	Days 1-7	Days 8-14	Days 15-21	Days 22-28	Days 29-35	Days 36-42	Removal from Protocol Therapy	Follow Up Ω #
REQUIRED STUDIES									
PHYSICAL									
History and Physical Exam £	X	X	X	X	X	X	X		X
Weight and Performance Status	X								
Toxicity Notation £	X	X	X	X	X	X	X		
LABORATORY									
CBC, Differential, Platelets £	X	X	X	X	X	X	X		X
Comprehensive Metabolic Panel £ β	X	X	X	X	X	X	X		X
Bone Marrow Aspirate and Biopsy #	X							X	
Lumbar Puncture ∑		X ∑							
FISH and/or PCR µ	X								
Neurologic Assessment &	X	X	X	X	X	X	X		
X-RAYS AND SCANS									
CT or MRI $		X						X	X
SPECIMEN SUBMISSION									
BM and PB for Cytogenetics ®		X						X	
Serum for Immunogenicity ∝								X	
TREATMENT Φ									
Blinatumomab		X	X	X	X				
IT Methotrexate		X ∑							

Note: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). The schedule for submission of these forms is listed in Section 14.0.

Click here for footnotes:

Footnotes for 9.2

£ Pre-txt, then weekly. All Gr. 3 or higher relevant infections will be evaluated every 6 months (see Section 11.5).
β Institutional standard metabolic panel is sufficient, providing it includes total bilirubin, AST and ALT, serum creatinine and alkaline phosphatase.
µ Cytogenetics (and FISH, if possible) analyses must be done up to 28 days prior to registration, then subsequently at any time a bone marrow biopsy is performed for disease assessment (see Sections 5.2a and 15.1).
& See Section 7.1c.2.
$ Only if there is evidence of extramedullary disease at diagnosis, CT scan or MRI of the chest, abdomen and pelvis will be performed pre-study, then every 3 months until CT/MRI is negative for extramedullary disease. Once negative, CT/MRI will be performed every 3 months for 2 years, then every 6 months until 5 years after initial registration. CT/MRI is also required at the time the patient is removed from protocol therapy for any reason.
® See Section 15.1. Note: Bone marrow aspirate or (if dry tap) peripheral blood should be submitted for cytogenetic (and FISH, if possible) any time a bone marrow biopsy is performed for disease assessment.
∝ See Sections 15.2 and 18.9.
∑ See Section 7.1a.
Ω Follow up visits/labs will be performed every 3 months for the first 2 years, then every 6 months for the next 2 years, then annually until 10 years from initial registration.
Φ See Section 7.2b for treatment days and details.
After CR or CRi, marrows will be obtained at the discretion of the treating physician.

NOTE: 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.

9.3 Cohort 1 – Ph-Negative Patients – Maintenance – POMP Chemotherapy

	Pre-Treatment	Days 1-7	Days 8-14	Days 15-21	Days 22-28	Removal from Protocol Therapy	Follow Up Ω #
REQUIRED STUDIES							
PHYSICAL							
History and Physical Exam %		X					X
Weight and Performance Status %		X					
Toxicity Notation %	X						
Intake Calendar ≠					X		
LABORATORY							
CBC, Differential, Platelets £	X	X		X			X
Comprehensive Metabolic Panel £ β	X	X		X			X
Bone Marrow Aspirate and Biopsy #	X					X	
Lumbar Puncture ∑		X ∑					
FISH and/or PCR µ	X						
Peripheral Neuropathy Assessment %	X						
X-RAYS AND SCANS							
CT or MRI $		X				X	X
SPECIMEN SUBMISSION							
BM and PB for Cytogenetics ®		X				X	
TREATMENT Φ							
Prednisone +		X					
Vincristine		X					
6-Mercaptopurine		X	X	X	X		
Methotrexate		X	X	X	X		
IT Methotrexate		X ∑					

Note: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). The schedule for submission of these forms is listed in Section 14.0.

Click here for footnotes.

Footnotes for Calendar 9.3:

£ Weekly for the first cycle, then every other week for subsequent cycles.
% Prior to Day 1 treatment each cycle.
β Institutional standard metabolic panel is sufficient, providing it includes total bilirubin, AST and/or ALT, serum creatinine and alkaline phosphatase. CMP should be checked weekly if Grade 3 ALT or AST elevations develop during maintenance therapy.
$ Only if there is evidence of extramedullary disease at diagnosis, CT scan or MRI of the chest, abdomen and pelvis will be performed pre-study, then every 3 months until CT/MRI is negative for extramedullary disease. Once negative, CT/MRI will be performed every 3 months for 2 years, then every 6 months until 5 years after initial registration. CT/MRI is also required at the time the patient is removed from protocol therapy for any reason.
® See Section 15.1. Note: Bone marrow aspirate or (if dry tap) peripheral blood should be submitted for cytogenetic (and FISH, if possible) any time a bone marrow biopsy is performed for disease assessment.
∑ See Section 7.1a.
µ Cytogenetics (and FISH, if possible) analyses must be done up to 28 days prior to registration, then subsequently at any time a bone marrow biopsy is performed for disease assessment (see Sections 5.3a and 15.1).
Ω Follow up visits/labs will be performed every 3 months for the first 2 years, then every 6 months for the next 2 years, then annually until 10 years from initial registration.
≠ CRA will review Intake Calendar at the end of each cycle (see Section 18.1).
Φ See Section 7.2c for treatment days and details.
After CR or CRi, marrows will be obtained at the discretion of the treating physician.
+ Prednisone dosing during the maintenance phase is limited to a maximum of 18 cycles.

NOTE: 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.

9.4 Cohort 2 – Newly-diagnosed Ph+ and Ph-like DSMKF Patients AND Relapsed/Refractory Ph+ and Ph-like DSMKF Patients who are naive to both dasatinib and other 2nd/3rd generation TKIs – Induction – Dasatinib/Prednisone λ

	Pre Tx	Days 1-7	Days 8-14	Days 15-21	Days 22-28	Days 29-35	Days 36-42	Days 43-49	Days 50-56	Days 57-63	Days 64-70	Days 71-77	Days 78-84	Removal from Protocol Therapy	Follow Up Ω #
REQUIRED STUDIES															
PHYSICAL															
History and Physical Exam £	X	X	X	X	X		X		X		X		X		X
Weight and Performance Status £	X	X	X	X	X		X		X		X		X		
Toxicity Notation £	X	X	X	X	X		X		X		X		X		
Intake Calendar ≠															
LABORATORY															
CBC, Differential, Platelets £	X	X	X	X	X		X		X		X		X		X
Comprehensive Metabolic Panel £ β	X	X	X	X	X		X		X		X		X		X
Bone Marrow Aspirate and Biopsy #	X				X				X√					X	
Biopsy for Testicular Involvement €	X														
Lumbar Puncture ∑	X							X ∑							
FISH and/or PCR µ	X														
CD4/Viral Load ϖ	X														
X-RAYS AND SCANS															
Chest X-Ray	X														
CT or MRI $	X							X						X	X
ECHO	X														
EKG	X														

Calendar continued on next page. Click here for footnotes.

	Pre Tx	Days 1-7	Days 8-14	Days 15-21	Days 22-28	Days 29-35	Days 36-42	Days 43-49	Days 50-56	Days 57-63	Days 64-70	Days 71-77	Days 78-84	Removal from Protocol Therapy	Follow Up Ω #
SPECIMEN SUBMISSION															
BM Aspirate/Biopsy - TM (MRD) *ƒ*	X				D28 α				D56 α√						
BMA Banking & Future Research Ѧ	X				D28 α				D56 α√						
BM and PB for Cytogenetics ®	X				D28 α				D56 α√					X	
TREATMENT Φ															
Prednisone		X	X	X	Xπ	Xπ									
Dasatinib		X	X	X	X	X	X	X	X	X	X	X	X		
IT Methotrexate		X ∑													

Note: Forms are found on the SWOG website (www.swog.org). The schedule for submission of these forms is listed in Section 14.0.

Click here for footnotes:

Footnotes for Calendar 9.4.

λ NOTE: Relapsed/Refractory Ph+ and Ph-like DSMKF patients who received dasatinib or another 2nd or 3rd generation TKI prior to Registration will begin protocol therapy with Re-Induction Cycle 1 (see Section 7.3b).
£ Pre-study, then weekly Days 1-28, then every other week Days 29-84.
β Institutional standard metabolic panel is sufficient, providing it includes total bilirubin, AST and/or ALT, serum creatinine and alkaline phosphatase.
$ Only if there is evidence of extramedullary disease at diagnosis, CT scan or MRI of the chest, abdomen and pelvis will be performed pre-study, then every 3 months until CT/MRI is negative for extramedullary disease. Once negative, CT/MRI will be performed every 3 months for 2 years, then every 6 months until 5 years after initial registration. CT/MRI is also required at the time the patient is removed from protocol therapy for any reason
π Tapering Days 25-32 (see Section 7.3a).
α ± 2 days.
® See Section 15.1. Note: Bone marrow aspirate or (if dry tap) peripheral blood should be submitted for cytogenetic (and FISH, if possible) any time a bone marrow biopsy is performed for disease assessment.
ƒ See Sections 15.3 and 18.4.
√ If necessary; see Section 7.3a.
€ Required only if clinical or ultrasound findings are equivocal.
µ Cytogenetics (and FISH, if possible) analyses must be done up to 28 days prior to registration, then subsequently at any time a bone marrow biopsy is performed for disease assessment (see Sections 5.1b and 15.1). For Ph+ patients, PCR for BCR/ABL should be obtained each time cytogenetics is performed. BCR/ABL is not required for Ph-like DSMKF patients (at baseline or subsequently). If not already known, baseline (up to 28 days prior to registration) PCR should include BCR-ABL status (both p190 and p210 analyses) for Ph+ patients. Subsequently, only the baseline positive (p190 or p210) result needs to be repeated.
∑ See Section 7.1a.
Ω Follow up visits/labs will be performed every 3 months for the first 2 years, then every 6 months for the next 2 years, then annually until 10 years after initial registration.
≠ CRA will review Intake Calendar at the end of each cycle (see Section 18.1).
Φ See Section 7.3a for treatment days and details.
ϖ Required for patients known to be HIV+ only (see Section 5.1r)
Ѧ See Section 15.5. Note: The banked samples will NOT be used for the translational medicine portion detailed in Section 18.15.
After CR or CRi, marrows will be obtained at the discretion of the treating physician.

NOTE: 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.

9.5 Cohort 2 – Re-Induction – Blinatumomab (Ph+ and Ph-like DSMKF Patients) λ

	Pre Tx	Days 1-7	Days 8-14	Days 15-21	Days 22-28	Days 29-35	Days 36-42	Removal from Prot Therapy	FU Ω #
REQUIRED STUDIES									
PHYSICAL									
H&P Exam £	X	X	X	X	X	X	X		X
WT & Perf Status £	X	X	X	X	X	X	X		
Toxicity Notation £	X	X	X	X	X	X	X		
LABORATORY									
CBC, Differential, Platelets £	X	X	X	X	X	X	X		X
Comprehensive Metabolic Panel £ β	X	X	X	X	X	X	X		X
PT/PTT/INR/ Fibrinogen ^	X	X	X	X	X				
BMA and Biopsy #						D35 %		X	
Lumbar Puncture ∑		X ∑							
FISH and/or PCR µ	X								
Neurologic Assessment &	X	X	X	X	X	X	X		
X-RAYS AND SCANS									
CT or MRI $		X						X	X
SPECIMEN SUBMISSION									
BM and PB for Cytogenetics ®		X						X	
Serum for Immunogenicity ∝	X						X	X	
BM Aspirate/Biopsy -TM (MRD) ƒ	X					D35 %			
BMA Banking & Future Research Ѧ	X					D35 %			
TREATMENT Φ									
Blinatumomab		X	X	X	X				
IT Methotrexate		X ∑							

Note: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). The schedule for submission of these forms is listed in Section 14.0.

Click here for Footnotes.

Footnotes for Calendar 9.5:

λ NOTE: Relapsed/Refractory Ph+ and Ph-like DSMKF patients who received dasatinib or another 2nd or 3rd generation TKI prior to Registration will begin protocol therapy with Re-Induction Cycle 1 (see Section 7.3b).
£ Pre-treatment and then weekly. All Grade 3 or higher relevant infections will be evaluated every 6 months (see Section 11.5).
β Institutional standard metabolic panel is sufficient, providing it includes total bilirubin, AST and/or ALT, serum creatinine and alkaline phosphatase.
& See Section 7.1c.2.
µ Cytogenetics (and FISH, if possible) analyses must be done up to 28 days prior to registration, then subsequently at any time a bone marrow biopsy is performed for disease assessment (see Sections 5.1b and 15.1). For Ph+ patients, PCR for BCR/ABL should be obtained each time cytogenetics is performed. BCR/ABL is not required for Ph-like DSMKF patients (at baseline or subsequently). If not already known, baseline (up to 28 days prior to registration) PCR should include BCR-ABL status (both p190 and p210 analyses) for Ph+ patients. Subsequently, only the baseline positive (p190 or p210) result needs to be repeated.
$ Only if there is evidence of extramedullary disease at diagnosis, CT scan or MRI of the chest, abdomen and pelvis will be performed pre-study, then every 3 months until CT/MRI is negative for extramedullary disease. Once negative, CT/MRI will be performed every 3 months for 2 years, then every 6 months until 5 years after initial registration. CT/MRI is also required at the time the patient is removed from protocol therapy for any reason.
® See Section 15.1. Note: Bone marrow aspirate or (if dry tap) peripheral blood should be submitted for cytogenetic (and FISH, if possible) any time a bone marrow biopsy is performed for disease assessment.
∝ See Sections 15.2 and 18.9. Note: Pretreatment and Day 36-42 specimens are needed for patient's first cycle of blinatumomab administration only. The follow-up specimen must be submitted within 30 days of the last dose of blinatumomab.
% ± 2 days.
^ Performed weekly during Days 1-28
∑ See Section 7.1a.
Ω Follow up visits/labs will be performed every 3 months for the first 2 years then every 6 months for the next 2 years, then annually until 10 years after initial registration.
ƒ To be obtained during Re-induction Cycle 1 for relapsed/refractory patients only. See Sections 15.3 and 18.4.
Ѧ To be obtained during Re-induction Cycle 1 for relapsed/refractory patients only. See Section 15.5. Note: The banked samples will NOT be used for the translational medicine portion detailed in Section 18.15.
Φ See Section 7.3b for treatment days and details.
After CR or CRi, marrows will be obtained at the discretion of the treating physician.

NOTE: 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.

9.6 Cohort 2 – Ph+ and Ph-like DSMKF Patients–Post-Remission –Blinatumomab/Dasatinib

	Pre Tx	Days 1-7	Days 8-14	Days 15-21	Days 22-28	Days 29-35	Days 36-42	Removal from Protocol Therapy	Follow Up Ω #
REQUIRED STUDIES									
PHYSICAL									
History and Physical Exam %	X	X	X	X	X	X	X		X
Weight and Performance Status %	X	X	X	X	X	X	X		
Toxicity Notation %	X	X	X	X	X	X	X		
Intake Calendar ≠							X		
LABORATORY									
CBC, Differential, Platelets £	X	X	X	X	X	X	X		X
Comprehensive Metabolic Panel £ β	X	X	X	X	X	X	X		X
Bone Marrow Aspirate and Biopsy #								X	
Lumbar Puncture ∑		X ∑							
FISH and/or PCR µ	X								
Neurologic Assessment &	X	X	X	X	X	X	X		
X-RAYS AND SCANS									
CT or MRI $		X						X	X
SPECIMEN SUBMISSION									
BM and PB for Cytogenetics ®		X						X	
Serum for Immunogenicity ∝	X						XΔ	X	
TREATMENT Φ									
Blinatumomab		X	X	X	X				
Dasatinib		X	X	X	X	X	X		
IT Methotrexate		X ∑							

Note: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). The schedule for submission of these forms is listed in Section 14.0.

Click her for footnotes.

Footnotes for Calendar 9.6

£ Performed twice weekly.
% Pre-treatment and then weekly. All Grade 3 or higher relevant infections will be evaluated every 6 months (see Section 11.5).
β Institutional standard metabolic panel is sufficient, providing it includes total bilirubin, AST and/or ALT, serum creatinine and alkaline phosphatase.
& See Section 7.1c.2.
µ Cytogenetics (and FISH, if possible) analyses must be done up to 28 days prior to registration, then subsequently at any time a bone marrow biopsy is performed for disease assessment (see Sections 5.2a and 15.1). For Ph+ patients, PCR for BCR/ABL should be obtained each time cytogenetics is performed. BCR/ABL is not required for Ph-like DSMKF patients (at baseline or subsequently). If not already known, baseline (up to 28 days prior to registration) PCR should include BCR-ABL status (both p190 and p210 analyses) for Ph+ patients. Subsequently, only the baseline positive (p190 or p210) result needs to be repeated.
$ Only if there is evidence of extramedullary disease at diagnosis, CT scan or MRI of the chest, abdomen and pelvis will be performed pre-study, then every 3 months until CT/MRI is negative for extramedullary disease. Once negative, CT/MRI will be performed every 3 months for 2 years, then every 6 months until 5 years after initial registration. CT/MRI is also required at the time the patient is removed from protocol therapy for any reason.
≠ CRA will review Intake Calendar at the end of each cycle (see Section 18.1).
® See Section 15.1. Note: Bone marrow aspirate or (if dry tap) peripheral blood should be submitted for cytogenetic (and FISH, if possible) any time a bone marrow biopsy is performed for disease assessment.
∝ See Sections 15.2 and 18.9.
∑ See Section 7.1a.
Ω Follow up visits/labs will be performed every 3 months for the first 2 years then every 6 months for the next 2 years, then annually until 10 years after initial registration.
Φ See Section 7.3c for treatment days and details.
After CR or CRi, marrows will be obtained at the discretion of the treating physician.
∆ For patients receiving their first cycle on blinatumomab.

NOTE: 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.
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9.7 Cohort 2 – Ph+ and Ph-like DSMKF Patients – Maintenance – Dasatinib/Prednisone

	Pre Treatment	Days 1-7	Days 8-14	Days 15-21	Days 22-28	Removal from Protocol Therapy	Follow Up Ω #
REQUIRED STUDIES							
PHYSICAL							
History and Physical Exam £	X	X					X
Weight and Performance Status	X	X					
Toxicity Notation £	X	X					
Intake Calendar ≠					X		
LABORATORY							
CBC, Differential, Platelets £	X	X					X
Comprehensive Metabolic Panel £ β	X	X					X
Bone Marrow Aspirate and Biopsy #	X					X	
Lumbar Puncture ∑		X ∑					
FISH and/or PCR µ	X						
X-RAYS AND SCANS							
CT or MRI $		X					
SPECIMEN SUBMISSION							
BM and PB for Cytogenetics ®		X				X	
TREATMENT Φ							
Prednisone +		X					
Dasatinib		X	X	X	X		
IT Methotrexate		X ∑					

Note: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). The schedule for submission of these forms is listed in Section 14.0.

Click here for footnotes.

Footnote for Calendar 9.7

£ Performed ON Day 1 of each cycle.

β Institutional standard metabolic panel is sufficient, providing it includes total bilirubin, AST and/or ALT, serum creatinine and alkaline phosphatase.

µ Cytogenetics (and FISH, if possible) analyses must be done up to 28 days prior to registration, then subsequently at any time a bone marrow biopsy is performed for disease assessment (see Sections 5.3a and 15.1). PCR for BCR/ABL should be obtained each time cytogenetics is performed. Baseline (up to 28 days prior to registration) PCR should include both p190 and p210 analyses. Subsequently, only the baseline positive (p190 or p210) result needs to be repeated.

$ Only if there is evidence of extramedullary disease at diagnosis, CT scan or MRI of the chest, abdomen and pelvis will be performed pre-study, then every 3 months for 2 years, then every 6 months until from years after initial registration. Once negative, CT/MRI will be performed every 3 months for 2 years, then every 6 months until 5 years after initial registration. CT/MRI is also required at the time the patient is removed from protocol therapy for any reason.

≠ CRA will review Intake Calendar at the end of each cycle (see Section 18.1).

® See Section 15.1. Note: Bone marrow aspirate or (if dry tap) peripheral blood should be submitted for cytogenetic (and FISH, if possible) any time a bone marrow biopsy is performed for disease assessment.

∑ See Section 7.1a.

Ω Follow up visits/labs will be performed every 3 months for the first 2 years then every 6 months for the next 2 years, then annually until 10 years after initial registration.

Φ See Section 7.3c for treatment days and details.

After CR or CRi, marrows will be obtained at the discretion of the treating physician.

+ Prednisone dosing during the maintenance phase is limited to a maximum of 18 cycles.

NOTE: 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.

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10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

Note: For all sites of extramedullary disease present prior to treatment, subsequent disease measurements must be made using the same techniques as at baseline.

10.1 Extramedullary Disease

a. Measurable Extramedullary Disease: Lesions that can be accurately measured in two dimensions by CT, MRI, medical photograph (skin or oral lesion), plain x-ray, or other conventional technique and a greatest transverse diameter of 1 cm or greater; or palpable lesions with both diameters ≥ 2 cm. Note: CT scans remain the standard for evaluation of nodal disease.

b. Non-measurable Extramedullary Disease: All other lesions including unidimensional lesions, lesions too small to be considered measurable, pleural or pericardial effusion, ascites, bone disease, leptomeningeal disease, lymphangitis, pulmonitis, abdominal masses not confirmed or followed by imaging techniques or disease documented by indirect evidence only (e.g., lab values).

c. Extramedullary Disease Status:

C1. Complete disappearance of all measurable and non-measurable extramedullary disease with the exception of lesions for which the following must be true: for patients with at least one measurable lesion, all nodal masses > 1.5 cm in greatest transverse diameter (GTD) at baseline must have regressed to ≤ 1.5 cm in GTD and all nodal masses ≥ 1 cm and ≤ 1.5 cm in GTD at baseline must have regressed to < 1 cm GTD or they must have reduced by 75% in sum of products of greatest diameters (SPD). No new lesions. Spleen and other previously enlarged organs must have regressed in size and must not be palpable. All disease must be assessed using the same technique as at baseline.

C2. Patient does not qualify for C1 status.

10.2 Complete Remission (CR)

a. < 5% marrow aspirate blasts. Blasts can be ≥ 5% if the blasts are found to be myeloid and there is no evidence of lymphoblasts by flow cytometry or immunostaining.

b. Neutrophils (ANC) > 1,000/mcL; platelets > 100,000/mcL; and no blasts in the peripheral blood.

c. C1 Extramedullary disease status (see Section 10.1c).

10.3 Complete Remission with Incomplete Platelet Recovery (CRi)

Same as CR but platelet count may be ≤ 100,000/mcL and/or ANC ≤ 1,000/mcL.

10.4 Partial remission (PR)

Improvement or no worsening of ALL, as indicated by all of the following:

a. No blasts in the peripheral blood

b. Neutrophils (ANC) ≥ 1,000/mcL; platelets > 100,000/mcL

c. Either or both of the following:

1. At least a 50% decrease in the marrow blast percentage, compared to the pretreatment value, and marrow blast percentage ≥ 5% and ≤ 25%.

2. C2 extramedullary disease status (see Section 10.1c).

10.5 Treatment Failures

Patients who fail to achieve CR, CRi, or PR following induction will be classified according to the type of failure:

a. Resistant Disease: patient survives ≥ 7 days following completion of initial treatment course and has persistent leukemia in the most recent peripheral blood smear or bone marrow and/or persistent disease involvement at any extramedullary site after completion of therapy.

b. Death during Aplasia: patient survives ≥ 7 days following completion of initial treatment course then dies while cytopenic, with the last post-induction bone marrow without leukemic blasts.

c. Indeterminate:

1. Patient survives < 7 days after completion of initial treatment course.

2. Patient survives ≥ 7 days following completion of initial treatment course then dies with no persistent leukemia in the peripheral smear but no post induction bone marrow examination or extramedullary disease examination.

10.6 Relapse from CR or CRi

a. Appearance of leukemic blasts in the peripheral blood.

b. Appearance of extramedullary disease.

c. ≥ 5% blasts in the bone marrow not attributable to another cause (e.g. recovery of normal cells following chemotherapy-induced aplasia). If there are no circulating blasts and no extramedullary disease and the bone marrow blast percentage is ≥ 5% but < 20%, then a repeat bone marrow performed at least 7 days after the first marrow examination and documenting bone marrow blast percentage is ≥ 5% is necessary to establish relapse.

10.7 Overall Survival (OS)

Overall survival will be measured from the day of registration on study until death from any cause with observations censored on the day of last contact for patients not known to have died.

10.8 Disease-Free Survival (DFS)

DFS will be defined only for patients who achieve CR or CRi and will be measured from the date the patient first achieves CR or CRi until relapse from CR/CRi or death from any cause. Observations will be censored on the day of last contact for patients not known to have relapsed from CR/CRi or to have died.

10.9 Toxicity Criteria

The NCI Common Terminology Criteria for Adverse Events will be used to determine severity of toxicity.

10.10 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 Ph-negative Cohort

a. Primary Objective

The primary objective of this study is to test whether overall survival (OS) at 3 years among elderly patients with newly diagnosed Ph-negative ALL is sufficiently high to warrant further investigation.

Historical estimates of OS in this patient population provide 3-year OS estimates ranging from 6-12%. (2,9) Based on this historical data, the current regimen would be of no further interest in the Ph-negative cohort if it yields a true 3-year OS rate of 10% or less (null), and would be of further interest if it yields a true 3-year OS rate of 33% or higher (alternative).

b. Analyses and Power Justification

Up to 26 eligible patients with Ph- ALL will be accrued. All eligible patients enrolled will be used in the analysis. Although a one-stage design will be used for patient accrual, an interim analysis of futility will be performed to allow for early termination. If among the first 11 eligible patients, at least 5 complete remissions (CR or CRi) are observed, then the study will continue to full accrual. If fewer than 5 complete remissions (CR or CRi) are observed, that will be considered evidence that this regimen does not warrant further testing, and the cohort will be closed. Accrual will continue while the CR data is being reviewed.

The final analysis will test whether the observed 3-year OS is improved over an historical rate of 10% with a one-sided binomial test at the 0.04 level. If 6 or more of the 26 patients are alive at three years after entering the study then the regimen will be considered sufficiently effective to warrant further investigation. Accounting for the interim analysis, this design has critical level (probability of erroneously concluding the regimen warrants further study) of 0.03 if the true response rate is 50% and the true probability of 3-year OS is 10%, and power (probability of correctly concluding the regimen warrants further study) of 0.89 if the true response rate is 70% and the true 3-year OS is 33%. In the event of censoring, the 3-year OS rate will be estimated using the method of Kaplan-Meier and a one-sided 90% confidence interval will be constructed with the standard error calculated using the log-log transformation.

With 26 patients in the study cohort, complete response (CR + CRi) rate can be estimated to within at most ± 20% (95% confidence interval). Distributions of disease-free survival and overall survival will be estimated using the method of Kaplan-Meier.

The probability of any particular toxicity of the blinatumomab and POMP regimen can be estimated to within at most ± 20% (95% confidence interval). Any toxicity having a true occurrence rate of 9% or more is very likely to be observed in at least one patient (probability ≥ 91%).

11.2 Ph- positive and Ph-like DSMKF Cohort

a. Primary Objective

The primary objective of this study is feasibility: to assess the safety of dasatinib/steroid based-induction followed by blinatumomab/dasatinib treatment followed by dasatinib-based maintenance in patients with newly diagnosed Ph-positive ALL, relapsed/refractory Ph-positive ALL, and either newly diagnosed or relapsed/refractory Ph-like ALL with dasatinib-sensitive mutations or kinase fusions.

b. Analyses

This study will initially accrue 9 eligible and evaluable patients to post-remission therapy. To be evaluable for DLT, patients must have experienced a DLT during Cycle 1 of blinatumomab post-remission therapy or must have received at least 75% of the prescribed dose of Cycle 1 blinatumomab of Post-Remission therapy. Accrual to Step 1 will be closed once 9 patients are enrolled to post-remission therapy. In the event that one or more of these 9 patients is not eligible and evaluable in Step 2, the study will re-open to enroll additional patients as needed.

The trial will employ careful adverse event monitoring on these 9 patients. The Study Chairs and Leukemia Committee chair will be responsible for evaluating safety. Dose-limiting toxicity (DLT) will be defined as any of the following events occurring during the first cycle of post-remission treatment that are possibly, probably, or definitely attributable to blinatumomab or dasatinib: (1) any Grade 3 or higher non-hematologic toxicity, with the exception of nausea, vomiting, or diarrhea (if manageable with supportive care measures and does not require hospitalization, TPN, or tube feeding); (2) any Grade 4 neutropenia that lasts > 42 days. If 3 or more patients experience a DLT, the study will be temporarily closed to accrual pending a decision as to whether to continue accrual. If, due to unexpected accrual patterns there are ultimately 12 patients evaluable for DLT, the following modified DLT rule will be evaluated: if 4 or more of the 12 patients experience a DLT, the study will be temporarily closed to accrual pending a

decision as to whether to continue accrual. If accrual is re-opened, a protocol revision will include justification for continued accrual and for any treatment regimen modification. Upon reopening of accrual, 8 additional eligible and evaluable patients will be enrolled for a total of 20 eligible and evaluable patients. Accounting for ineligibility and non-evaluability, this will require approximately 11 additional patients.

Statistical Considerations for 20 Evaluable Patients

The activity (response rate, disease-free survival and overall survival) of this combination will be estimated in a preliminary manner given the small number of patients. With 20 patients receiving post-remission therapy, the response rate and DFS and OS at a particular time point can be estimated to within at most 23% (95% confidence interval). Distributions of disease-free survival and overall survival will be estimated using the method of Kaplan-Meier.

With 20 patients, the probability of any particular toxicity can be estimated to within at most 23% (95% confidence interval). Any toxicity having a true occurrence rate of 15% or more is likely to be observed in at least one patient (probability ≥ 96%).

11.3 Minimal Residual Disease

Minimal residual disease (MRD) negativity and time to achieve MRD negativity will be examined separately in descriptive analyses within each cohort (Cohort 1: Ph-negative and Cohort 2: Ph-positive or Ph-like DSMKF).

11.4 Accrual

Based on S0333, and after consideration of the difference in eligible age, the expected accrual rate is 15 Ph-negative patients per year and 10 Ph-positive/Ph-like DSMKF patients per year. Accounting for the possibility of a 5% ineligibility rate, the study will accrue approximately 31 Ph-negative patients and 27 Ph-positive/Ph-like DSMKF patients (to have 20 Ph-positive/Ph-like DSMKF patients who receive post-remission therapy and are evaluable for DLTs). Accrual to the Ph-negative cohort is estimated to complete in approximately 23 months. Accrual to the Ph-positive and Ph-like DSMKF cohort is estimated to take 38 months, not accounting for temporary closures.

11.5 Monitoring for Infection Rate of 72-Hour and 96-Hour Bag Changes in Blinatumomab Administration

The rate of Grade 3 or higher relevant infections (defined as sepsis, bacteremia, device or catheter-related infection) will be monitored among patients who received blinatumomab with the infusion bag changed up to 96 hours. We will consider the 72 hour and 96 hour bag changes acceptable if the infection rate is 5% or less for each bag change time. All Grade 3 or higher relevant infections will be evaluated every six months and the infection rate will be tested to determine whether the true rate is 5% using exact one-sided one-sample binomial test, and the results will be presented to DSMC. If at one of scheduled analyses, the one- sided p-value of the test is less than 0.05 for either the 72 hour or the 96 hour bag change, then that respective bag change would be considered unacceptable and the DSMC will be consulted regarding whether the bag change frequency should be changed back to 48 hours or 72 hours, respectively. The two-sided 90% confidence interval for the infection rate will also be provided. For example, if at one of scheduled analyses, 35 patients were treated in blinatumomab arm with the 96 hour bag change, with the monitoring rule as described above, the 96 hour bag change would be considered unacceptable if we observe 5 or more patients with grade 3 or higher relevant infection. At this time point (with 35 patients), the probability of concluding 96 hour bag change is unacceptable is 0.03 if the true but unknown rate of grade 3 or higher relevant infections is

5%; the probability of concluding 96 hour bag change is unacceptable is 0.27 if the true but unknown rate of Grade 3 or higher relevant infections is 10%; and the probability of concluding 96 hour bag change is unacceptable is 0.86 if the true but unknown rate of Grade 3 or higher relevant infections is 20%. The overall probability of concluding that the 96 hour bag change is unacceptable depends on the number of analyses and the number of patients treated at the times of those analyses.

11.6 Data and Safety Monitoring

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 changes to blinatumomab administration.

In addition to the above DSMC review, toxicity and accrual monitoring are done routinely by the Study Chair, study Statistician, and the Disease Committee Chair. Endpoint monitoring is done by the study Statistician and Study Chair. Accrual reports are generated weekly, and formal toxicity reports are generated every 6 months. In addition, the SWOG Statistics and Data Management Center, Adverse Event Coordinator at the Operations Office, SAE Physician Reviewer, and Study Chair monitor toxicities on an ongoing basis.

12.0 DISCIPLINE REVIEW

This study will not utilize discipline review.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

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

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 SWOG 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.

a. 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). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/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 CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and 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 PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found 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 >.

b. CTSU Registration Procedures

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

1. **IRB Approval:**

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. 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 Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572

- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRB Manager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. 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.

2. Downloading Site Registration Documents:

Site registration forms may be downloaded from the **S1318** protocol 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 RSS.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the SWOG link to expand, then select **S1318**.
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

3. Requirements for **S1318** Site Registration:

IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

4. Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission

When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

5. Checking Your Site's Registration Status:

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

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. 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.

13.3 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.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type. If a DTL is required for the study, the registrar(s) must also be assigned the OPEN Registrar task on the DTL.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval. If a DTL is required for the study, the IVR or NPIVR must also be assigned the appropriate OPEN-related tasks on the DTL.

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

13.4 Registration Procedures

a. All site staff will use OPEN to enroll patients to this study. OPEN is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org, from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

b. Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met 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).

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

d. Further instructional information is provided on the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

13.5 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 Section 14.3a 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. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, you must have an active CTEP-IAM account (check at https://eapps-ctep.nci.nih.gov/iam/index.jsp) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Upon initial site registration approval for the study in 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 users 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. Please note, site users 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.

Users 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 under the Rave tab 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 web site (https://swog.org).

For difficulties with the CRA Workbench, please e-mail 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 OF INITIAL REGISTRATION (STEP 1):

Submit the following:

S1318 Onstudy Form

S1318 Baseline Abnormalities Form

S1318 Baseline Disease Assessment Form

Pathology Report

If the patient is a relapsed/refractory patient with prior dasatinib exposure and/or exposure to other 2nd or 3rd generation TKIs, two pathology reports must be submitted within 7 days of initial registration:

1. Confirming diagnosis within 28 days prior to registration to step 1
2. Confirming diagnosis within 28 days prior to start of first induction of previous therapy

For relapsed/refractory patients in Cohort 2: Cytogenetics report (from time of original diagnosis).

b. WITHIN 14 DAYS AFTER INITIAL REGISTRATION (STEP 1):

Submit the following:

Specimens as outlined in Section 15.0

c. WITHIN 28 DAYS AFTER INITIAL REGISTRATION (STEP 1):

Submit the following:

Cytogenetics and/or FISH Reports from lab (see Section 15.1a.1)

S1318 Cytogenetics and FISH Analysis Form

d. WITHIN 14 DAYS AFTER EACH CYCLE OF PROTOCOL TREATMENT:

Submit the following:

Appropriate **S1318** Treatment Form

S1318 Adverse Event Form

If applicable, **S1318** Blinatumomab Related Infection Monitoring Form

Specimens as outlined in Section 15.0

e. COHORT 2 (Ph+ or Ph-like DSMKF): AT THE END OF EACH WEEK OF POST-REMISSION THERAPY DURING CYCLE 1:

Submit the following:

S1318 Adverse Event Form

(Note: It is important that the Adverse Event Form is updated / amended WEEKLY in RAVE).

f. WITHIN 14 DAYS AFTER EACH DISEASE ASSESSMENT:

Submit the following:

ALL Disease Assessment Form documenting results of assessment

Pathology Report

g. WITHIN 14 DAYS OF DISCONTINUATION OF TREATMENT AT EACH REGISTRATION STEP:

Submit the following:

Off Treatment Notice

Appropriate **S1318** Treatment Form

S1318 Adverse Event Form

If applicable, **S1318** Blinatumomab Related Infection Monitoring Form

h. WITHIN 14 DAYS AFTER POST-REMISSION REGISTRATION (STEP 2):

Submit the following:

S1318 Post-Remission Eligibility Form

i. WITHIN 14 DAYS AFTER MAINTENANCE REGISTRATION (STEP 3):

Submit the following:

S1318 Maintenance Eligibility Form

j. WITHIN 14 DAYS OF PROGRESSION/RELAPSE:

Submit final appropriate **S1318** Treatment Form and appropriate **S1318** Adverse Event Form (if the patient was still on protocol treatment) or Leukemia Follow-Up Form (if the patient was off protocol treatment) documenting date, site and method for determining progression/relapse.

k. EVERY 3 MONTHS FOR THE FIRST YEAR, EVERY 6 MONTHS FOR THE SECOND AND THIRD YEARS, THEN ANNUALLY UNTIL 10 YEARS FROM INITIAL REGISTRATION:

Submit the following:

Leukemia Follow Up Form

S1318 Transplant Form (if patient received HCT)

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)

l. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Submit the following:

Notice of Death

Final appropriate **S1318** Treatment Form

S1318 Adverse Event Form if the patient was still on protocol treatment) or Leukemia Follow-Up Form (if the patient was off protocol treatment) documenting death information.

15.0 SPECIAL INSTRUCTIONS

Purpose	Specimens	Timepoint	Patients	Additional required information
Cytogenetics and FISH (if possible) (see Section 15.1)	Bone Marrow Aspirate (or peripheral blood if dry tap)	(1) Pre-Treatment (up to 28 days prior to registration). See Section 15.1a.1. (2) At any time point that a bone marrow biopsy is performed for disease assessment.	(1) REQUIRED FOR ALL PATIENTS (2) For Ph-positive patients, PCR for BCR/ABL should be obtained each time cytogenetics are performed.	The **S1318** Cytogenetics Lab Report Form must be submitted to the laboratory with the specimen. The lab will return the completed form with results to the email address for the Data Manager, as provided on the form. The **S1318** Cytogenetics and FISH Analysis Form must be completed in Medidata Rave® using the information provided by the lab.
Blinatumomab Immunogenicity Testing (see Section 15.2)	5 mL Serum	(1) a) **For Ph-negative Patients**: Pre-Treatment (up to 28 days prior to registration). b) **For Ph-positive and Ph-like DSMKF Patients**: Up to 28 days prior to receiving the first dose of blinatumomab. (2) Between Days 36-42 AFTER initial blinatumomab administration. (3) Within 30 days of last dose of blinatumomab.	REQUIRED FOR ALL PATIENTS	At each timepoint serum must be centrifuged aliquoted, pipetted, and then frozen per instructions in Section 15.2b. A lab manual with complete specimen processing and shipment information is posted on the SWOG protocol abstract page at www.swog.org.

MRD – Correlative studies (see Section 15.3)	With patient's consent, 1-2 mL anticoagulated bone marrow aspirate from first draw OR in event of dry tap, submit bone marrow biopsy (core, plug).	Ph-negative patients: (1) Pre-Treatment (up to 28 days prior to registration). (2) Day 35 of Induction Cycle 1 (± 2 days). (3) Day 35 of Re-Induction Cycle 1 (± 2 days, if applicable). Ph-positive and Ph-like DSMKF patients (newly diagnosed): 1) Pre-Treatment (up to 28 days prior to registration). (2) Day 28 of Induction Cycle 1 (± 2 days). (3) Day 56 of Induction Cycle 1 (± 2 days, if applicable). Ph-positive and Ph-like DSMKF patients (relapsed/refractory): (1) Pre-Treatment (up to 28 days prior to registration). (2) Day 35 of Re-Induction Cycle 1 (± 2 days). (3) Day 35 of Re-Induction Cycle 1 (± 2 days, if applicable). (3) Day 35 of Re-Induction Cycle 2 (± 2 days; if applicable	OPTIONAL for ALL PATIENTS	Ship to Lab #103: Wood Lab Phone 206/288-7060
Bone Marrow Aspirate (banking) for Future Research (see Section 15.4)	With patient's consent, 3-4 mL bone marrow aspirate OR 3mL peripheral blood in event of dry tap, if the patient's bone marrow blast count is ≥30%, or if bone marrow aspirate is not done (at physician discretion).	Drawn at time of diagnosis and submitted at time of registration of Ph-Negative patients	OPTIONAL for Ph-Negative Patients	Ship to Lab #200 SWOG Specimen Repository – Leukemia Division, Lab #200
Banking – Future Correlative Studies (see Section 15.5)	With patient's consent, 7-8 mL bone marrow aspirate AND 22-24 mL peripheral blood in EDTA tube. (In event of dry tap, submit only the peripheral blood.)	Ph-negative patients: (1) Pre-Treatment (up to 28 days prior to registration). (2) Day 35 of Induction Cycle 1 (± 2 days).	OPTIONAL for ALL PATIENTS	Ship to Lab #200 SWOG Specimen Repository – Leukemia Division, Lab #200

Banking – Future Correlative Studies (see Section 15.5) (contd.)		(3) Day 35 of Re-Induction Cycle 1 (± 2 days, if applicable). Ph-positive and Ph-like DSMKF patients: (1) Pre-Treatment (up to 28 days prior to registration). (2) Day 28 of Induction Cycle 1 (± 2 days). (3) Day 56 of Induction Cycle 1 (± 2 days, if applicable).		

15.1 Cytogenetics and FISH (Required)

Specimens for cytogenetic (and FISH if possible) analysis must be submitted to the site's preferred local CLIA-approved laboratory.

a. Specimens (bone marrow aspirate, or peripheral blood if dry tap) must be submitted for cytogenetic (and FISH if possible) analysis at the following time points:

1. Pre-treatment (up to 28 days prior to registration)

   If the patient is a relapsed/refractory patient with prior dasatinib exposure and/or exposure to other 2nd or 3rd generation TKIs, pre-treatment cytogenetic and/or FISH analysis must be performed up to 28 days prior to the start of the *first induction of the previous therapy*. For these patients only, cytogenetic and/or FISH analysis is not required up to 28 days prior to registration to **S1318**.

2. Any time a bone marrow biopsy is performed for disease assessment.

   For **Ph+ patients**, PCR for BCR/ABL (for both p190 and p210 transcripts) should be obtained each time cytogenetics are performed.

b. Cytogenetics lab report forms must be submitted as outlined in Section 14.0.

c. The **S1318** Cytogenetics Lab Report Form must be submitted to the laboratory along with the specimen. The laboratory will then return the completed form with the results. E-mail contact information for the Data Manager at the site must be provided to the lab performing cytogenetic studies. The institution will complete the **S1318** Cytogenetics and FISH Analysis Form in Medidata Rave® using the information provided by the lab.

15.2 Blinatumomab Immunogenicity Assessment (Required)

Also see Section 18.9.

a. Specimens (serum) must be submitted for blinatumomab immunogenicity assessment at the following timepoints:

1. Pre-treatment (Cohort 1: up to 28 days prior to registration for Ph-negative patients; Cohort 2: up to 28 days prior to receiving first dose of blinatumomab for Ph-positive or Ph-like DSMKF patients).

2. Between Days 36-42 after initial blinatumomab administration

3. Within 30 days after last dose of blinatumomab

b. At each timepoint, 5 mL of blood will be drawn into the provided Vacutainer. Vacutainer will be inverted 5 times after specimen collection (one complete turn of the wrist, 180 degrees and back), then will be left to stand upright for 30 minutes. Tubes will then be centrifuged for 10 minutes at 3500-4500 rpm (preferably with swing bucket rotor). Specimen is properly centrifuged when solid black components and liquid are approximately equally separated. Serum will then be aliquoted with pipette into two red capped cryovials (1 mL per vial). Specimen will be immediately frozen at ≤ 20°C. Specimen must be shipped on dry ice via courier service.

A lab manual containing complete specimen collection, processing and shipment instructions can be found on the protocol abstract page of the SWOG website (www.swog.org).

c. Specimen collection kits may be ordered by submitting the LabConnect Kit Order Form via the instructions on the form.

d. In the online specimen tracking system, the appropriate SWOG laboratory for submission of serum specimens for blinatumomab immunogenicity testing is identified as follows:

Lab #215: LabConnect
Phone: 800/501-7947
Contact: Ben Booher

15.3 Translational Medicine (MRD) (optional for patient) (see Section 18.4)

a. With patient's consent to MRD, specimens (1-2 mL anticoagulated bone marrow aspirate from the first draw) must be submitted at the timepoints listed below. In the event of dry tap, submit bone marrow biopsy (core, plug). A minimum of 2 cm of marrow space, excluding the cortical bone must be submitted in RPMI as indicated in Section 15.3c. (Purple/Lavender top tubes not accepted for biopsy.)

Cohort 1 Ph-negative patients:

1. Pretreatment (up to 28 days prior to registration).

2. Day 35 of Induction Cycle 1 (± 2 days).

3. Day 35 of Re-Induction Cycle 1 (± 2 days, if applicable).

Cohort 2 Ph-positive and Ph-like DSMKF patients (newly diagnosed patients):

1. Pretreatment (up to 28 days prior to registration).

2. Day 28 of Induction Cycle 1 (± 2 days).

3. Day 56 of Induction Cycle 1 (± 2 days; if applicable).

Cohort 2 Ph-positive and Ph-like DSMKF patients (relapsed/refractory patients previously treated with dasatinib or other TKI):

1. Pretreatment (up to 28 days prior to registration).

2. Day 35 of Re-Induction Cycle 1 (± 2 days).

3. Day 35 of Re-Induction Cycle 2 (± 2 days; if applicable).

b. Batch shipping is not allowed. Specimens must be transported the same day as collected via overnight express courier (at room temperature) to arrive on Monday through Saturday. A cool pack in the container during the summer season is strongly encouraged.

c. Specimen collection kits are not being provided for this submission; sites will use institutional supplies. Bone marrow aspirates are to be submitted in either a) RPMI 1640 containing 10% fetal calf serum and EDTA (20 mg/mL) added as an anticoagulant or b) purple/lavender top tubes. Bone marrow biopsies are to be submitted in RPMI 1640 containing 10% fetal calf serum (purple top tubes are not acceptable for biopsies).

d. In the online specimen tracking system, the appropriate SWOG laboratory for submission of bone marrow, serum, and peripheral blood samples for SWOG MRD testing is identified as follows:

Lab #103: Wood Lab
Phone: 206/288-7060
Contact: Brent Wood, M.D., Ph.D.

15.4 Collection of Bone Marrow Aspirate for Future Research (optional for Ph-Negative patients)

a. With patient's consent, 3-4 mL of bone marrow aspirate (from specimen drawn prior to receiving treatment) must be submitted at time of registration of all Ph-Negative (Ph-) patients. In the event of the following, 3 mL (purple top) of peripheral blood should be submitted instead of a bone marrow aspirate: i) the patient's bone marrow blast count is ≥ 30%, ii) a bone marrow aspirate is not done (at physician discretion), or iii) if in case of a dry tap.

b. Specimen Collection and Submission Instructions

1. Specimens must be collected into a heparinized syringe and transferred to an EDTA (purple) vacutainer for transport to the SWOG Specimen Repository – Leukemia Division, Lab #200.

2. EDTA (purple top) vacutainer must be transported with a cold pack. The vacutainer should be wrapped in absorbent material to prevent direct

contact with the cold packs (which could result in freezing and lysis of the sample).

3. Batch shipping is not allowed. Specimens must be transported the same day as specimen collection via overnight courier.

4. 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).

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

d. Specimen collection kits are not being provided for this submission; sites will use institutional supplies. If Ph status cannot be determined 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 and 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.

15.5 Banking for Future Correlatives (optional for patient)

a. With patient’s consent to banking, an additional 7-8 mL of bone marrow aspirate, and 22-24 mL peripheral blood must be submitted in separate EDTA tubes (additional details below) at the same timepoints (as for MRD- Section 15.3).

Note: If bone marrow aspirate is “dry tap” or if there is no diagnostic bone marrow specimen available, submit only the 22-24 mL peripheral blood. Questions regarding banked specimens should be directed to leukemia@swog.org.

Cohort 1 Ph-negative patients:

1. Pretreatment (up to 28 days prior to registration).

2. Day 35 of Induction Cycle 1 (± 2 days).

3. Day 35 of Re-Induction Cycle 1 (± 2 days, if applicable).

Cohort 2 Ph-positive and Ph-like DSMKF patients (newly diagnosed patients):

1. Pretreatment (up to 28 days prior to registration).

2. Day 28 of Induction Cycle 1 (± 2 days).

3. Day 56 of Induction Cycle 1 (± 2 days; if applicable).

Cohort 2 Ph-positive and Ph-like DSMKF patients (relapsed/refractory patients previously treated with dasatinib or other TKI):

1. Pretreatment (up to 28 days prior to registration).

2. Day 35 of Re-Induction Cycle 1 (± 2 days).

3. Day 35 of Re-Induction Cycle 2 (± 2 days; if applicable).

b. The EDTA (purple top) vacutainer must be transported with a cold pack. The vacutainer should be wrapped with absorbent material to prevent direct contact with the cold packs (which could result in freezing and lysis of the sample).

1. Batch shipping is not allowed. Specimens must be transported the same day as specimen collection via overnight courier to

Lab #200: SWOG Specimen Repository – Leukemia Division
Nationwide Children's Hospital
700 Children's Drive, Room C1961
Columbus, OH 43205
Contact: Denise Ell
Phone: 614/722-2866
Email: mglab@nationwidechildrens.org

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

d. Batch shipping is not allowed. Specimens must be transported the same day as specimen collection via overnight courier.

e. 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)

15.6 General Specimen Submission Information

a. In instances when a pre-treatment specimen must be submitted before the patient is consented to **S1318**, sites may consent patients to specimen submission only using local IRB approved specimen submission consent forms. For sites that do not have local specimen submission consents, a template has been included in Section 18.6. Please note that sites must obtain a SWOG patient ID from the SWOG Specimen Tracking System (STS) to be used on the specimen label. This patient ID will be used at the time of patient registration (see Section 13.1).

b. SWOG Specimen Tracking System (STS)

All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. SWOG members may log on the online system via the CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org) and logon to the Members Area. After you have logged on using your SWOG roster ID number and password, click on the *CRA Workbench* link to access the home page for CRA Workbench website. First time non- SWOG users must refer to start-up instructions located at https://gill:crab.org/SpecTrack/.

A copy of the Shipment Packing List produced by the online Specimen Tracking system should be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag.

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.

To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an email to technicalquestion@crab.org. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page (http://dnet.crab.org/SpecTrack/Documents/Instructions.pdf); or contact the SWOG Statistics and Data Management Center at 206/652-2267 to be routed to the Data Coordinator for further assistance.

c. Federal guidelines for the shipment of blood products:

1. The tube must be wrapped in an absorbent material.

2. The tube must then be placed in an AIRTIGHT container (like a resealable bag).

3. Pack the resealable bag and tube in a Styrofoam shipping container.

4. Pack the Styrofoam shipping container in a cardboard box.

5. Mark the box "Biohazard".

15.7 Cohort 2, Run-in Phase Only - Mandatory Conference Calls

A mandatory conference call for study teams with **active patients in Cycle 1 of post-remission therapy** will take place twice a month. The call will update participants on the current status of the Cohort 2 Run-In Phase portion of the trial and will include representatives from the study team, investigators from all participating institutions and representatives from Amgen. At this time any serious toxicities encountered will be discussed and appropriate action taken. In between these regularly scheduled conference calls, investigators will be informed of important study decisions via e-mail.

Institutional participation on these calls requires the identification of an investigator contact and a CRA contact. **Prior to registration of the first patient, each institution must provide the contact names, e-mail addresses, and phone numbers to the SWOG Operations Office. Institutions will be responsible for keeping this information up-to-date and must notify the study Leukemia Protocol Coordinator (Cynthia Smithcsmith@swog.org) of any changes.** The investigator and the contact CRA will receive e-mail reminders with the conference call information.

The conference call schedule is as follows:

- Second and Fourth Friday of each month at 1:00 p.m. ET (10:00 a.m. PT)

PRIOR TO EACH SCHEDULED CONFERENCE CALL: Study teams with active patients in Cycle 1 of post-remission therapy **MUST** provide an e-mail to the Protocol Coordinator in advance of the call providing the information below. The compiled information will be distributed for use on the conference calls.

- Patient's SWOG ID
- Patient's current treatment status

- Toxicity information
- Any other information the study team feels is relevant

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.

Publication and Industry Contact

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines in addition to the provisions in the "Intellectual Property Option to Collaborator".
(http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award apply to the use of the Agent in this study:

1. Agent(s) may not be used outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the

proposed combination protocol, and the existence of any obligations which would tend to restrict NCI's participation in the proposed combination protocol.

b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to the Collaborator(s) for Phase III studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to the Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/media presentation should be sent to:

E-mail: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to the Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of the Collaborator's confidential/proprietary information.

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.

16.1 Adverse Event Reporting Requirements

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 event reporting use the Cancer Therapy Evaluation Program Adverse Events 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 16.1) via CTEP-AERS.

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 16.1.

In the rare event when internet connectivity is disrupted a 24-hour notification is made to NCI by telephone at 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Any supporting documentation should be submitted to CTEP per NCI guidelines for AE reporting located at: http://ctep.cancer.gov/protocolDvelopment/electronic_applications/docs/aeguidelines.pdf.

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 investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent(s) as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agents used in this study are blinatumomab and dasatinib. 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 16.1:
Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention[1] Blinatumomab or Dasatinib.

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 the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR or [Section 16.1f.]

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

May 5, 2011

f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Late Phase 2 and Phase 3 Studies Utilizing an Agent under a CTEP IND:**

1. **Group-specific instructions**

Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. In addition, you may be asked to submit supporting clinical data to the Operations Offices in order to complete the evaluation of the event. If requested, the supporting data should be sent within **5 calendar days** by fax to 210-614-0006. Supporting clinical data submitted should include:

- Printed copy of the first page of the CTEP-AERS Report.
- Copies of clinical sourced documentation of the event.
- If applicable, and they have not yet been submitted to the SWOG Statistics and Data Management Center, copies of Off Treatment Notice and/or Notice of Death.

2. The adverse events listed below also require expedited monitoring for this trial:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization, regardless of any exception indicated in the SPEER(s) for assigned agent(s).
- Grade 3 adverse events, regardless of any exception indicated in the SPEER(s) for assigned agent(s).
- Any Grade 3 or higher infection (defined as sepsis, bacteremia, device or catheter-related infection) that occurs while the patient is on protocol treatment or within 30 days of the last administration of the investigational agent, regardless of attribution, must be reported via CTEP-AERS according to the timeframes outlined in Table 16.1. Any Grade 3 or higher infection (defined as sepsis, bacteremia, device or catheter-related infection) that occurs more than 30 days after the last administration of the investigational agent and has an attribution of possible, probable, or definite must also be reported via CTEP-AERS.

g. ***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.

CTEP requires all secondary malignancies that occur following treatment with an agent under an 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/docs/aeguidelines.pdf with instructions provided by the CTEP-AERS system. 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.

h. **Reporting Pregnancy, Pregnancy Loss, 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 "Fetal Loss at any gestational age" 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 "Neonatal loss of life"** 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 "Death Neonatal", 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

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18.0 APPENDIX

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18.1 Intake Calendars - Dasatinib

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

Institution/Affiliate _____ Physician _____

Instructions for the participant:
The chart below is a monthly 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.
- 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 dasatinib.
- 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. You will take dasatinib with a nurse (not at home) on the days you come in for appointments.
- Do not throw away any study pill 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 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.

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

Clinician review at each visit – date and initials_____ _____ _____ _____ _____

DASATINIB INTAKE CALENDAR

Date	Was Dose Taken?	At What Time?	Total # of Pills Taken?
__/ __/ __ Day 1	☐ Yes ☐ No	____:____ AM / PM	____50 mg ____20 mg
__/ __/ __ Day 2	☐ Yes ☐ No	____:____ AM / PM	____50 mg ____20 mg
__/ __/ __ Day 3	☐ Yes ☐ No	____:____ AM / PM	____50 mg ____20 mg
__/ __/ __ Day 4	☐ Yes ☐ No	____:____ AM / PM	____50 mg ____20 mg
__/ __/ __ Day 5	☐ Yes ☐ No	____:____ AM / PM	____50 mg ____20 mg
__/ __/ __ Day 6	☐ Yes ☐ No	____:____ AM / PM	____50 mg ____20 mg
__/ __/ __ Day 7	☐ Yes ☐ No	____:____ AM / PM	____50 mg ____20 mg
__/ __/ __ Day 8	☐ Yes ☐ No	____:____ AM / PM	____50 mg ____20 mg
__/ __/ __ Day 9	☐ Yes ☐ No	____:____ AM / PM	____50 mg ____20 mg
__/ __/ __ Day 10	☐ Yes ☐ No	____:____ AM / PM	____50 mg ____20 mg
__/ __/ __ Day 11	☐ Yes ☐ No	____:____ AM / PM	____50 mg ____20 mg
Comments:			
Clinician review at each visit – date and initials _____ _____ _____ _____ _____ _____			

__/__/__ Day 12	☐ Yes ☐ No	____:____ AM / PM	____50 mg ____20 mg
__/__/__ Day 13	☐ Yes ☐ No	____:____ AM / PM	____50 mg ____20 mg
__/__/__ Day 14	☐ Yes ☐ No	____:____ AM / PM	____50 mg ____20 mg
__/__/__ Day 15	☐ Yes ☐ No	____:____ AM / PM	____50 mg ____20 mg
__/__/__ Day 16	☐ Yes ☐ No	____:____ AM / PM	____50 mg ____20 mg
__/__/__ Day 17	☐ Yes ☐ No	____:____ AM / PM	____50 mg ____20 mg
__/__/__ Day 18	☐ Yes ☐ No	____:____ AM / PM	____50 mg ____20 mg
__/__/__ Day 19	☐ Yes ☐ No	____:____ AM / PM	____50 mg ____20 mg
__/__/__ Day 20	☐ Yes ☐ No	____:____ AM / PM	____50 mg ____20 mg
__/__/__ Day 21	☐ Yes ☐ No	____:____ AM / PM	____50 mg ____20 mg
__/__/__ Day 22	☐ Yes ☐ No	____:____ AM / PM	____50 mg ____20 mg
__/__/__ Day 23	☐ Yes ☐ No	____:____ AM / PM	____50 mg ____20 mg
Comments:			

Clinician review at each visit – date and initials_____ _____ _____ _____ _____ _____			
__/ __/ __ Day 24	☐ Yes ☐ No	____:____ AM / PM	____50 mg ____20 mg
__/ __/ __ Day 25	☐ Yes ☐ No	____:____ AM / PM	____50 mg ____20 mg
__/ __/ __ Day 26	☐ Yes ☐ No	____:____ AM / PM	____50 mg ____20 mg
__/ __/ __ Day 27	☐ Yes ☐ No	____:____ AM / PM	____50 mg ____20 mg
__/ __/ __ Day 28	☐ Yes ☐ No	____:____ AM / PM	____50 mg ____20 mg
Comments:			
Clinician review at each visit – date and initials _____ _____ _____ _____ _____ _____ _____ _____ _____ _____			
Pill bottle(s) returned? Yes / No (circle one) # of pills returned (to be completed by RN or MD) 50mg _____ 20mg_____ FINAL REVIEW AND COLLECTION			
Patient Signature: _____ Date: __/ __/ __ MD/RN Signature: _____ Date: __/ __/ __			

[Note to investigators: For cycles of dasatinib that are longer than 28 days, 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.]

18.1 Intake Calendars – 6-Mercaptopurine

SWOG Patient ID_____ Patient Initials (L, F, M) _____ **SWOG Study #_____**
Institution/Affiliate _____ Physician _____

Instructions for the participant:
The chart below is a monthly intake calendar for 6-mercaptopurine on which you are to record the number of 6-mercaptopurine 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: _____

- Doses should be taken without milk or citrus products.
- Doses should be taken at least one hour after the evening meal.
- Missed doses should be made up as soon as possible, unless your doctor advises you not to make up the dose.
- Your nurse or doctor will review your prescribed dose with you.
- Record all doses or missed doses in this pill diary.
- 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.
- 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 have stopped therapy, bring all pill bottles and extra pills to your next clinic visit to be counted and then the study nurse or doctor will tell you when you can throw them away.
- 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.]***

Clinician review at each visit – date and initials_____ _____ _____ _____ _____

6-MERCAPTOPURINE INTAKE CALENDAR

Date	Was Dose Taken?	At What Time?	Total # of Pills Taken?
__/__/__ Day 1	☐ Yes ☐ No	____:____ AM / PM	____ whole pills ____ half pills
__/__/__ Day 2	☐ Yes ☐ No	____:____ AM / PM	____ whole pills ____ half pills
__/__/__ Day 3	☐ Yes ☐ No	____:____ AM / PM	____ whole pills ____ half pills
__/__/__ Day 4	☐ Yes ☐ No	____:____ AM / PM	____ whole pills ____ half pills
__/__/__ Day 5	☐ Yes ☐ No	____:____ AM / PM	____ whole pills ____ half pills
__/__/__ Day 6	☐ Yes ☐ No	____:____ AM / PM	____ whole pills ____ half pills
__/__/__ Day 7	☐ Yes ☐ No	____:____ AM / PM	____ whole pills ____ half pills
__/__/__ Day 8	☐ Yes ☐ No	____:____ AM / PM	____ whole pills ____ half pills
__/__/__ Day 9	☐ Yes ☐ No	____:____ AM / PM	____ whole pills ____ half pills
__/__/__ Day 10	☐ Yes ☐ No	____:____ AM / PM	____ whole pills ____ half pills
__/__/__ Day 11	☐ Yes ☐ No	____:____ AM / PM	____ whole pills ____ half pills
Comments:			
Clinician review at each visit – date and initials_____ _____ _____ _____ _____ _____			

__/__/__ Day 12	☐ Yes ☐ No	____:____ AM / PM	____ whole pills ____ half pills
__/__/__ Day 13	☐ Yes ☐ No	____:____ AM / PM	____ whole pills ____ half pills
__/__/__ Day 14	☐ Yes ☐ No	____:____ AM / PM	____ whole pills ____ half pills
__/__/__ Day 15	☐ Yes ☐ No	____:____ AM / PM	____ whole pills ____ half pills
__/__/__ Day 16	☐ Yes ☐ No	____:____ AM / PM	____ whole pills ____ half pills
__/__/__ Day 17	☐ Yes ☐ No	____:____ AM / PM	____ whole pills ____ half pills
__/__/__ Day 18	☐ Yes ☐ No	____:____ AM / PM	____ whole pills ____ half pills
__/__/__ Day 19	☐ Yes ☐ No	____:____ AM / PM	____ whole pills ____ half pills
__/__/__ Day 20	☐ Yes ☐ No	____:____ AM / PM	____ whole pills ____ half pills
__/__/__ Day 21	☐ Yes ☐ No	____:____ AM / PM	____ whole pills ____ half pills
__/__/__ Day 22	☐ Yes ☐ No	____:____ AM / PM	____ whole pills ____ half pills
__/__/__ Day 23	☐ Yes ☐ No	____:____ AM / PM	____ whole pills ____ half pills
Comments:			

Clinician review at each visit – date and initials_____ _____ _____ _____ _____ _____

__/ __/ __ Day 24	☐ Yes ☐ No	____:____ AM / PM	____ whole pills ____ half pills
__/ __/ __ Day 25	☐ Yes ☐ No	____:____ AM / PM	____ whole pills ____ half pills
__/ __/ __ Day 26	☐ Yes ☐ No	____:____ AM / PM	____ whole pills ____ half pills
__/ __/ __ Day 27	☐ Yes ☐ No	____:____ AM / PM	____ whole pills ____ half pills
__/ __/ __ Day 28	☐ Yes ☐ No	____:____ AM / PM	____ whole pills ____ half pills
Comments:			
Clinician review at each visit – date and initials _____ _____ _____ _____ _____ _____ _____ _____ _____ _____			
Pill bottle(s) returned? Yes / No (circle one) # of unused pills to be discarded pills (to be completed by RN or MD) 50mg _____ FINAL REVIEW AND COLLECTION			
Patient Signature: _____ Date: __/ __/ __ MD/RN Signature: _____ Date: __/ __/ __			

18.1 Intake Calendars - Methotrexate

SWOG Patient ID_____ Patient Initials (L, F, M) _____ **SWOG Study #_____**
Institution/Affiliate _____ Physician _____

Instructions for the participant:
The chart below is a monthly intake calendar for methotrexate on which you are to record the number of methotrexate 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: _____

- Your nurse or doctor will review your prescribed dose with you.
- Record all doses or missed doses in this pill diary.
- 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.
- 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 have stopped therapy, bring all pill bottles and extra pills to your next clinic visit to be counted and then the study nurse or doctor will tell you when you can throw them away.
- 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.
- Do not take NSAIDS, penicillins, proton pump inhibitors, or Bactrim on the same day as methotrexate.
- Missed doses should be made up as soon as possible, unless your doctor advises you not to make up the dose.
- Take your doses this cycle as your doctor has written them in the special instructions below.
- Only take methotrexate on Days 1, 8, 15 and 22 of each cycle.
- Even though you don’t take methotrexate every day of the cycle, please write down that you did not take drug on days methotrexate is not taken. If you accidentally take methotrexate on a day it should not be taken, please write that down as well.

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

Clinician review at each visit – date and initials_____ _____ _____ _____ _____

METHOTREXATE INTAKE CALENDAR – ORAL WEEKLY EVERY 28 DAYS

Date	Was Dose Taken?	At What Time?	Total # of Pills Taken?
__/ __/ __ Day 1	☐ Yes ☐ No	____:____ AM / PM	_____
__/ __/ __ Day 2	☐ Yes ☐ No	____:____ AM / PM	_____
__/ __/ __ Day 3	☐ Yes ☐ No	____:____ AM / PM	_____
__/ __/ __ Day 4	☐ Yes ☐ No	____:____ AM / PM	_____
__/ __/ __ Day 5	☐ Yes ☐ No	____:____ AM / PM	_____
__/ __/ __ Day 6	☐ Yes ☐ No	____:____ AM / PM	_____
__/ __/ __ Day 7	☐ Yes ☐ No	____:____ AM / PM	_____
__/ __/ __ Day 8	☐ Yes ☐ No	____:____ AM / PM	_____
__/ __/ __ Day 9	☐ Yes ☐ No	____:____ AM / PM	_____
__/ __/ __ Day 10	☐ Yes ☐ No	____:____ AM / PM	_____
__/ __/ __ Day 11	☐ Yes ☐ No	____:____ AM / PM	_____
Comments:			
Clinician review at each visit – date and initials_____ _____ _____ _____ _____ _____			

__/__/__ Day 12	☐ Yes ☐ No	____:____ AM / PM	_____
__/__/__ Day 13	☐ Yes ☐ No	____:____ AM / PM	_____
__/__/__ Day 14	☐ Yes ☐ No	____:____ AM / PM	_____
__/__/__ Day 15	☐ Yes ☐ No	____:____ AM / PM	_____
__/__/__ Day 16	☐ Yes ☐ No	____:____ AM / PM	_____
__/__/__ Day 17	☐ Yes ☐ No	____:____ AM / PM	_____
__/__/__ Day 18	☐ Yes ☐ No	____:____ AM / PM	_____
__/__/__ Day 19	☐ Yes ☐ No	____:____ AM / PM	_____
__/__/__ Day 20	☐ Yes ☐ No	____:____ AM / PM	_____
__/__/__ Day 21	☐ Yes ☐ No	____:____ AM / PM	_____
__/__/__ Day 22	☐ Yes ☐ No	____:____ AM / PM	_____
__/__/__ Day 23	☐ Yes ☐ No	____:____ AM / PM	_____
Comments:			
Clinician review at each visit – date and initials_____ _____ _____ _____ _____ _____			

__/ __/ __ Day 24	☐ Yes ☐ No	____:____ AM / PM	_____
__/ __/ __ Day 25	☐ Yes ☐ No	____:____ AM / PM	_____
__/ __/ __ Day 26	☐ Yes ☐ No	____:____ AM / PM	_____
__/ __/ __ Day 27	☐ Yes ☐ No	____:____ AM / PM	_____
__/ __/ __ Day 28	☐ Yes ☐ No	____:____ AM / PM	_____
Comments:			
Clinician review at each visit – date and initials _____ _____ _____ _____ _____ _____ _____ _____ _____ _____			
Pill bottle(s) returned? Yes / No (circle one) # of unused pills to be discarded (to be completed by RN or MD) 2.5mg _____ FINAL REVIEW AND COLLECTION			
Patient Signature: _____ Date: __/ __/ __ MD/RN Signature: _____ Date: __/ __/ __			

18.1 Intake Calendars – Prednisone

SWOG Patient ID_____ Patient Initials (L, F, M) _____ **SWOG Study #_____**
Institution/Affiliate _____ Physician
_____

Instructions for the participant:
The chart below is a monthly intake calendar for prednisone on which you are to record the number of prednisone 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: _____

- Your nurse or doctor will review your prescribed dose with you.
- Record all doses or missed doses in this pill diary.
- 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.
- 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 have stopped therapy, bring all pill bottles and extra pills to your next clinic visit to be counted and then the study nurse or doctor will tell you when you can throw them away.
- 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.
- Missed doses should be made up as soon as possible, unless your doctor advises you not to make up the dose.
- Even though you don’t take prednisone every day of the cycle, please write down that you did not take prednisone on days it is not taken. If you accidentally take prednisone on a day it should not be taken, please write that down as well.
- 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.}***

Clinician review at each visit – date and initials_____ _____ _____ _____ _____

PREDNISONE INTAKE CALENDAR - ORAL

Date	Was Dose Taken?	At What Time?	Total # of Pills Taken?
__/ __/ __ Day 1	☐ Yes ☐ No	____:____ AM / PM	_____
__/ __/ __ Day 2	☐ Yes ☐ No	____:____ AM / PM	_____
__/ __/ __ Day 3	☐ Yes ☐ No	____:____ AM / PM	_____
__/ __/ __ Day 4	☐ Yes ☐ No	____:____ AM / PM	_____
__/ __/ __ Day 5	☐ Yes ☐ No	____:____ AM / PM	_____
__/ __/ __ Day 6	☐ Yes ☐ No	____:____ AM / PM	_____
__/ __/ __ Day 7	☐ Yes ☐ No	____:____ AM / PM	_____
__/ __/ __ Day 8	☐ Yes ☐ No	____:____ AM / PM	_____
__/ __/ __ Day 9	☐ Yes ☐ No	____:____ AM / PM	_____
__/ __/ __ Day 10	☐ Yes ☐ No	____:____ AM / PM	_____
__/ __/ __ Day 11	☐ Yes ☐ No	____:____ AM / PM	_____
Comments:			
Clinician review at each visit – date and initials_____ _____ _____ _____ _____ _____			

__/__/__ Day 12	☐ Yes ☐ No	____:____ AM / PM	_____
__/__/__ Day 13	☐ Yes ☐ No	____:____ AM / PM	_____
__/__/__ Day 14	☐ Yes ☐ No	____:____ AM / PM	_____
__/__/__ Day 15	☐ Yes ☐ No	____:____ AM / PM	_____
__/__/__ Day 16	☐ Yes ☐ No	____:____ AM / PM	_____
__/__/__ Day 17	☐ Yes ☐ No	____:____ AM / PM	_____
__/__/__ Day 18	☐ Yes ☐ No	____:____ AM / PM	_____
__/__/__ Day 19	☐ Yes ☐ No	____:____ AM / PM	_____
__/__/__ Day 20	☐ Yes ☐ No	____:____ AM / PM	_____
__/__/__ Day 21	☐ Yes ☐ No	____:____ AM / PM	_____
__/__/__ Day 22	☐ Yes ☐ No	____:____ AM / PM	_____
__/__/__ Day 23	☐ Yes ☐ No	____:____ AM / PM	_____
Comments:			

Clinician review at each visit – date and initials____ _ _____ _____ _____ _____ _____			
__/ __/ __ Day 24	☐ Yes ☐ No	____:____ AM / PM	_____
__/ __/ __ Day 25	☐ Yes ☐ No	____:____ AM / PM	_____
__/ __/ __ Day 26	☐ Yes ☐ No	____:____ AM / PM	_____
__/ __/ __ Day 27	☐ Yes ☐ No	____:____ AM / PM	_____
__/ __/ __ Day 28	☐ Yes ☐ No	____:____ AM / PM	_____
Comments:			
Clinician review at each visit – date and initials _____ _____ _____ _____ _____ _____ _____ _____ _____ _____			
Pill bottle(s) returned? Yes / No (circle one) # of unused pills to be discarded (to be completed by RN or MD) 50mg _____ 20mg_____ 10mg _____ 5mg____ 2.5mg _____ 1mg____ FINAL REVIEW AND COLLECTION			
Patient Signature: _____ Date: __/ __/ __ MD/RN Signature: _____ Date: __/ __/ __			

[Note to investigators: For cycles of prednisone that are longer than 28 days, 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 Drugs Known to be Metabolized by CYP450 Isoenzymes 2D6 and 3A4

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/; medical reference texts such as the Physicians' Desk Reference may also provide this information.

CYP2D6	
Substrates	
Amitriptyline (hydroxylation)	Methamphetamine
Amphetamine	Metoclopramide
Betaxolol	Metoprolol
Bisoprolol	Mexitetine
Brofaromine	Mianserin
Buturolol	Mirtazapine (hydroxylation)
Bupropion	Molindone
Captopril	Morphine
Carvedilol	Nortriptyline (hydroxylation)
Cevimeline	Olanzapine (minor, hydroxymethylation)
Chlorpheniramine	Ondansetron
Chlorpromazine	Orphenadrine
Cinnarizine	Oxycodone
Clomipramine (hydroxylation)	Papaverine
Clozapine (minor pathway)	Paroxetine (minor pathway)
Codeine (hydroxylation, O-demethylation)	Penbutolol
Cyclobenzaprine (hydroxylation)	Pentazocine
Cyclophosphamide	Perhexiline
Debrisoquin	Perphenazine
Delavirdine	Phenformin
Desipramine	Pindolol
Dexfenfluramine	Promethazine
Dextromethorphan (O-demethylation)	Propafenone
Dihydrocodeine	Propranolol
Diphenhydramine	Quetiapine
Dolasetron	Remoxipride
Donepezil	Risperidone
Doxepin	Ritonavir (minor)
Encainide	Ropivacaine
Fenlluramine	Selegiline
Flecainide	Sertindole
Fluosetine (minor pathway)	Sertratine (minor pathway)
Fluphenazine	Sparteine
Haiofantrine	Tamoxifen
Haioperidol (minor pathway)	Thioridazine
Hydrocodone	Tiagabine
Hydrocortisone	Timolol
Hydroxyamphetamine	Tolterodine
Imipramine (hydroxylation)	Tramadol
Labetalol	Trazodone
Loratadine	Trimipramine
Maprotiline	Tropisetron
m-Chlorophenylpiperazine (m-CPP)	Venlafaxine (O-demethylation)
Meperidine	Yohimbine
Methadone	

INHIBITORS	
Amiodarone	Methadone
Celecoxib	Mibefradil
Chloroquine	Moclobemide
Chlorpromazine	Nortluoxeline
Cimelidine	Paroxetine
Citalopram	Perphenazine
Clomipramine	Propafenone
Codeine	Quinacrine
Deiavirdine	Quinidine
Desipramine	Ranitidine
Dextropropoxyphene	Risperidone (weak)
Diitiazem	Ritonavir
Doxorubicin	Sertindole
Entacapone (high dose)	Sertraline (weak)
Fluoxetine	Thioridazine
Fluphenazine	Vaiprolc acid
Fluvoxamine	Venlafaxine (weak)
Haloperidol	Vinblastine
Labetalol	Vincristine
Lobeline	Vinorelbine
Lomustine	Yohimbine

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	Nefazodone
Digitoxin	Nelfinavir
Diltiazem	Nevirapine

CYP3A3/4 (contd.)	
Substrates	
Disopyramide	Nicardipine
Docetaxel	Nifedipine
Dolasetron	Niludipine
Donepezil	Nimodipine
Doxorubicin	Nisoldipine
Doxycycline	Nitrendipine
Dronabinol	Omeprazole (sulfonation)
Enalapril	Ondansetron
Erylhromycin	Oral contraceptives
Estradiol	Orphenadrine
Ethinyl estradiol	Paclitaxel
Ethosuximide	Pantoprazole
Etoposide	Pimozide
Exemestene	Pioglitazone
Dofetilide (minor)	Pravastatin
Felodipine	Prednisone
Fentanyl	Progesterone
Fexotenadine	Proguanil
Finaxteride	Propafenone
Fluoxetine	
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
Toremifene	Tiagabine
Trazodone	Tolterodine
Tretinoin	Vincristine

FLUTAMIDE (contd.)	
Substrates	
Triazolam	Warfarin (R-warfarin)
Troglitazone	Yohimbine
Troleandomycin	Zaleplon (minor pathway)
Venlafaxine (N-demethylation)	Zatoestron
Verapamil	Zileuton
Vinblastine	Ziprasidone
	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	Mibefradil
Anastrozole	Miconazole (moderate)
Azithromycin	Nefazodone
Cannabinoids	Nelfinavir
Cimetidine	Nevirapine
Clarithromycin	Norfloxacin
Clotrimazole	Norfluoxetine
Cyclosporine	Omeprazole (weak)
Danazol	Oxiconazole
Delavirdine	Paroxetine (weak)
Dexamethasone	Posaconozole
Diethyldithiocarbamate	Propoxyphene
Diltiazem	Quinidine
Dirithromycin	Quinine
Disulfiram	Quinupristin and dalfopristin
Entacapone (high dose)	Ranitidine
Erythromycin	Ritonavir
Ethinyl estradiol	Saquinavir
Fluconazole (weak)	Sertindole
Fluoxetine	Sertraline
Fluvoxamine	Troglitazone
Gestodene	Troleandomycin
Grapefruit juice	Valproic acid (weak)
Indinavir	Verapamil
Isoniazid	Voriconazole
Itraconazole	Zafirlukast
Ketoconazole	Zileuton
Metronidazole	

(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)

18.3 Writing Test

Patient ID_____

Instructions for the Patient:

Enter the date and time of test. Rewrite the phrase listed.

Study Day	Date	Time	***Sweet as apple pie***	Study Staff Initial and Date

18.4 Translational Medicine (MRD)

a. Objective: To estimate the rate of minimal residual disease (MRD) negativity and the time to achieve MRD negativity.

b. Background:

Older patients with acute lymphoblastic leukemia (ALL) have a significantly worse outcome than their younger adult peers. Disease fundamental biological differences (mainly increased incidence of poor risk cytogenetics), together with coexisting medical disorders leading to decreased tolerance to chemotherapy are the main causes for low rates of disease free survival. Complete remission rates in older adults with ALL are typically greater than 50%, but overall survival at 3 years remains around 10%. *(1)* Additionally, despite being the adult sub-group with highest incidence of leukemia, older patients have been underrepresented in prospective clinical trials, and very few clinical trials have focused on therapies designed specifically for older patients.

The prevalence of Philadelphia chromosome, a cytogenetic abnormality that strongly correlates with worse outcome, clearly increases with age, and its incidence peaks at over 50% in patients 55 or older. *(2)* Since the incorporation of tyrosine kinase inhibitors (TKIs) to frontline therapies CR rates achieved with chemotherapy alone have increased significantly in patients with Ph+ ALL, although improvements in long-term survival are still needed. However, no new drugs have made an improvement in the outcome of Ph-negative patients.

Blinatumomab is a constructed monoclonal antibody that belongs to the family of T cell engaging bispecific antibodies (BiTE). It binds to CD19 and to the CD3 site of T cells activating the T cells to exert cytotoxic activity on the target cell. CD19 is an antigen expressed on the surface of essentially all B cells, in all stages of differentiation, so virtually all lymphoblasts in B-ALL will express CD19. Studies with Blinatumomab in minimal residual disease setting and relapsed/resistant ALL have demonstrated impressive results. *(3,4)*

The mechanism of resistance in ALL is unknown. Recently, mutations in Ikaros, CRLF2, JAK1, JAK 2, Ras, and PAX5, and P2RY8-CRLF2 rearrangements, have been found in high-risk pediatric ALL. The gene expression profile in these high-risk cases exhibit a “Ph-like” pattern. In addition, poor risk is associated with “cryptic” translocations involving kinases with immunoglobulin gene rearrangements. *(5)*

c. Experimental Approach and Assays

Flow cytometry detection of MRD. This will be done in the SWOG CAP/ CLIA referral lab of Dr. Brent Wood at the University of Washington. MRD will be assessed by standard methods employed in other COG and SWOG trials. On the pre-treatment sample, the reference laboratory receives a specimen that is used to identify immunophenotypic abnormalities characteristic of the patient’s leukemia and confirms that the antibody combination is informative for MRD detection. Two separate aliquots of the diagnostic sample are stained for 6-color flow cytometry using the following antibody combinations selected and optimized for their ability to detect MRD in B lineage ALL: CD20 FITC/ CD10 PE/ CD38 PerCP-Cy5.5/ CD19 PE-Cy7/ CD58 APC/ CD45 APC-H7 and CD9 FITC/ CD13+CD33 PE/ CD34 PerCP-Cy5.5/ CD19 PE-Cy7/ CD10 APC/ CD45 APC-H7. Given the use of an anti-CD19 directed therapy on this trial, one additional

aliquot of sample will be stained with a combination containing additional B cell antigens as follows: CD10 BV421/ CD20 FITC/ CD22 PE/ CD34 PerCP-Cy5.5/ CD13/33 PE-Cy7/ CD38 A594/ CD24 APC/ CD45 APC-H7. In cases in which the combination outlined above is not informative, additional markers may be employed in the panel.

For the follow-up MRD analysis (see Section 15.3), aliquots of the marrow specimen are prepared using the same antibody panel and a minimum of 750,000 cells acquired through the flow cytometer. Clusters of events that are distinct from positions occupied by normal B cells are identified are dual-parameter displays of antigenic intensity, using the diagnostic displays as a guide. Clusters of events will allow the recognition of abnormal populations at a level of sensitivity of 0.01%; in practice, well-defined clusters can be recognized when they constitute as few as 15-20 cells, so that in many cases sensitivity is better than 0.01%. In a separate tube, the fraction of nucleated cells that are B cells is determined by using the SYTO16 dye as a marker for nucleated cells, and results from the two tubes combined to define the percentage of MRD as a fraction of all nucleated cells.

References:

1 Stock W, Johnson J, Stone R, et al. Dose intensification of daunorubicin and cytarabine during treatment of acute lymphoblastic leukemia: results of Cancer and Leukemia Group B CALGB 19802. Cancer 2013; 119: 90-8.

2 Topp M, Kufer P, Goekbuget N, et al. Targeted therapy with the T-cell engaging antibody Blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rates and prolonged leukemia-free survival. Journal of Clinical Oncology 2011; 29:2043-8.

3 Topp M, Kufer P, Goekbuget N, et al. Targeted therapy with the T-cell engaging antibody Blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rates and prolonged leukemia-free survival. Journal of Clinical Oncology 2011; 29:2043-8.

4 Topp M, Goekbuget N, Zugmaier G, et al. Effect of anti-CD19 BiTE blinatumomab on complete remission rate and overall survival in adult patients with relapsed/refractory B precursor ALL. Journal of Clinical Oncology 2012, Abstract 6500.

5 Roberts KG, Morin RD, Zhang J, et al. Genetic alterations activating kinase and cytokine receptor signaling in high risk acute lymphoblastic leukemia. Cancer Cell 2012; 22(2) 153-66.

18.5 Categories of CNS and Steinherz/Bleyer Method of Evaluating Initial Traumatic Lumbar Punctures

Categories of CNS

- CNS 1: CSF has < 5 WBC/mcL with cytospin negative for blasts; or > 10 RBC/mcL with cytospin negative for blasts.
- CNS 2: CSF has < 5 WBC/mcL with cytospin positive for blasts; or > 10 RBC/mcL with cytospin positive for blasts; or ≥ 10 RBC/mcL, WBC/mcL ≥ 5, but less than Steinherz/Bleyer algorithm with cytospin positive for blasts (see below).
- CNS 3: CSF has ≥ 5 WBC/mcL with cytospin positive for blasts; or ≥ 10 RBC/mcL, ≥ 5 WBC/mcL and positive by Steinherz/Bleyeer algorithm (see below); or clinical signs of CNS leukemia (such as facial nerve palsy, brain/eye involvement or hypothalamic syndrome).

Steinherz/Bleyer Method of Evaluating Initial Traumatic Lumbar Punctures

If the patient has leukemia cells in the peripheral blood and the lumbar puncture is traumatic and contains ≥ 5WBC/mcL with blasts, the following algorithm should be used to define CNS disease:

$$\frac{\text{CSF WBC}}{\text{CSF RBC}} \quad >2x \quad \frac{\text{Blood WBC}}{\text{Blood RBC}}$$

Example:

A patient with CSF WBC ≥ 5/mcL with blasts whose CSF WBC/RBC is greater than twice the blood WBC/RBC ratio has CNS disease at diagnosis. If the CSF WBC=60/mcL; CSF RBC=1500/mcL; blood WBC=46,000/mcL; blood RBC=3 x 10^6/mcL:

$$\frac{60/\text{mcL}}{1500/\text{mcL}} = 0.04, \text{ and is } >2x \quad \frac{46{,}000/\text{mcL}}{3\text{x}10^6/\text{mcL}} = 0.015$$

18.6 Specimen Submission Consent

* NOTES FOR LOCAL INVESTIGATORS:

- This template specimen submission consent is provided as a tool to be used when specimens must be submitted prior to the patient being consented to the clinical trial if a local specimen submission consent is not available. This consent is not mandatory. Sites may use local specimen consent forms, modify specimen collection consents to include specimen submission information, or consent the patient to the clinical trial for the purpose of specimen submission, so long as specimen submission consent is obtained in some written and IRB approved form prior to specimen shipment.
- This template has been reviewed by the DCTD/NCI. Local IRB changes to this document are allowed without prior approval from the SWOG Operations Office. It is suggested that sections of this document that are in bold type be used in their entirety.

* These notes for investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

Specimen Submission Consent

What is the purpose of this consent form?

You are going to have a bone marrow exam and blood tests to see if you have cancer. Your doctor will remove some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care.

If you do have cancer, one of your treatment options might be a clinical trial. A clinical trial is a type of research study. If your doctor thinks a clinical trial would be a good option for you, he or she will discuss everything that would be involved in taking part in the study, like what type of treatment you would get and what tests you will need to take part.

Many clinical trials require that samples (specimens) of your bone marrow and blood be submitted before you start treatment. The specimens are used for testing that is needed as part of the clinical trial.

The purpose of this consent form is to ask your permission to draw extra blood and bone marrow at the same time they are being taken for your diagnosis to send to a central laboratory, so that if you decide to take part in a clinical trial you will not have to have another bone marrow and blood draw. If you agree, you will have an extra 2 teaspoons of bone marrow and 1-2 tablespoons of blood taken. The extra marrow and blood can usually be taken through the same needle stick and do not require extra procedures. By taking the extra marrow and blood at the time of diagnosis, we hope to prevent the need for an extra marrow/blood draw if the clinical trial requires them.

No tests will be done on any of your specimens without your permission. If you and your doctor do not feel that a clinical trial is your best option after getting your diagnosis, or if you decide not to take part in the clinical trial for any reason, your specimens will not be used for testing.
If you and your doctor decide a clinical trial is your best option, and the trial requires specimens before you start treatment, you will be told about any tests that will be done with your specimens as part of the clinical trial consent. Your specimens will not be used unless you agree to take part in the clinical trial.

By signing this consent form you are agreeing to allow extra bone marrow and blood to be drawn at the time specimens are being taken to get your diagnosis, and to allow these specimens to be sent to the central laboratory to be used as part of a clinical trial if you take part in one. You are not consenting to take part in a clinical trial or to have your specimens used for any other research.

What are the risks?

The bone marrow and blood draws are part of your regular cancer screening and care, so your doctor will discuss their risks with you. The risks that are part of collecting extra specimens are unlikely, but are:

- **Extra pain during the bone marrow draw**
- **A second needle stick might be needed to get enough bone marrow or blood**

Your name and identifying information will not be sent with your specimens, so there is little risk of anyone getting your identifying information. Instead, your specimens will be labeled with a number that is assigned by the clinical trials registration system. Your identifying information will be linked to the number in a secure database to help make sure it cannot be accessed.

Signature
I have been given a copy of all 2 pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

18.7 Clinical Site Management of Out-Patient Treatment Using CTEP-Supplied Blinatumomab

- PREPARED IV INFUSION BAGS MAY NOT BE CHANGED BY THE STUDY SUBJECT
- PREPARED INFUSION BAGS OR INTACT VIALS MUST NOT BE TRANSPORTED TO ANOTHER LOCATION BY THE STUDY SUBJECT

AGENT PREPARATION AND ADMINISTRATION OPTIONS

- Prepare all out-patient infusion bags at the registering/treating NCTN Network institution. Study subjects should return to the registering/treating institution for all infusion bag changes.

- For study subjects that cannot return to the registering/treating institution every 96-hours for infusion bag exchanges, the next preference would be for **another NCTN Network institution that is participating on the trial and is closer to the subject's home take over** responsibility for the study subject's protocol participation. In such cases, transfer of the subject's protocol registration to another participating investigator and institution should be considered.

- If transferring the subject's protocol registration to another participating investigator and trial site within the NCTN Network is not feasible, use of **a local outpatient infusion center** could be considered.

    a. First preference would be for all infusion bags to be prepared by the registering/treating institution and shipped via overnight courier delivery service in a 2º to 8ºC pre-qualified shipping container to the local out-patient infusion center.

    b. The prepared infusion bags are stored at the local outpatient infusion center. The infusion center would perform each infusion bag change.

    c. If the local outpatient infusion center will not administer prepared infusion bags admixed by the registering/treating institution, the registering/treating institution may provide intact vials of blinatumomab to the local outpatient infusion center, with infusion bags prepared and administered by the local outpatient infusion center staff.

    d. In either case, the local outpatient infusion center would be managed as a satellite pharmacy of the registering/treating institution (see evaluation criteria below).

    e. If physical transport of intact vials of blinatumomab from the registering/treating institution to the local infusion center by registering/treating institution or local infusion center staff is not possible, CTEP will allow shipment of the vials from the registering/treating institution to the local infusion center via overnight courier delivery service in a 2º to 8ºC pre-qualified shipping container.

- If an outpatient infusion center is not an option, use of a **home health care service** provider can be considered.

    a. The first preference would be for all outpatient infusion bags to be prepared by the registering/treating institution and shipped via overnight courier delivery service in a 2º to 8ºC pre-qualified shipping container to the servicing home health care agency.

    b. The prepared infusion bags are stored by the home health care agency and each individual infusion bag transported to the subject's home by the home health care service nursing staff under refrigerated storage conditions for each infusion bag change.

c. If home health care agency will not administer prepared infusion bags admixed by the registering/treating institution, the registering/treating institution may provide intact vials of blinatumomab to the home health care agency, with infusion bags prepared and administered by the home health care agency staff.

d. In either case, the home health care agency would be managed as a satellite pharmacy of the registering/treating institution (see evaluation criteria below).

e. If physical transport of intact vials of blinatumomab from the registering/treating institution to the home health care agency by registering/treating institution or home health care agency staff is not possible, CTEP will allow shipment of the vials from the registering/treating institution to the home health care agency via overnight courier delivery service in a 2º to 8ºC pre-qualified shipping container.

- If all options above are not feasible, shipping the prepared infusion bags directly to patient's home via overnight courier delivery service for administration by home healthcare agency staff is acceptable.

a. The prepared infusion bags are to be shipped in a 2º to 8ºC pre-qualified shipping container containing one infusion bag per box. Example, if you are making 2 x 48 hour infusion bags, each infusion bag will be shipped in a separate 2º to 8ºC pre-qualified shipping container. The number of infusion bags that may be prepared and shipped is dependent on the duration the shipping container used is qualified to maintain 2º to 8ºC temperature.

b. Patients should NOT open the shipping container upon arrival. Shipping containers are to be stored in a secured area away from reach of children or pets.

c. Shipping containers must only be opened by the home health care service staff at the time of the infusion bag change. Only one shipping container should be opened at a time. If cold-chain management of the prepared infusion bag has been interrupted by opening of the shipping container or storage of the prepared infusion bag in the shipping container exceeds the duration of the qualified time the container will maintain 2º to 8ºC temperature, the infusion bag should not be used.

The home health care service staff should immediately contact the registering/treating institution site pharmacy as indicated on the shipment form. Within 1 business day, the registering/treating institution site should inform the SWOG Operations office at (210/614-8808) to report such occurrences. SWOG should notify PMB/CTEP at PMBafterhours@mail.nih.gov of all such occurrences of prepared, unusable infusion bags shipped to a patient's home within 1 business day of receiving notification from the registering/treating institution.

d. Form documenting the time of packaging in the shipping container, duration of time the container will maintain 2º to 8ºC temperature and verification that cold-chain management was maintained prior to administration must be included in each shipping container and returned to registering/treating institution for documentation purposes.

e. Home health care service staff is to use GCP guidelines.

EVALUATION OF POTENTIAL SATELLITE PHARMACY SITES

When the registering/treating institution is considering use of a local infusion center or home health care agency as a satellite pharmacy, the following must be assessed by the registering/treating institution in relation to the suitability of the local infusion center or home health care agency:

- Ability to appropriately store (temperature and security) the intact agent vials and/or prepared infusion bags.
- Ability to provide documentation of controlled and monitored temperature storage conditions while the IND agent is in the local infusion center or home health care agency possession.
- Availability of appropriately trained staff to prepare doses in compliance with USP <797> guidelines and the protocol, to label infusion bags according to the protocol instructions and to store agent doses under appropriate controlled temperature conditions.
- For home health care agency services, the ability to transport each prepared dose individually to the subject's home under appropriate controlled storage conditions or the ability to assess and confirm that cold-chain management of prepared infusion bags shipped to the subject's home is maintained prior to administration.
- Availability of appropriately trained staff to administer the prepared doses and perform the infusion bag changes according to the protocol.
- Methods for proper disposal of the waste, empty vials, IV bags, etc. are in place.
- Plan for return of unused intact vials to the registering/treating institution is in place.
- Source documentation to confirm agent administration must be maintained by the local infusion center or home health care agency and must be provided to the registering/treating institution for incorporation into the patient's medical/research records and for audit purposes.
- Plan for handling missed doses is in place.
- Agent accountability must be maintained via use of the NCI Drug Accountability Record Form (DARF). The originating site must keep a Control DARF and the local infusion center or home health care agency would be required to maintain a Satellite DARF if receiving and storing supplies of intact vials or receiving and storing infusion bags prepared by the registering/treating institution. Maintenance of a Satellite DARF is not required by home health care agency staff for prepared infusions bags shipped to the subject's home.
- The DARF must be provided to the registering/treating institution for record keeping purposes and audits.
- Documentation of IRB coverage for the protocol must be maintained. The IRB of record for the site must be informed that the study subject may receive therapy administered by a non-research site (i.e., the local infusion center or home health care agency).

TRAINING FOR ALL PARTICIPATING SITES

The Lead Network Group for the trial must work with participating sites to:

a. Implement a training process for participating NCTN Network sites regarding blinatumomab preparation and administration. Documentation of participating site training must be submitted via RSS as a protocol specific requirement at the time of site activation for participation on the trial

b. Develop a plan for participating NCTN Network sites to assess and train local outpatient infusion centers or home health care agency for patient treatment if required and document training of such sites

c. Have a training manual available for local outpatient infusion centers or home health care agencies on the clinical trial, appropriate agent preparation, handling and administration requirements and appropriate record keeping requirements

d. Create a definitive written communication plan for use between registering/treating institution and the local outpatient infusion centers or home health care agency on an ongoing basis during subject's treatment regimen, including emergency contact information for the registering/treating institution and investigator

18.8 6-Mercaptopurine Dosing Guidelines

6-mercaptopurine 60 mg/m^2/day continuously for 28 days (cumulative weekly dose approximately 420 mg/m^2) (1 tablet = 50 mg)

Body Surface Area (m^2)	**Cumulative Weekly Dose**	***Daily Dose for per Week****
1.26 - 1.30	550 mg	1 ½ tablets/day for 6 days; 2 tablets for 1 day
1.31 - 1.36	575 mg	2 tablets/day for 2 days; 1½ tablets/day for 5 days
1.37 - 1.43	600 mg	2 tablets/day for 3 days; 1 ½ tablets/day for 4 days
1.44 - 1.49	625 mg	2 tablets/day for 4 days; 1 ½ tablets/day for 3 days
1.50 - 1.55	650 mg	2 tablets/day for 5 days; 1 ½ tablets/day for 2 days
1.56 - 1.61	675 mg	2 tablets/day for 6 days; 1 ½ tablets/day for 1 day
1.62 - 1.67	700 mg	2 tablets/day for 7 days
1.68 - 1.73	725 mg	2 tablets/day for 6 days; 2 ½ tablets/day for 1 day
1.74 - 1.79	750 mg	2 ½ tablets/day for 2 days; 2 tablets/day for 5 days
1.80 - 1.85	775 mg	2 ½ tablets/day for 3 days; 2 tablets/day for 4 days
1.86 - 1.91	800 mg	2 ½ tablets/day for 4 days; 2 tablets/day for 3 days
1.92 - 1.97	825 mg	2 ½ tablets/day for 5 days; 2 tablets/day for 2 days
1.98 - 2.03	850 mg	2 ½ tablets/day for 6 days; 2 tablets/day for 1 day

* The daily dose per week refers to 7-day cycles within the continued 28 day daily administration cycle (see Section 7.2c). Doses should be taken in the evening, at least one hour after the evening meal.

18.9 Blinatumomab Immunogenicity Assessment

Blinatumomab is a novel protein therapeutic under clinical development by Amgen, Inc. As outlined in the Draft Guidance: Immunogenicity Assessment for Therapeutic Protein Products (Feb 2013) pre-specified immunogenicity sampling will be performed as part of Amgen's initiative to evaluate and mitigate risk (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM338856.pdf).

Blood samples for the assessment of blinatumomab immunogenicity will be collected to determine whether anti-idiotype antibodies directed against blinatumomab have been developed. Screening for these antibodies will be done by ELISA assay on ECL Basis (electrochemiluminescence), and binding will be confirmed with a Biacore assay to measure protein-protein interaction and binding affinity.

In a tiered approach patient samples are initially tested in a screening assay. Samples that produce signals above a certain screening cut point (classified as "positive") may be subjected to a confirmatory assay. The screening assay is designed to minimize false negatives, so positive screening assays need to be confirmed as positive. These are performed using the same format as the screening assay. A comparison of patient serum in the presence and absence of excess blinatumomab is used to confirm or deny the existence of anti blinatumomab antibodies. The screening and confirmation assay in the context of blinatumomab clinical studies will be performed according to an internal standardized protocol using a validated assay.

Immunoassay-positive samples will be analyzed in a third step using a cell based blinatumomab-mediated cytotoxicity assay to determine if the detected antibodies have neutralizing properties. Detection of neutralizing anti-blinatumomab antibodies relies on a validated bioassay measuring changes in the biologic activity of blinatumomab triggered by the presence of the antibody.

Serum samples for antibody testing are being collected on all patients receiving blinatumomab for the measurement screening of anti-blinatumomab binding antibodies. Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further characterized for quantity/titer, isotype, affinity and presence of immune complexes. The 'cell based assay' for neutralizing antibody detection tests patient sera in a model cell based system. This does not require patient cells or additional serum to be collected. Both the screening and the neutralizing assays are well-established at the Amgen Research Munich laboratory.

SWOG will be notified of any positive neutralizing antibody results to blinatumomab. If results are not provided, no neutralizing antibodies to blinatumomab have been detected.

Patients who test positive for neutralizing antibodies to blinatumomab at the final scheduled study visit will be asked to return for additional follow-up testing. This testing is to occur approximately every three months starting from when the site has been notified of the positive result, until: (1) neutralizing antibodies are no longer detectable or (2) the subject has been followed for a period of at least one year (± 4 weeks) post administration of blinatumomab. All follow-up results, both positive and negative will be communicated to SWOG. More frequent testing (e.g. every month) or testing for a longer period of time may be requested in the event of safety-related concerns. Follow-up testing is not required where it is established that the subject did not receive blinatumomab. Patients who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered potentially related to an anti-blinatumomab antibody response may also be asked to return for additional follow-up testing.

18.10 Summary of Treatment Outcomes in Patients ≥ 60 Years with Acute Lymphoblastic Leukemia

Reference	N	N ≥ 60 years of age	CR	TRM	OS
Larson (CALGB 8811)[4,b]	197	18	39%	50%	17% (3 yr estimated)
Larson (CALGB 9111)[5,b]	198	41	77%	25%	17% (3 yr estimated)
Stock (CALGB 19802)[9,b]	163	33	61%	21%	6% (5 yr estimated)
Sive (MRC UKALL XII/ECOG 2993)[10,a,b]	1914	100	73%	18%	21% (5 yr estimated)
O'Brien (MDACC)[11,c,d]	531	122	84%	10%	20% (5 yr estimated)
Thomas (Edouard Herriot Hospital)[23,d]	378	69	62%	24%	10% (3 yr estimated)
Martell (Princess Margaret Hospital)[24,c,d]	51	51	75%	20%	40% (5 yr estimated)
Taylor (Royal Victoria Infirmary)[25, a,e]	157	49	67%	16%	4% (5 yr actuarial)
Gokbuget (GMALL)[26,b]	268	268	76%	14%	23% (5 yr estimated)
Delannoy (Hopital de Jolimont, Belgium)[27,a,d]	18	18	44%	28%	3 months (median OS)
Ferrari (University La Sapienza)[28,d]	49	N/A	59%	23%	9 months (median OS)
Bassan (Ospedali Riuniti, Bergamo Italy)[29,b]	22	22	59%	18%	23% (estimated at 2.6 years)
Offidani (GIMEMA 0288)[30,b]	17	17	41%	35%	12% (3 yr estimated)

Reference	N	N ≥ 60 years of age	CR	TRM	OS
Offidani (GIMEMA VDXD)[30,b]	17	17	76.5 %	17.5%	23% (3 yr estimated)
LeGrand (Hopital Hotel-Dieu, Paris France)[31,c]	148	46	43%	18%	7.6% (5 yr estimated)
Pagano (Universita Cattolica del Sacro Cuore, Rome, Italy)[32,c,d]	119	37	67%	24%	8% (7 yr estimated)
Nagura (Chubu National Hospital, Nagoya Japan)[33,c]	20	20	55%	Unknown	10% (2 yr estimated)
Robak (PALG)[34,c]	87	87	45%	15%	2.4 months (median OS)
Spath-Schwalbe (University of Ulm, Germany)[35c,d]	29	29	43%	37.5%	3% (actuarial)
Delannoy (LALAG97)[36,b]	58	58	58%	12%	<10% (3 yr estimated)
Hunault-Berger (GRAALL-SA1)[37, a,b]	60	60	82%	8%	29% (2 yr estimated)
Moorman (Northern England United Kingdom)[38],[e]	349	124	N/A	N/A	12% (5 yr estimated)
Juliusson (Swedish Acute Leukemia Registry)[39],[e]	464	217	N/A	N/A	5 yr OS by decade: 5% for 75-84 yrs 15% for 65-74 yrs 30% for 55-64 yrs
Toft (Danish Cancer Registry)[40,e]	277	65 (≥65 years)	40%	N/A	6.5% (4 yr estimated)

N = number of patients; **CR** = complete remission; **TRM** = treatment related mortality; **OS** = overall survival
[a] reference 10, 25, 27, and 37 included patients aged 55 and older
[b]prospective studies for older patients with ALL treated with intensive chemotherapy
[c] retrospective analysis of older patients with ALL treated with intensive chemotherapy
[d]single institution data
[e] population-based studies

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18.11 Dasatinib Handout and Wallet Card

*SWOG Protocol#: **S1318***

INFORMATION ON POSSIBLE DRUG INTERACTIONS

Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

[Note to investigators: This appendix consists of an "information sheet" to be handed to the patient at the time of enrollment. Use or modify the text as appropriate for the study agent, so that the patient is aware of the risks and can communicate with their regular prescriber(s) and pharmacist. A convenient wallet-sized information card is also included for the patient to clip out and retain at all times.]

*The patient _____ is enrolled on a clinical trial S1318 using the experimental agent **Dasatinib**. This clinical trial S1318 is sponsored by SWOG. This form is addressed to the patient, but includes important information for others who care for this patient.*

Dasatinib interacts with many drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or herbal supplements.

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you and keep the attached information card in your wallet**. These are the things that you and they need to know:

Dasatinib interacts with a certain specific enzyme in your liver.

- The enzyme in question is **CYP3A4**. **Dasatinib** is broken down by this enzyme in order to be cleared from your system. The dose of this drug that you are taking assumes that these enzymes are working normally.
- Certain drugs may reduce the activity of **CYP3A4**, which can increase the amount of active drug in your system. This increases your chances of experiencing harmful side effects. Other drugs might increase the activity of **CYP3A4**, reducing the level of active drug in your system and making it less effective.
- **Dasatinib** must be used very carefully with such drugs; it is therefore vitally important that you provide your study doctor with a complete list of your medications. Before you begin the study, your study doctor will work with your regular prescriber to switch any medicines that are considered inducers or strong inhibitors of CYP3A4, drugs that are generally accepted to have a risk of causing Torsades de Pointes, medications that inhibit platelet function, and antacids, proton pump inhibitors or H2 antagonists. Once the study begins, you and your healthcare providers must be very careful about adding or removing any drugs in this category. Your prescribers should look at the following web sites http://medicine.iupui.edu/clinpharm/ddis/main-table/
  or your study doctor to see if any medicine they want to prescribe is on a list of drugs to avoid. Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small and located above or below the brand name, and printed in the ingredient list. Find the generic name and determine, with the pharmacist's help, whether there could be an adverse interaction.

Be careful:

- If you take acetaminophen regularly: You should not take more than 12 regular strength (or 8 extra-strength) tablets a day if you are an adult or 7 regular strength (or 4 extra-strength) tablets a day if you are older than 65 years of age. If you have questions about the correct dose please ask your study doctor. Read labels carefully! Acetaminophen is an ingredient in many medicines for pain, flu, and cold.
- If you drink grapefruit juice or eat grapefruit: Avoid these until the study is over.
- If you take herbal medicine regularly: You should not take St. John's wort while you are taking **Dasatinib**.
  Be careful:
  Other medicines can be a problem with your study drug.
- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is

_____

and he or she can be contacted at _____

INFORMATION ON POSSIBLE DRUG INTERACTIONS You are enrolled on a clinical trial S1318 using the experimental agent **Dasatinib.** This clinical trial is sponsored by SWOG. **Dasatinib** interacts with drugs that are processed by your liver. Because of this, it is very important to: ☐☐Tell your doctors if you stop taking regular medicine or if you start taking a new medicine. ☐☐Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, pharmacist) that you are taking part in a clinical trial. ☐☐Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	**Dasatinib** interacts with a specific liver enzyme called **CYP3A4**, and must be used very carefully with other medicines that interact with this enzyme. ☐☐Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "potent or moderate inhibitors or inducers of CYP3A4, sensitive CYP3A4 substrates, and CYP3A4 substrates with a narrow therapeutic window**"**. ☐☐Before prescribing new medicines, your regular prescribers should go to **http://medicine.iupui.edu/clinpharm/ddis/main-table/** for a list of drugs to avoid, or contact your study doctor. ☐☐Your study doctor's name is _____ and can be contacted at _____.

18.12 Medication Guide Blinatumomab

MEDICATION GUIDE BLINATUMOMAB FOR INJECTION

Read this Medication Guide before you receive BLINATUMOMAB and before each BLINATUMOMAB infusion. There may be new information. This information does not take the place of talking with your study doctor about your medical condition or treatment.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT BLINATUMOMAB?

Call your study doctor or get emergency medical help right away if you get any of the symptoms listed below.

BLINATUMOMAB may cause serious side effects that can be severe, life- threatening, or lead to death, including:

- **Cytokine Release Syndrome (CRS) and Infusion Reactions. Symptoms of CRS and infusion reactions may include:**
  - fever
  - tiredness or weakness
  - dizziness
  - headache
  - low blood pressure
  - nausea
  - vomiting
  - chills
  - face swelling
  - wheezing or trouble breathing
  - skin rash
- **Neurologic problems. Symptoms of neurologic problems may include**:
  - seizures
  - difficulty in speaking or slurred speech
  - loss of consciousness
  - confusion and disorientation
  - loss of balance

Your study doctor will check you for these problems during treatment with BLINATUMOMAB. Your study doctor may temporarily stop or completely stop your treatment with BLINATUMOMAB, if you have severe side effects.

See **"What are the possible side effects of BLINATUMOMAB?"** below for other side effects of BLINATUMOMAB.

WHAT IS BLINATUMOMAB?

BLINATUMOMAB is a prescription medicine used to treat a certain type of acute lymphoblastic leukemia (ALL). Acute lymphoblastic leukemia is a cancer of the blood in which a particular kind of white blood cell is growing out of control.

WHO SHOULD NOT RECEIVE BLINATUMOMAB?

Do not receive BLINATUMOMAB if you are allergic to blinatumomab or to any of the ingredients of BLINATUMOMAB. See the end of this Medication Guide for a complete list of ingredients in BLINATUMOMAB.

WHAT SHOULD I TELL MY STUDY DOCTOR BEFORE RECEIVING BLINATUMOMAB?

Before you receive BLINATUMOMAB, tell your study doctor about all of your medical conditions, including if you:

- have a history of neurological problems, such as seizures, confusion, trouble speaking or loss of balance.
- have an infection.
- have ever had an infusion reaction after receiving BLINATUMOMAB or other medications.

Tell your study doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of your medicines with you and show it to your study doctor when you get a new medicine.

HOW WILL I RECEIVE BLINATUMOMAB?

- BLINATUMOMAB will be given to you by intravenous (IV) infusion into your vein by an infusion pump.

- If you are in the Ph-negative (Ph-) study group, then:
  - Induction: You will receive BLINATUMOMAB by continuous IV infusion for 4 weeks (28 days), followed by a 2-week break during which you will not be given BLINATUMOMAB. This is one treatment cycle, and this first cycle is considered the "Induction" cycle.
  - Re-Induction: After the 2-week break, your study doctor will conduct a bone marrow exam to see if your leukemia is gone. If it is not gone, you will receive another "Re-Induction" cycle (continuous IV infusion for 4 weeks, followed by a 2-week break), and then you will have another bone marrow exam.
  - Post-Remission: If the leukemia goes away after either the Induction cycle or the Re-Induction cycle, then you will receive 3 more cycles of blinatumomab as "Post-Remission" treatment.

- If you are in the Ph-positive (Ph+) or Ph-like mutation study group, then:
  - If you have newly diagnosed ALL or if you have relapsed/refractory ALL and have not previously received dasatinib or another tyrosine kinase inhibitor (medication similar to blinatumomab), then you will start protocol treatment with Induction therapy (below) and then (if your leukemia is not gone) receive Re-Induction therapy (below), and (if your leukemia is gone) receive Post-Remission therapy (below).
  - If you have relapsed/refractory ALL and have previously received dasatinib or another tyrosine kinase inhibitor (medication similar to blinatumomab), then you will start protocol treatment with Re-Induction therapy (below), and then (if your leukemia is gone) receive Post-Remission therapy (below).
    - Induction: You will receive different study drugs (dasatinib by mouth on days 1-84 and prednisone by mouth on days 1-32) for your first treatment ("Induction") cycle (as described in the informed consent document). You will be given a bone marrow exam at 4 weeks and 8 weeks after you start study treatment. If your leukemia is gone after either bone marrow exam you will go on to receive "Post-Remission" therapy.
    - Re-Induction: If your leukemia is not gone, you will receive one cycle of "Re-Induction" therapy, where you will receive BLINATUMOMAB by continuous IV infusion for 4 weeks (28 days), followed by a 2-week break during which you will not be given BLINATUMOMAB. About 1 week after you stop taking, blinatumomab, you will receive a bone marrow exam to see if your leukemia is gone. If your leukemia is not gone then you will receive one more "Re-Induction" cycle (continuous IV infusion of blinatumomab for 4 weeks, followed by a 2-week break), and then you will have another bone marrow exam. If your leukemia is still not gone, then you will not receive any further treatment on this study. If your leukemia is gone after either "Re-Induction" cycle, then you will receive "Post-Remission" treatment.
    - Post-Remission: One "Post-Remission" cycle is 6 weeks, during which you will receive dasatinib by mouth every day. You will also receive BLINATUMOMAB by continuous IV infusion for the first 4 weeks (28 days) of each Post-Remission cycle, followed by a 2-week break during which you will not be given BLINATUMOMAB. You will receive 3 cycles of Post-Remission treatment.

- Most patients will receive BLINATUMOMAB in the hospital for about the first 9 days of the first treatment cycle (that includes blinatumomab treatment) and for the first 2 days of every additional cycle (that includes blinatumomab treatment) to check you for side effects. If you achieve a remission, then you may only be hospitalized for 3 days of the first treatment cycle that includes blinatumomab and then for the first 2 days of every additional cycle that includes blinatumomab. If you experience side effects, you may also be admitted to the hospital.

- Your study doctor may change your dose of BLINATUMOMAB, delay, or completely stop treatment with BLINATUMOMAB if you have certain side effects.

- Your study doctor will do blood tests during treatment with BLINATUMOMAB to check you for side effects.

- Before you receive BLINATUMOMAB, you will be given a corticosteroid medicine to help reduce infusion reactions.

- It is very important to keep the area around the IV catheter clean to reduce the risk of getting an infection. Your study doctor will show you how to care for your catheter site.

- **Do not change the settings on your infusion pump**, even if there is a problem with your pump or your pump alarm sounds. Any changes to your infusion pump settings may cause a dose that is too high or too low to be given.

CALL YOUR STUDY DOCTOR OR NURSE RIGHT AWAY IF YOU HAVE ANY PROBLEMS WITH YOUR PUMP OR YOUR PUMP ALARM SOUNDS.

WHAT SHOULD I AVOID WHILE RECEIVING BLINATUMOMAB?

Do not drive, operate heavy machinery, or do other dangerous activities while you are receiving BLINATUMOMAB because BLINATUMOMAB can cause neurological symptoms such as dizziness, seizures, and confusion.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF BLINATUMOMAB?

See "What is the most important information I should know?" BLINATUMOMAB may cause serious side effects, including:

- **Infections.** BLINATUMOMAB may cause life-threatening infections that may lead to death. Tell your study doctor right away if you develop an infection.

- **Low white blood cell counts (neutropenia).** Neutropenia is common with BLINATUMOMAB treatment and may sometimes be life-threatening. Low white blood cell counts can increase your risk of infection. Tell your study doctor right away if you get a fever.

- **Abnormal liver blood test.** Your study doctor will do blood tests before you start BLINATUMOMAB and during treatment with BLINATUMOMAB to check your liver.

The most common side effects of BLINATUMOMAB include:
- fever
- headache
- swelling of hands, ankles or feet
- nausea
- constipation
- shaking (tremor)
- rash

Tell your study doctor if you have any side effect that bothers you or that does not go away.
These are not all the possible side of effects of BLINATUMOMAB.

HOW SHOULD I STORE BLINATUMOMAB?

Intravenous bags containing BLINATUMOMAB for infusion will arrive in a special package.

- Do not open the package.
- Do not freeze the package.
- The package containing BLINATUMOMAB will be opened by the home healthcare infusion nurse at the time of administration of the drug. Only one shipping container should be opened at a time.
- Do not throw away (dispose of) any BLINATUMOMAB in your household trash. Talk with your study doctor about disposal of BLINATUMOMAB and used supplies.

KEEP BLINATUMOMAB AND ALL MEDICINES OUT OF REACH OF CHILDREN.

General information about BLINATUMOMAB
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use BLINATUMOMAB for a condition for which it was not prescribed. Do not give BLINATUMOMAB to other people even if they have the same symptoms that you have. It may harm them.
If you would like more information about BLINATUMOMAB, talk with your study doctor. You can ask your pharmacist or study doctor for information about BLINATUMOMAB that is written for health professionals. For more information, go to www.blinatumomab.com.

WHAT ARE THE INGREDIENTS IN BLINATUMOMAB?

Active ingredient: blinatumomab

Inactive ingredients: citric acid monohydrate, lysine hydrochloride, polysorbate 80, trehalose dehydrate, sodium hydroxide and water for injection.

18.13 Shipment of Blinatumomab IV Bag from Site/Pharmacy to Patient's Home

To be completed by Site/Pharmacy:

From: (Investigator Name, Address)	**To Patient:** (Patient Initials, Study ID No) _____ ; _____ Patient Initials Study ID Number	**Protocol No.:**
Site Pharmacy contact — — —		

Prepare shipment of IV bag at 2°C to 8°C in validated/pre-qualified insulated shipper as per manufacturer instructions (see shipping container instructions). Please take care to use the applicable instructions for summer or winter package preparation, respectively.

IV Bag number	**Date of packaging** [DD/MMM/YYYY]	**Time of packaging** [hh:mm]	**pack**

Please tick the boxes and fill in the information below when preparing the IV bag shipment!

☐ Validated/pre-qualified shipping container duration of time 2°C to 8°C temperature is maintained: _____ hours

☐ Cooling elements for provided box used according to manufacturer's instruction

Confirmed by: _____ _____
(print name, signature) (date)

To be completed by Ambulant/Home Care Service Provider:

Shipment box unopened and content intact? **YES** ☐

NO ☐

IF NO, please comment_____

Date and time shipment box opened:_____ _____
(date) (time)

Confirmed by: _____ _____
(print name, signature) Amb. Care Service (date)

Note: If content is not intact, please do not use IV bag and inform site pharmacy immediately! If time box opened minus time of packaging exceeds the time duration the shipping container maintains 2°C to 8°C, please do not use IV bag and inform site pharmacy immediately!

18.14 Specimen Banking Instructions for the Specimen Repository – Leukemia Division (Lab #200)

Future Research
One 3-4 mL bone marrow aspirate purple top (EDTA) tube will be submitted at diagnosis and at time of registration for Ph-Negative patients *.

*If dry tap and bone marrow blast count is ≥30%, 3mL peripheral blood purple top (EDTA) tube will be submitted.

Upon receipt, the SWOG Biospecimen Bank will isolate white blood cells from the bone marrow EDTA sample using a Ficoll gradient procedure at diagnosis and red blood cell lysing procedure at time of registration for Ph-Negative patients. If peripheral blood is received in leu of bone marrow, the Bank will isolate white blood cells from the EDTA sample using a red blood cell lysing procedure. Specimens will be stored in aliquots in a liquid nitrogen (vapor phase) freezer for protocol designated future research.

Future Correlative Studies
For Cohort 1 - Ph-negative patients, one 7-8 mL bone marrow aspirate purple top (EDTA) tube will be submitted at Pre-Treatment, Day 35 of Induction Cycle 1, and Day 35 of Re-Induction Cycle 1.

For Cohort 2 - Ph-positive and Ph-like DSMKF patients, one 7-8 mL bone marrow aspirate purple top (EDTA) tube and 22-24 mL peripheral blood in purple top (EDTA) tubes will be submitted at Pre-Treatment, Day 28 of Induction Cycle 1, and Day 56 of Induction Cycle 1.

**If dry tap, only 22-24 mL peripheral blood in purple top (EDTA) tubes will be submitted.

Upon receipt, the SWOG Biospecimen Bank will isolate white blood cells from the bone marrow EDTA sample using a Ficoll gradient procedure for Cohort 1 and 2 at pretreatment and the Bank will isolate white blood cells from the bone marrow and peripheral blood EDTA samples using a red blood cell lysing procedure for Cohort 1 and 2 patients at Day 28 of Induction Cycle 1 and Day 56 of Induction Cycle 1. Specimens will be stored in aliquots in a liquid nitrogen (vapor phase) freezer for future correlative studies (to be determined).

18.15 Translational Medicine: Ph-Like Signatures

a. Objectives

1. To estimate the incidence of the Ph-like signature in elderly patients (≥ 65 years of age) with newly diagnosed Philadelphia-chromosome negative ALL.

2. To estimate the incidence of the various tyrosine-kinase fusions, making up the Ph-like signature in elderly patients with newly diagnosed Philadelphia-chromosome negative ALL.

3. To evaluate outcomes (EFS and OS) in patients with the Ph-like signature versus those without the Ph-like signature in Ph-negative ALL.

b. Background and Rationale

Acute lymphoblastic leukemia (ALL) in adults remains a difficult disease to treat and only approximately 40% of adults are cured with standard therapy. The prognosis of elderly adults (defined as ≥ 65 years of age) remains particularly poor, with only 10% of patients alive at 5 years. The poor prognosis of this group has been attributed to an increased incidence of poor risk cytogenetics (more than half have the Ph chromosome) in addition to poor tolerance of intensive chemotherapy. This study evaluates the new BiTE specific antibody (Blinatumomab) in combination with low dose chemotherapy (prednisone, vincristine, methotrexate, 6-mercaptopurine) to see if such a strategy might improve outcomes in this elderly population. This trial is an intergroup collaboration, and includes both Ph-positive and Ph-negative ALL.

Another possible explanation for the poor prognosis of Ph-negative elderly ALL could be the presence of the “Ph-like” signature. This signature has been recently identified in children and young adults with ALL and has been associated with a poor prognosis with respect to both event-free and overall survival. (*1*) However, such work has not been conducted in the elderly population. Such data could be very important since the presence of such a signature (Ph-like) would have therapeutic implications and may inform future clinical trials. Previous data has demonstrated the presence of fusions carrying FLT3, Ras mutations, the IL7 receptor, JAK2, PDGFRB, and ABL1/ ABL2 in children and young adults with the Ph-like signature. (*2*) Current therapeutics are already available to target these including ruxolitinib (JAK inhibitors), imatinib (PDGFR inhibitor). This clinical trial represents the best opportunity to study elderly Ph-negative ALL samples since it is an intergroup collaboration, and this is a rare disease.

c. Laboratory Assay Methods

1. Laboratory Information:

The analyses will be done in the laboratory of Dr. Cheryl Willman, who has pioneered the work in this particular arena.

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2. Assay Information

The Ph-like gene expression signature was originally defined in childhood B-ALL using more than 100 probe sets on the Affymetrix U133_Plus_2.0 chip, but has since been distilled by Dr. Willman's group to just eight genes with quantitative PCR assays on a low-density array (LDA) card. The performance of the LDA card has been validated using more than 5,000 childhood ALL samples as well as more than 1,000 adolescent and young adult cases. In addition to having significantly worse outcomes, patients with the signature have an extremely high frequency of CRLF2 fusions, gene fusions involving tyrosine kinase genes and mutations of JAK1 and JAK2. Dr. Willman's group designed and developed the LDA assay and currently has one issued US patent and another one pending. Additionally, the Ph-like Gene Expression Signature Assay has been approved by the Cancer Therapy Evaluation Program (CTEP) Biomarker Review Committee (BRC). The Center for Devices and Radiological Health at the FDA (CDRH) has determined that this assay, together with confirmatory gene fusion tests, is considered a nonsignificant risk device for screening patients in the COG clinical trial AA1131. Based on the FDA review of the assay, it is considered to be analytically and clinically validated and was deemed a nonsignificant risk device with abbreviated IDE status. Samples will be obtained from banked samples previously collected from the Cohort 1 group. Samples will be shipped to the Center for Molecular and Cellular Diagnostics laboratory. The assay is being run in Dr. Willman's CLIA laboratory at the University of New Mexico.

The experimental approach is to test the RNA of diagnostic samples using the LDA assay to determine whether they have the Ph-like expression signature. Those patients with the signature will then be subsequently tested for CRLF2 fusions (by PCR and FISH) as well as for fusions involving tyrosine kinase genes (PCR and/or RNA-seq). Patients will be run in batches of eight samples on the LDA cards and the results will be available the same day. Samples with the signature will be tested for the other fusions will be batched and tested for the other fusions within two weeks.

The assays will require 3-4 mL of bone marrow aspirate from the diagnostic (pre-treatment) specimen collected in EDTA (purple top) vacutainer tubes.

Total RNA is isolated from the Ficolled sample and 1 mcg is converted into cDNA for the LDA card. The custom cards are run on an Applied Biosystems QuantStudio 12K Flex instrument (~2 hours/run). The raw data are analyzed using proprietary software and the results are reported as either Ph-like or not. Additional information provided by the card indicates whether the sample is *P2RY8-CRLF2* or is likely to have an *IGH-CRLF2* fusion.

Figure 2 shows the pipeline for the analysis. The predictor score is calculated from the gene expression on the LDA card. If the score is less than 0.5 the sample is not Ph-like. If the score is ≥ 0.5, then the sample is Ph-like unless either the *BCR-ABL1* or *ETV6-RUNX1* fusions are present.

Several isoforms of these fusions are included on the LDA card and used to exclude those cases that have other fusions. The LDA card also includes an assay for the *P2RY8-CRLF2* fusion, which is relatively common among Ph-like cases. Similarly, high expression of the CRLF2 gene is predictive of CRLF2 rearrangements (CRLF2-R), both P2RY8 and other types. It may be used to identify Ph-like patients who may be screened by FISH to identify CRLF2-R. The remaining patients who are not CRLF2-R are candidates for additional fusion analysis, either by sequencing or other methods.

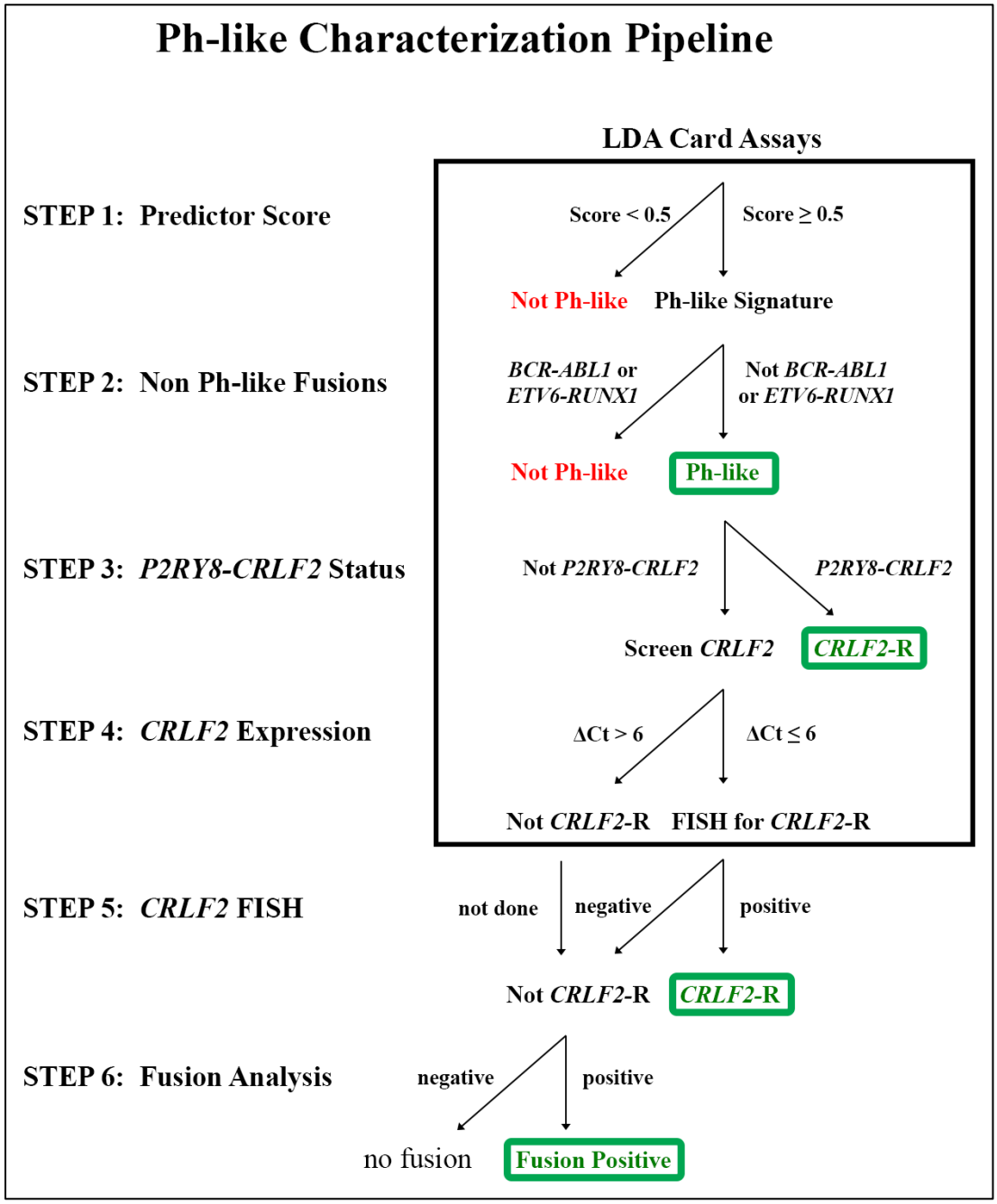

Figure 2: Steps in the LDA Testing Pipeline

3. Result Reporting

Results of the assays will not be reported to the patient or treating institution.

d. Statistical Considerations

Based on SWOG ALL study S0530, it is expected that 95% of eligible patients (n=26) will provide pre-treatment specimens or specimens from later time points so it is anticipated that about 25 patients may be used in these integrated translational medicine analyses. Note that Ph-like patients enrolled in Cohort 2 will not be included in this translational medicine study.

The number and proportion of patients with a Ph-like signature will be tallied and an exact binomial confidence interval for the proportion will be calculated. With 25 patients, the incidence rate can be estimated to within at most 20% (95% confidence interval). Among those with the Ph-like signature, the number and proportion of the various tyrosine-kinase fusions making up the Ph-like signatures will be tallied and an exact binomial confidence interval for the proportion will be calculated. Assuming 50% of patients (n=12) have the Ph-like signature, the incidence rate of any particular tyrosine-kinase fusion can be estimated to within at most 29% (95% confidence interval).

Distributions of EFS and OS, stratified by Ph-like signature (Ph-like or not), will be estimated using the method of Kaplan-Meier. There will be low power to test EFS or OS between the two groups. Assuming 2 years of accrual, 10 years of follow-up, overall 3-year OS rate of 33% (alternative as stated in Section 11.0) and that 50% have the Ph-like signature, the study will have 77% power to detect a hazard ratio of 2.65 for a one-sided test at the 5% level. This corresponds to a 3-year OS rate of 50% among those without the Ph-like signature and 16% otherwise.

References

1 Loh M, Chang Jinghui, Harvey RC, et Harvey RC, Mulligan CG, Wang X, et al. Identification of novel cluster groups in pediatric high-risk B-precursor acute lymphoblastic leukemia with gene express.

2 Harvey RC, Mulligan CG, Wang X, et al. Identification of novel cluster groups in pediatric high-risk B-precursor acute lymphoblastic leukemia with gene expression profiling: correlation with genome-side DNA copy number alterations, clinical characteristics, and outcome. Blood 116(23): 4874-84, 2010.