Protocol Update #11
XX/XX/17

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO CALGB 10701/CTSU 10701

A PHASE II STUDY OF DASATINIB (SPRYCEL®) (IND #73969, NSC #732517) AS PRIMARY THERAPY FOLLOWED BY TRANSPLANTATION FOR ADULTS ≥ 18 YEARS WITH NEWLY DIAGNOSED PH+ ACUTE LYMPHOBLASTIC LEUKEMIA BY CALGB, ECOG AND SWOG

Investigational Agent: Dasatinib (IND #73969, NSC # 732517 will be supplied by NCI DCTD

Companion Studies for Alliance Institutions: CALG 8461 (required), 9665 (optional)

Companion Study for ECOG-ACRIN Institutions: E3903 (required)

[X]	**Update:**	[ ]	**Status Change:**
[ ]	Eligibility changes	[ ]	Activation
[ ]	Therapy / Dose Modifications / Study Calendar changes	[ ]	Closure
[ ]	Informed Consent changes	[ ]	Suspension / temporary closure
[ ]	Scientific / Statistical Considerations changes	[ ]	Reactivation
[X]	Data Submission / Forms changes		
[ ]	Editorial / Administrative changes		
[ ]	Other :		

Expedited review is allowed. IRB approval (or disapproval) is required within 90 days. Please follow your IRB of record guidelines.

UPDATES TO THE PROTOCOL:

Section 6.1 Data Submission

- In the data submission table, the form "C10701 ABL1 Mutational Analysis Form" has been added prior to "During Treatment (Course I)." This form must be completed for all patients and mailed to the Alliance Statistics and Data Center.
- In the data submission table, under "During Treatment (Course VI) and Post-Treatment Follow-Up," the form "C10701 ABL1 Mutational Analysis Form" has been added. This form must be completed for all patients and mailed to the Alliance Statistics and Data Center.

Section 10.13 Filgrastim (G-CSF: Granulocyte Colony-Stimulating Factor; Neupogen; recombinant-methionyl human granulocyte-colony stimulating factor; r-methHuG-CSF; filgrastim-sndz, Zarxio(R))

Zarxio can be used in place of neupogen, therefore, the text "filgrastim-sndz, Zarxio(R)" has been added to the end of the section title.

UPDATES TO THE DONOR CONSENT:

No changes have been made to the Donor Consent.

UPDATES TO THE RECIPIENT CONSENT:

No changes have been made to the Recipient Consent.

A replacement protocol document and model consent have been issued.

This study remains closed to new patient accrual.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

CC: CTSU

Activation Date: 12/15/10

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

CALGB 10701/CTSU C10701

A PHASE II STUDY OF DASATINIB (SPRYCEL®) (IND #73969, NSC #732517) AS PRIMARY THERAPY FOLLOWED BY TRANSPLANTATION FOR ADULTS ≥18 YEARS WITH NEWLY DIAGNOSED PH+ ACUTE LYMPHOBLASTIC LEUKEMIA BY CALGB, ECOG AND SWOG

Investigational Agent: Dasatinib (IND # 73969, NSC # 732517) will be supplied by NCI DCTD
Companion Studies for Alliance Institutions: CALGB 8461 (required), 9665 (optional)
Companion Study for ECOG-ACRIN Institutions: E3903 (required)

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206 Email: CTSURegulatory@ctsu.coccg.org (for submitting regulatory documents only)	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.	Alliance Statistics and Data Center RO FF-3-24-CC/NW Clinic 200 First Street Southwest Rochester, MN 55905 Data Operations Sites should submit Teleforms electronically using the "Submit to CALGB" button or by Mail. See Section 6.1 Data Submission Section for details on forms submission. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
The study protocol and all related forms and documents must be downloaded from the protocol-specific page of the CTSU Member website located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For patient eligibility or treatment-related questions contact the Study PI of the Coordinating Group.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org		

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A PHASE II STUDY OF DASATINIB (SPRYCEL®) (IND #73969, NSC #732517) AS PRIMARY THERAPY FOLLOWED BY TRANSPLANTATION FOR ADULTS ≥ 18 YEARS WITH NEWLY DIAGNOSED PH+ ACUTE LYMPHOBLASTIC LEUKEMIA BY CALGB, ECOG AND SWOG

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ELIGIBILITY CRITERIA:

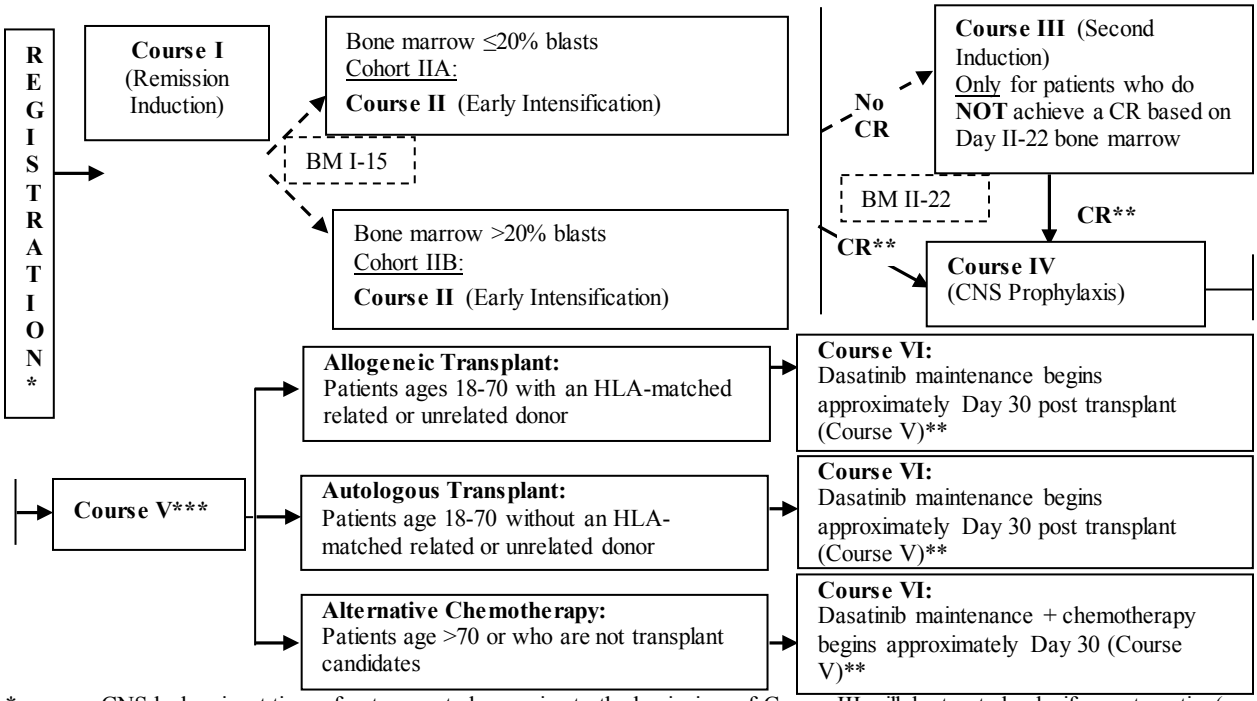
- Unequivocal histologic diagnosis of acute lymphoblastic leukemia (ALL).
- Detection of the t(9;22)(q34;q11) or 3-way variant by metaphase cytogenetics or BCR-ABL positive by molecular analysis (Q-PCR or FISH) in a CLIA-approved laboratory.
- Prior therapy excluded except for up to one week of corticosteroids and/or hydroxyurea to enable time for the detection of t(9;22)(q34;q11) or BCR-ABL.
- Age ≥ 18 years.
- Non-pregnant and non-nursing (see Section 4.5).
- Left ventricular ejection fraction ≥ lower limit of institutional normal.
- No myocardial infarction within 6 months.
- No ventricular tashyarrhythmia within 6 months.
- No major conduction abnormality (unless a cardiac pacemaker is present).

STUDY MONITORING:

A representative from each institution with one of the first 24* patients enrolled on the trial ARE REQUIRED to participate in a teleconference with members of the Alliance Statistics and Data Center and Alliance Protocol Operations Program Office staff.
* Based on the results of the first interim analysis for feasibility and safety, it was decided that the monitoring teleconferences would be extended from 12 patients to 24 patients.
Institutions that do not participate in the teleconferences may be denied future registrations to this trial. See Section 5.1.2 for details.

SCHEMA OVERVIEW:

Treatment courses are specified using a roman numeral followed by a cardinal numeral indicating the number of days from the start of that course of therapy (i.e., Day III-28 is the 28th day of Course III).
Patients undergoing peripheral stem cell transplant on this protocol should receive this portion of their therapy at an Alliance,-SWOG-, ECOG-ACRIN- or FACT-credentialed transplant facility, experienced in the applicable techniques of stem cell procurement, storage, and administration in conjunction with high-dose, myeloablative chemotherapy.



* CNS leukemia at time of entry on study or prior to the beginning of Course III will be treated only if symptomatic (see Sections 8.7 and 8.9). Testicular disease at time of entry onto study will be treated according to Section 8.10.

** CNS leukemia either during hematologic remission (CR or PR) or after having completed protocol therapy without marrow relapse will be treated according to Sections 8.8 and 8.9. Testicular disease during therapy without marrow relapse will be treated according to Section 8.10.

*** The treating physician should consult with the Study Chair regarding frail patients who may need to skip Course V and continue on to Course VI.

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COURSE I (Induction Therapy)

Specimens submitted for quantitative polymerase chain reaction (Q-PCR) are required prior to initiation of protocol therapy. Specimens should be submitted to a CLIA-approved institutional laboratory.

To control the peripheral blast count for as many as seven days while confirmation of t(9;22)(q34;q11) or BCR/ABL occurs, patients may receive dexamethasone 10 mg/m^2/day PO or IV (either once daily or in divided doses) or similar corticosteroid regimen. Hydroxyurea also is permitted to control leukocytosis, although no other ALL-directed therapy is allowed.

- Dasatinib 140 mg PO daily continuously during Course I.
- Dexamethasone 10 mg/m^2/day PO or IV (either once daily or in divided doses) on days I-1 through I-7. Round dose to nearest 0.75 mg.
- Bone marrow examination on day I-15.
- Lumbar puncture on day I-15 (and, in consenting patients, procure CSF for dasatinib levels; see Section 6.4). CNS leukemia at time of entry on study or prior to the beginning of Course III will only be treated if symptomatic. Give IT methotrexate 15 mg + hydrocortisone 50 mg twice weekly for at least 6 doses and until the CSF is clear. See Section 8.7 for more detail.

COURSE II (Early Intensification Therapy)

Treatment in this course will depend on the results from the bone marrow examination on day I-15. Patients with ≤ 20% blasts will be in Cohort IIA; patients with > 20% blasts will be in Cohort IIB. It is recommended that patients continue with dasatinib and onto Course II regardless of counts.

Cohort IIA (≤ 20% blasts in Day I-15 bone marrow examination)

	Cotrimoxazole DS PO BID 3 days/week continuously during Course IIA →																	
	Dasatinib continuously during Course IIA →																	
	Dex →																	
																		BM
Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**...**	**22**

- Cotrimoxazole DS one tablet PO BID 3 days/week continuously during Course IIA, or if allergic to sulfonamides, inhaled pentamidine 300 mg once per month or dapsone 100 mg/day. Patients treated with dapsone should be ruled out for G6PD deficiency.
- Dasatinib 140 mg PO daily continuously during Course IIA.
- Dexamethasone (Dex)10 mg/m^2/day PO or IV (either once daily or in divided doses) on days II-1 through II-7. Round dose to nearest 0.75 mg.
- Bone marrow (BM) examination on day II-22 for all patients to assess response.

Cohort IIB (> 20% blasts in Day I-15 bone marrow examination)

	Cotrimoxazole DS PO BID 3 days/week continuously during Course IIB →																	
	Dasatinib continuously during Course IIB →																	
	Dex →																	
	VCR							VCR							VCR			
	DNR							DNR							DNR			
																		BM
Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**...**	**22**

- Cotrimoxazole DS one tablet PO BID 3 days/week continuously during Course IIB, or if allergic to sulfonamides, inhaled pentamidine 300 mg once per month or dapsone 100 mg/day. Patients treated with dapsone should be ruled out for G6PD deficiency.
- Dasatinib 140 mg PO daily continuously during Course IIB.
- Dexamethasone (Dex) 10 mg/m^2/day PO or IV (either once daily or in divided doses) on days II-1 through II-7. Round dose to nearest 0.75 mg.
- Vincristine (VCR) 2 mg (flat dose) IV on days II-1, II-8, and II-15. If use of an azole antifungal is necessary, it is recommended that an agent with the least inhibitory affect on CYP3A4 be selected if possible. The following azoles appear in order of strength of inhibition of CYP3A4: voriconazole, itraconazole, posaconazole, and fluconazole. Fluconazole at doses of 200 mg or less is not thought to be a significant inhibitor of CYP3A4. Azole antifungal agents should not be administered within 5 half lives of vincristine.
- Daunorubicin (DNR) 30 mg/m^2 IV on days II-1, II-8, and II-15.
- Bone marrow (BM) examination on day II-22 for all patients to assess response.

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COURSE III (Second Induction Therapy)
(ONLY for patients not yet in CR or CRi by Day II-22)

Treatment in this course will depend on the results from the bone marrow examination on day II-22. Until the results are available, patients will continue dasatinib 140 mg PO daily.

If patients have not achieved a complete remission (CR) (see Section 12.1) based on day II-22 bone marrow they will receive Course III therapy. If, however, patients have achieved hematologic and morphologic CR based on day II-22 bone marrow, then they will proceed directly to Course IV without receiving Course III.

	Cotrimoxazole DS PO BID 3 days/week continuously during Course III →																			
	Dasatinib continuously during Course III →																			
	CTX																			
	VCR							VCR												
	DNR							DNR												
	Dex →																			
									G-CSF to continue for at least 7 days and until ANC >1000/μL											
																				BM
Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**...**	**22**	**…**	**28**	**29**

- Cotrimoxazole DS one tablet PO BID 3 days/week continuously during Course III, or if allergic to sulfonamides, inhaled pentamidine 300 mg once per month or dapsone 100 mg/day PO. Patients treated with dapsone should be ruled out for G6PD deficiency.
- Dasatinib 140 mg PO daily continuously during Course III.
- Cyclophosphamide (CTX) 1000 mg/m^2 IV on day III-1.
- Daunorubicin (DNR) 30 mg/m^2 IV on days III-1 and III-8.
- Vincristine (VCR) 2 mg (flat dose) IV on days III-1 and III-8. If use of an azole antifungal is necessary, it is recommended that an agent with the least inhibitory affect on CYP3A4 be selected if possible. The following azoles appear in order of strength of inhibition of CYP3A4: voriconazole, itraconazole, posaconazole, and fluconazole. Fluconazole at doses of 200 mg or less is not thought to be a significant inhibitor of CYP3A4. Azole antifungal agents should not be administered within 5 half lives of vincristine.
- Dexamethasone (Dex) 10 mg/m^2/day PO or IV (either once daily or in divided doses) on days III-1 through III-7. Round dose to nearest 0.75 mg.
- G-CSF subcutaneously (SC) beginning on day III-9 and continuing for at least 7 days and then until ANC > 1000/μL on any one determination after the nadir. For patients <78 kg use 300 mcg, and for patients ≥78 kg use 480 mcg. One dose of PEG-filgrastim (6 mg) on day III-9 may be substituted for G-CSF.
- Bone marrow (BM) examination on day III-29 for all patients to assess response.

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COURSE IV (CNS Prophylaxis)

It is recommended that IV vincristine be administered prior to the initiation of the high-dose IV methotrexate infusion. The IT methotrexate should be administered later in the day (at any time during the IV methotrexate infusion) to avoid any possible confusion between the IV vincristine and the IT methotrexate.

	Cotrimoxazole DS PO BID 3 days/week continuously during Course IV →													
	VCR							VCR						
	IV MTX							IV MTX						
	IT MTX							IT MTX						
	PO MTX	PO MTX						PO MTX	PO MTX					
		SM		SM					SM		SM			
		IV LCV							IV LCV					
			PO LCV	PO LCV						PO LCV	PO LCV			
Day	**1**	**2**	**3**	**4**	**5**	**…**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**

	Cotrimoxazole DS PO BID 3 days/week continuously during Course IV →																					
												Dasatinib →										
								VCR														
								IV MTX														
								IT MTX														
								PO MTX	PO MTX													
									SM		SM											
									IV LCV													
										PO LCV	PO LCV											
																						BM
																						MRD
Day	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**42**	**42**	**43**

- Cotrimoxazole DS one tablet PO BID 3 days/week continuously for PCP prophylaxis during Course IV, or if allergic to sulfonamides, inhaled aerosolized pentamidine (300 mg once per month) or dapsone 100 mg/day. Patients treated with dapsone should be ruled out for G6PD deficiency. Cotrimoxazole should be stopped 3 days before and resumed 3 days after each dose of methotrexate.
- Dasatinib 140 mg PO daily beginning after recovery from the final methotrexate dose (methotrexate level <0.05 µM).
- IT Methotrexate (IT MTX) 15 mg total intrathecal once every two weeks on Days IV-1, IV-15, and IV-29. Hydrocortisone 50 mg should be included with preservative free methotrexate.
- Vincristine (VCR) 2 mg (flat dose) IV once every two weeks on Days IV-1, IV-15, and IV-29. If use of an azole antifungal is necessary, it is recommended that an agent with the least inhibitory affect on CYP3A4 be selected if possible. The following azoles appear in order of strength of inhibition of CYP3A4: voriconazole, itraconazole, posaconazole, and fluconazole. Fluconazole at doses of 200 mg or less is not thought to be a significant inhibitor of CYP3A4. Azole antifungal agents should not be administered within 5 half lives of vincristine.
- IV Methotrexate (IV MTX) 500 mg/m^2 in one liter of D_5W or NS IV over 3 hours on days IV-1, IV-15, and IV-29). Prior to beginning IV Mtx, patients should be pre-hydrated with 500 mL - 1000 mL of D_5W or NS plus 100 mEq/L of sodium bicarbonate. Continue vigorous hydration as tolerated over the course of the day to maintain hydration and urine pH>6. Please check with pharmacy to ensure that patients are not receiving any medications (e.g., sulfonamides, salicylates, penicillins, other organic acids, proton pump inhibitors) that may interfere with methotrexate clearance. During IV infusion, administer IT Mtx. See Section 8.4 for hydration instructions.
- Oral Methotrexate (PO MTX) 25 mg/m^2 PO q6 hours x 4 doses (total) beginning 6 hours after starting each dose of IV Mtx (Days 1 & 2, Days 15 & 16, and Days 29 & 30). The dose of oral methotrexate will be adjusted to maintain a serum methotrexate level between 1-2 µM according to the instructions in Section 8.4.2.
- Serum Mtx (SM) levels should be obtained on Days 2, 4, 16, 18, 30, and 32 (i.e., two levels following each dose of IV Mtx, the first at 30 hours after the start of IV Mtx. See Section 8.4.2).
- IV Leucovorin (IV LCV) 25 mg/m^2 IV 6 hours after the 4th (last) PO Mtx dose (i.e., 30 hours after starting IV Mtx).
- Oral Leucovorin (PO LCV) 5 mg/m^2 PO q6 hours for a planned 8 doses or until serum Mtx level < 0.05 µM, beginning 12 hours after IV Lcv.
- Bone marrow (BM) examination must be obtained for all patients on Day IV-43 to assess response.
- MRD assessment on peripheral blood and bone marrow aspirate by institutional Q-PCR.

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COURSE V

The treating physician should consult with the Study Chair regarding frail patients who may need to skip Course V and continue on to Course VI.

This course include 3 different options:

(1) Allogeneic Transplantation: for patients age 18-70 with an HLA-matched related or unrelated donor

Discontinue dasatinib during Course V allogeneic transplant until approximately Day 30 (see Section 8.6.1).

Patients must be treated at or referred to an Alliance-approved, ECOG-ACRIN-approved, SWOG-approved or FACT-credentialed allogeneic transplant center to be eligible to receive this portion of the therapy. Course V should begin no later than 10 days following count recovery in Course IV. To receive allogeneic transplant, the patient must have adequate organ function (renal, liver, cardiac, and pulmonary) to meet institutional requirements. See Section 8.5.1.9 for antibacterial, antifungal, and Pneumocystis pneumonia prophylaxis.

Mobilization of allogeneic donor peripheral blood stem cells will be performed according to institutional guidelines. Peripheral blood stem cell collection should target an optimal CD34+ cell dose > 5 x 10^6 cells/kg (actual weight) with a maximum of 10 x 10^6 CD34+ cells/kg. Stem cells may be collected at any time prior to transplant.

	F	F	F	F	F											
	A	A	A	A	A											
						M										
						Tacrolimus — *at varying doses (see below) contingent on levels* →										
								PBSCT								
									GCSF →							
																BM
																MRD
Day	**-7**	**-6**	**-5**	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**...**	**30**

- Fludarabine (F) 30 mg/m^2/day (actual body weight) IV on days -7, -6, -5, -4, and -3. At a minimum of one hour prior to the first dose, begin IV hydration to induce at least 100 mL/hr urine output. Fludarabine will be administered prior to alemtuzumab.
- Alemtuzumab (A) 20 mg/day (flat dose) IV on days -7, -6, -5, -4, and -3. Alemtuzumab will be given within one hour of completion of fludarabine. Premedicate with acetaminophen, diphenhydramine (or equivalent), and methylprednisolone (or equivalent).
- Melphalan (M) 140 mg/m^2/day (corrected body weight) IV on day -2.
- Allogeneic peripheral blood stem cell transplant (PBSCT) on day 0.
- G-CSF 5 mcg/kg/day (actual body weight) subcutaneously (SC) on day +1 until at least ANC > 1500/µL for two consecutive days or > 5000/µL for one day.
- Tacrolimus:

In Matched Related Donors:

- On day -2 through +3 tacrolimus 0.05 mg/kg/day by continuous IV infusion (CIVI).
- On day +4 through +14 tacrolimus 0.03 mg/kg/day by CIVI.
- On Day +15 through +100 tacrolimus 0.03 mg/kg/day by CIVI or in divided doses every 12 hours IV or oral. Oral dose is 3x the last IV dose. Adjust to maintain a trough level of ~ 10-20 ng/mL.
- Beyond day +100, taper tacrolimus according to institutional guidelines.

In Mismatched Related Donors or Unrelated Donors:

- Initial tacrolimus dosing will be the same as in matched-related donors above (also Section 8.5.1.5).
- Beyond day +180, taper tacrolimus by 20% per week.
- Bone marrow (BM) examination on day V-30 for all patients.
- MRD assessments on bone marrow aspirate by institutional Q-PCR on Day+30 and one year post transplant.

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(2) Autologous Transplantation: for patients age 18-70 without an HLA-matched donor

Patients must be treated at or referred to an Alliance-approved, ECOG-ACRIN-approved, SWOG-approved or FACT-credentialed autologous transplant center to be eligible to receive this portion of the therapy. Course V should begin no later than 10 days following count recovery in Course IV. To receive autologous transplant, the patient must have adequate organ function (renal, liver, cardiac, and pulmonary) to meet institutional requirements. See Section 8.5.2.4 for antibacterial, antifungal, and Pneumocystis pneumonia prophylaxis.

Discontinue dasatinib during Course V autologous transplant until after stem cells have been collected (see Section 8.5.2.8).

Mobilization

	VP16	VP16	VP16	VP16					
	ara-C	ara-C	ara-C	ara-C					
					Antibiotic & Antifungal Therapy			When WBC > 10,000/μL begin PBSC collection and MRD assessment of daily PBSC product. Continue GCSF until collection is complete or WBC > 50,000/μL ↓	
								G-CSF →	
									Dasatinib
Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**14** →	

- Etoposide (VP16): In patients age ≤ 65 years, 10 mg/kg/day (corrected body weight) by CIVI on days 1-4. Total dose is 40 mg/kg. In patients age > 65 years, 5 mg/kg/day (corrected body weight) by CIVI on days 1-4. Total dose is 20 mg/kg.
- Cytarabine (ara-C) In patients age ≤ 65 years, 2000 mg/m^2 IV over 2 hours every 12 hours x 8 doses on days 1-4. In patients age > 65 years, 1000 mg/m^2 IV over 2 hours every 12 hours x 8 doses on days 1-4.
- G-CSF *f*g-c 10 mcg/kg/day subcutaneously in one or two injections beginning on day +14. G-CSF must be continued until PBSC collection has been completed or WBC > 50,000/μL. Do not skip or dose reduce for bone pain. Round to nearest vial sizes.
- Leukapheresis will begin when WBC > 10,000/μL. The target is ≥ 5 x 10^6 CD34+ cells/kg. Samples from each PBSC product (1 x 10^7 cells from each daily sample) must be sent for institutional Q-PCR.
- Dasatinib Discontinue dasatinib until after stem cell collection is complete. Resume dasatinib 140 mg PO daily. Dasatinib must be continued until 3 days prior to autologous transplant.
- It is recommended that patients remain in hospital until full hematologic recovery.

Autologous Peripheral Blood Stem Cell Transplant (PBSCT)

Peripheral blood stem cell transplantation should take place no earlier than 4 weeks following hospital discharge and after recovery from toxicity related to myelosuppression. The preparative regimen should begin no sooner than 72 hours after the last dose of dasatinib. Patients must meet institutional criteria for PBSCT and have neither active infection nor need for ongoing antibiotics. Patients must remain in complete remission as documented by normal bone marrow morphology with < 5% blasts within 2 weeks of transplant therapy, and have stable or improving peripheral blood counts. ANC must be > 500/μL and platelet count > 50,000/μL. Patients with falling blood counts should be observed to exclude relapse as the cause of the change. Prior to autologous transplant, MRD assessment should be performed on bone marrow aspirate by institutional Q-PCR.

				M	M					
						PBSCT				
						G-CSF ——— *(see text below)* ——→				
										BM
										MRD
Day	**-5**	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**...**	**30**

- Melphalan (M) 100 mg/m^2/day (corrected body weight) IV on days -2 and -1. Total dose is 200 mg/m^2.
- Autologous peripheral blood stem cell transplant (PBSCT) on day 0.
- G-CSF 5 mcg/kg/day (actual body weight) SC beginning on day 0 and continued until ANC ≥ 1500/μL for two days or ≥ 5000/μL for one day.
- Bone marrow (BM) examination on day V-30 for all patients.
- MRD assessment on bone marrow aspirate by institutional Q-PCR on Day+30 and one year post transplant.

A PHASE II STUDY OF DASATINIB (SPRYCEL®) (IND #73969, NSC #732517) AS PRIMARY THERAPY FOLLOWED BY TRANSPLANTATION FOR ADULTS ≥ 18 YEARS WITH NEWLY DIAGNOSED PH+ ACUTE LYMPHOBLASTIC LEUKEMIA BY CALGB, ECOG AND SWOG

(3) Alternative Chemotherapy Regimen: for those patients age > 70, or who are not candidates for transplantation, or those without transplant insurance coverage

Patients who are age > 70, who are not candidates for transplantation or for those without transplant insurance coverage should not be removed from protocol therapy. Rather, these patients will receive an alternative chemotherapy regimen including etoposide and high-dose ara-C. Therapy should begin no sooner than 72 hours and no later than 10 days following the last dose of dasatinib in Course IV.

	VP16	VP16	VP16	VP16								
	ara-C	ara-C	ara-C	ara-C								
										G-CSF →		
												BM
Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**...**	**14**	**...**	**30**

- Etoposide (VP16): In patients age ≤ 65 years, 10 mg/kg/day (corrected body weight) by CIVI on days 1-4. Total dose is 40 mg/kg. In patients age > 65 years, 5 mg/kg/day (corrected body weight) by CIVI on days 1-4. Total dose is 20 mg/kg.
- Cytarabine (ara-C): In patients age ≤ 65 years, 2000 mg/m^2 IV over 2 hours every 12 hours x 8 doses on days 1-4. In patients age > 65 years, 1000 mg/m^2 IV over 2 hours every 12 hours x 8 doses on days 1-4.
- G-CSF 5 mcg/kg/day subcutaneously in one or two injections beginning on day +14.
- Bone marrow (BM) examination on day V-30 for all patients. MRD assessment on bone marrow aspirate by institutional Q-PCR at one year.

COURSE VI (Dasatinib Maintenance Therapy)

Treatment in this course will depend on the treatment delivered in Course V.

For Those Patients who Received Allogeneic Transplantation

- Dasatinib 50 mg/day PO beginning on about day V-30 post transplant (if tolerable). Increase dose to 100 mg PO once daily after two weeks, if tolerated. Dasatinib maintenance to continue for a minimum of 12 months after the first dose of dasatinib. Discontinue dasatinib maintenance when any ONE of the following criteria are met: 1) Completion of 12 months of maintenance if two consecutive negative RT-PCR assays performed in a local CLIA-approved laboratory three months apart are documented; 2) After 12 months of maintenance when two consecutive negative RT-PCR assays performed in a local CLIA-approved laboratory three months apart are documented; or 3) At relapse.
- Bone marrow examinations will occur every 3 months for 2 years and at relapse. Institutional Q-PCR should be performed on peripheral blood every 3 months for 5 years from study entry. At time of relapse, MRD assessment on bone marrow aspirate or peripheral blood by institutional Q-PCR should be performed.

For Those Patients who Received Autologous Transplantation

- Dasatinib 100 mg PO once daily beginning on about day V-30 post transplant (if tolerable). Dasatinib maintenance to continue for a minimum of 12 months after the first dose of dasatinib. Discontinue dasatinib maintenance when any ONE of the following criteria are met: 1) Completion of 12 months of maintenance if two consecutive negative RT-PCR assays performed in a local CLIA-approved laboratory three months apart are documented; 2) After 12 months of maintenance when two consecutive negative RT-PCR assays performed in a local CLIA-approved laboratory three months apart are documented; or 3) At relapse
- Bone marrow examinations will occur every 3 months for 2 years and at relapse. Institutional Q-PCR should be performed on peripheral blood every 3 months for 5 years from study entry. At time of relapse, MRD assessment on bone marrow aspirate or peripheral blood by institutional Q-PCR should be performed.

For Those Patients who Received Alternative Chemotherapy Regimen

- Dasatinib 100 mg PO once daily beginning on day V-30 (30 days after starting etoposide/cytarabine).
- Vincristine 2 mg IV every 4 weeks.
- Dexamethasone 10 mg/day for 5 days every 4 weeks.
- 6-Mercaptopurine 60 mg/m2/day PO in the evening.
- Methotrexate 20 mg/m2 PO once per week.
- Adjust doses of 6-mercaptopurine and methotrexate to keep the ANC > 1000/μL and the platelet count > 75,000/μL.
- Dasatinib maintenance to continue for a minimum of 12 months after the first dose of dasatinib. Discontinue dasatinib maintenance when any ONE of the following criteria are met: 1) Completion of 12 months of maintenance if two consecutive negative RT-PCR assays performed in a local CLIA-approved laboratory three months apart are documented; 2) After 12 months of maintenance when two consecutive negative RT-PCR assays performed in a local CLIA-approved laboratory three months apart are documented; or 3) At relapse
- Bone marrow examinations will occur every 3 months for 2 years and at relapse. Institutional Q-PCR should be performed on peripheral blood every month for the first year, every 3 months for the following two years, and every six months for 5 years from study entry. At time of relapse, MRD assessment on bone marrow aspirate or peripheral blood by institutional Q-PCR should be performed.

A PHASE II STUDY OF DASATINIB (SPRYCEL®) (IND #73969, NSC #732517) AS PRIMARY THERAPY FOLLOWED BY TRANSPLANTATION FOR ADULTS ≥18 YEARS WITH NEWLY DIAGNOSED PH+ ACUTE LYMPHOBLASTIC LEUKEMIA BY CALGB, ECOG AND SWOG

Schema for Specimen Submission

At diagnosis	**Alliance Patients**	Signed the CALGB 8461 model consent. * →	**(See CALGB 8461)** Submit to your local cytogeneticist: bone marrow peripheral blood
		Signed the CALGB 9665 model consent. →	**(See CALGB 9665)** Submit: bone marrow aspirate whole blood buccal cell sample
	ECOG-ACRIN Patients →	Signed the ECOG E3903 model consent. * →	**(See ECOG E3903)** Submit: blood bone marrow karyotypes
Prior to initiation of remission induction therapy	**All Patients** →	Signed the CALGB 10701 model consent. * →	**(See section 6.3)** Submit: 3 unstained bone marrow smears 3 unstained blood smears 1 H&E stained biopsy slide 4 unstained biopsy sections
Course I, Day 15 (+/- 1 day)	**All Patients** →	Answered, "yes" to "*I agree that my specimen(s) may be used for the research described above*" (Question #1) in the model consent. →	**(See section 6.4)** Submit: 3 mL peripheral blood 3 mL of cerebrospinal fluid
At Complete Remission	**Alliance Patients**	Signed the CALGB 8461 model consent. * →	**(See CALGB 8461)** Submit to your local cytogeneticist: bone marrow peripheral blood
		Signed the CALGB 9665 model consent. →	**(See CALGB 9665)** Submit: bone marrow aspirate whole blood
At Relapse	**Alliance Patients**	Signed the CALGB 8461 model consent. * →	**(See CALGB 8461)** Submit to your local cytogeneticist: bone marrow peripheral blood
		Signed the CALGB 9665 model consent. →	**(See CALGB 9665)** Submit: bone marrow aspirate whole blood

* Patient is not eligible for participation in CALGB 10701 if this model consent is not signed.

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SECTION **PAGE**

1.0 INTRODUCTION

1.1 Acute Lymphoblastic Leukemia with t(9;22); Philadelphia (Ph) Chromosome Positive ALL

The oncogenic fusion gene BCR/ABL that results from the reciprocal translocation t(9;22)(q34;q11.2) is the sine qua non for chronic myeloid leukemia (CML). However, the Philadelphia chromosome (Ph) that results from the t(9;22) is also the single most frequent chromosome abnormality in adult acute lymphoblastic leukemia (ALL), detected in 11% to 34% of patients with ALL. The prevalence is increased in older adults, especially in individuals over 60 years of age. The reciprocal translocation between chromosomes 9 and 22 results in the head-to-tail fusion of variable numbers of 5' *BCR* exons on chromosome band 22q11.2 with the exon 2 of the *ABL* gene located on chromosome band 9q34. The protein product of the fusion gene resulting from the t(9;22) plays a central role in the development of this form of ALL. Two main fusion proteins, $p190^{BCR/ABL}$ and $p210^{BCR/ABL}$, each containing NH2-terminal domains of Bcr and COOH-terminal domains of Abl, are produced depending on the location of the breakpoint within the *BCR* gene. The $p190^{BCR/ABL}$ product contains the first exon of *BCR* and occurs in 50-78% of the ALL cases with t(9;22). The $p210^{BCR/ABL}$ product contains either exon 13 or exon 14 of *BCR* and is ubiquitous in CML and is considerably less frequent in ALL. Of note, $p190^{BCR/ABL}$ transcripts are frequently detected at a low level in $p210^{BCR/ABL}$-positive ALL.

Ph+ ALL has been associated with an unfavorable outcome but this has changed since the advent of imatinib mesylate. This introduction will describe the milestones achieved and why improvements are still needed beyond imatinib mesylate.

1.2 Imatinib Mesylate in Combination with Chemotherapy

Imatinib mesylate. The first BCR-ABL inhibitor to gain clinical approval was imatinib mesylate, which partially blocks the adenosine triphosphate binding site of BCR-ABL, preventing a conformational switch of the oncogenic protein to the activated form [1]. Early studies showed that many previously-treated Ph+ ALL patients responded to imatinib monotherapy (400 mg^2 or 600 mg/day) initially (CR rates 20%) but then quickly (median treatment duration of 58 days) relapsed. Thus, although imatinib was well-tolerated and produced a modest response for previously-treated Ph+ ALL when used as single-agent therapy, responses were short-lived, and relapse was common [2, 3].

TKIs with steroids alone

The treatment of elderly patients with Ph+ ALL has been limited by intolerance to chemotherapy, the inability to undergo alloSCT because of comorbidities, and the biological characteristics of the disease [4]. Several approaches to using TKI-based therapy have been explored in these patients, including a chemotherapy-free treatment based only on a TKI and steroids. In one study from the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA), 61–83 years old Ph+ ALL patients received a 7-day steroid pretreatment followed by a 45-day induction of imatinib (800 mg/day) plus prednisone (40 mg/m^2 per day) [5]. Therapy was well tolerated, and no major toxicities were reported. All 29 assessable patients (100%) experienced a CHR, and at 12 months, the OS and DFS probabilities were 74% and 48%. The GIMEMA prospective study LAL1205 has evaluated a similar regimen using dasatinib (70 mg) in adult Ph+ ALL patients (median age, 54 years) [6]. All 34 (100%) evaluable patients treated with this regimen achieved a CHR, and the OS rate at 10 months was 80.7%. Adding mixed-agent chemotherapy to TKI-steroid treatments does not appear to substantially increase 1-year OS or decrease relapse rates in elderly Ph+ ALL patients. The Group for Research in Adult Acute Lymphoblastic Leukemia AFR09 study, which combined standard induction therapy with

imatinib and prednisone, reported 1-year relapse and OS rates of 58% and 66% [7]. While these values were significantly improved from historical controls treated with chemotherapy without imatinib, they appear to be at par with chemotherapy-free regimens that include only TKIs and steroids. It would be of interest to combine TKIs and steroids with other established non-myelotoxic agents, e.g., vincristine, in elderly Ph+ ALL patients.

Table 1: Effect of Imatinib and Chemotherapy Combination on Outcome in Ph+ Adult and Elderly Patients

Study	No. patients	Median age (range)	Induction regimen	CR, %	DFS, % (yr)	Benefit of alloSCT	Survival, % (yr)
Adult patients							
JALSG ALL 202 [8]	103	45 (15-64)	Imatinib, CTX, daunorubicin, VCR, PRED	97.1	NA	Relapse: 13% w/alloSCT; 90% w/o alloSCT*	56.8 (3)
Modified Linker [9]	19†	37 (15-67)	Imatinib, daunorubicin, ASNase, VCR, PRED	95	NA		NA
GMALL [10]	47-Alternate	43.5 (19-65)	Concurrent or alternating imatinib with dexamethasone, VCR, daunorubicin, pegaspargase, CTX, Ara-C, 6-mercaptopurine, methotrexate, G-CSF	NA	52 (2)‡		36 (2)
	45-Concurrent			95	61 (2)‡		43 (2)
Hyper-CVAD [11]	54†	51 (17-84)	Imatinib, CTX, VCR, doxorubicin, dexamethasone	93	76 vs. 63= (3)	3 yr OS: 90% w/alloSCT ; 33% w/o alloSCT‖	NA
GRAAPH-2003 [12]§	45	45 (16-59)	Daunorubicin, CTX, VCR, PRED, L-asparaginase, CTX, VCR, PRED, ASNase, triple intrathecal	NA	43 (4)	4 yr OS: 55% w/alloSCT; 80% w/auto-SCT; 25% w/o SCT¶	52 (4)
Elderly patients							
GRALL AFR 09 [7]†	29†	65.8 (58-78)	VCR, CTX, daunorubicin, PRED	72	58 (1)		66 (1)
GIMEMA [5]	29†	69 (61-83)	Imatinib, PRED	100	48 (1)		74 (1)

Abbreviations: Allo, allogeneic; Ara-C, cytarabine; Auto, autologous; CTX, cyclophosphamide; G-CSF, granulocyte-colony stimulating factor; GIMEMA, Gruppo Italiano Malattie EMatologiche dell'Adulto; GMALL, German Multicenter Trials of Adult ALL; GRALL, Group for Research in Adult Acute Lymphoblastic Leukemia (Ph-); GRAAPH, Group for Research on Adult Acute Lymphoblastic Leukemia (Ph+); hyper CVAD, fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone; JALSG, Japan Adult Leukemia Study Group; PRED, prednisone; SCT, stem cell transplant; VCR, vincristine; W, with; W/O, without; Yr, year;

* Relapsed occurred in 18 of 20 (90%) of patients in whom alloSCT was not performed in CR1 but in only seven of 54 (13%) who underwent alloSCT in CR1.
† Evaluable patients.
‡ Estimated probability of remission.
§ Imatinib during consolidation therapy.
= The 3-year CR duration was 76% for 13 patients who achieved major molecular response prior to alloSCT compared with 63% for the 31 patients who did not, p=0.2.
‖ In de novo patients ≤40 years of age, 3-year overall survival was 90% with alloSCT (n=10) vs. 33% without alloSCT (n=6), p=0.005.
¶ The 4-year OS in the alloSCT, autoSCT and no SCT groups were 55%, 80% and 25% (alloSCT versus autoSCT, p=0.16; alloSCT versus no SCT, p=0.05; autoSCT versus no SCT, p=0.008).

1.3 Mechanisms of Resistance to Imatinib Mesylate

Four mechanisms of resistance to imatinib mesylate have been described to date. These are (1) mutations at the kinase site, (2) reduced intracellular imatinib mesylate concentration, (3) gene amplification, and (4) alternative signaling pathways functionally compensating for the imatinib-sensitive mechanisms.

Mutations at the kinase domain impair imatinib's binding to varying degrees and represent the most common (approximately 40-50%) mechanism of resistance. Recently, kinase domain mutations were found to precede imatinib-based therapy and gave rise to relapse in patients with de novo Ph+ ALL [13]. Of note, 12 (46%) of 26 patient samples harbored P-loop (e.g., G250E, Q252H, Y253H, E255K/V) mutations and 6 (23%) of 26 patient samples demonstrated gatekeeper (e.g., F311I, T315I, F317L) mutations at diagnosis. Interestingly, remission duration did not differ significantly between patients with or without a detectable early mutation in that study. At relapse, ten patients with mutations at diagnosis demonstrated the same mutation while one patient demonstrated a different mutation at relapse. These data suggest that, in contrast to CML, it may be worthwhile to consider mutational analysis at diagnosis in Ph+ ALL and tailor treatment accordingly. Novel drugs that overcome kinase domain mutations are discussed below.

A previous study [13] concluded that other mechanisms of resistance also exist, as three patients with wild-type *BCR-ABL* at diagnosis relapsed without any mutations. Intracellular imatinib mesylate concentration has been shown to correlate with response in CML though no such data are yet available in Ph+ ALL. Briefly, drug efflux proteins, such as Permeability-glycoprotein (Pgp, the gene product of *ABCB1*, formerly *MDR1*) [14] and breast cancer resistance protein (Bcrp1, *ABCG2*) [15] were shown to lower intracellular imatinib mesylate concentrations in CML. Similarly, imatinib mesylate was shown to be a substrate for the organic cation influx transporter 1 (OCT1) and reduced OCT1 activity is the cause of low in vitro sensitivity to imatinib mesylate in CML [16]. Finally, plasma α1-acid glycoprotein concentrations had a marked influence on total imatinib mesylate concentrations in CML [17]. While in CML, decreased intracellular imatinib mesylate concentrations are addressed by intensifying the therapy with higher imatinib mesylate doses (up to 800 mg/day), this approach is not proved valid for Ph+ ALL. As discussed below, some of the novel Bcr-Abl kinase inhibitors are not subject to some of these mechanisms and are also markedly more potent than imatinib mesylate.

BCR-ABL gene amplification is another mechanism of resistance to imatinib mesylate in CML. Though no such data exist so far in Ph+ ALL, duplication of the Ph chromosome was shown to be associated with worse outcome in Ph+ ALL in the pre-imatinib era [18]. Further, the effect of novel Bcr-Abl kinase inhibitors with significantly more potent anti-Bcr-Abl activity in imatinib-resistant cases suggests that this mechanism prevails in Ph+ ALL, too.

Alternative signaling pathways have been implicated in resistance to imatinib mesylate. Specifically, the Src (sarcoma) family kinase members, Lyn, Hck, and Fgr, have been shown to be elevated in the hematopoietic cells of mice with Ph+ ALL and these proteins are required for the induction of Ph+ ALL in mice [19]. Dasatinib (Sprycel®) and bosutinib (SKI-606) target the Src family kinase members in addition to Bcr/Abl as will be discussed below. Stromal support is another alternative pathway involved in imatinib resistance in Ph+ ALL. While the Bcr-Abl kinase continued to be inhibited by imatinib mesylate, resistant cells proliferated in the presence of stromal support [20]. The stromal effect did not require direct cell-cell contact, and stromal cell derived factor-1α substituted for the presence of the stromal cells. These data suggest that the stroma selects for imatinib mesylate resistant Bcr-Abl cells that are less dependent on the kinase activity; interrupting the interaction between lymphoblasts and the stroma may be of benefit in Ph+ ALL.

Another recently identified mechanism of TKI resistance involves the expression of spliced isoforms of Ikaros *(IKZF1)* [21]. IKZF1 functions as a critical regulator of normal lymphocyte development and is involved in the rapid development of leukemia in mice expressing non-DNA-binding isoforms [22]. The *IK6* isoform, lacking all 4 N-terminal zinc fingers responsible for DNA-binding, was detected in 43 of 47 (91%) Ph+ ALL patients resistant to imatinib or dasatinib [21]. In addition, the expression level of *IK6* correlated with the BCR-ABL transcript level. Hence, restoring Ikzf1 function may provide another approach to combating TKI resistance in the future.

1.4 New Drugs to Overcome Resistance: Dasatinib for Ph+ ALL

Dasatinib, a dual SRC and ABL inhibitor, has a 325-fold greater potency than imatinib in cells transduced with unmutated BCR-ABL and is active against many of the BCR-ABL mutations conferring imatinib resistance [23]. Furthermore, dasatinib's cellular uptake is not dependent on OCT-1 activity [24], though like imatinib, it is a substrate for efflux proteins [25].

The START (SRC/ABL Tyrosine kinase inhibition Activity Research Trials of dasatinib) L (imatinib-resistant or -intolerant lymphoid blast crisis and ALL) reported that dasatinib (70 mg bid) was relatively well tolerated and produced a major hematological response (MHR) in 41% and major cytogenetic response (MCyR) in 57% of patients after a minimum follow-up of 12 months [26]. The discrepancy between hematologic and cytogenetic responses likely stems from the high incidence of cytopenias induced by dasatinib. Median OS was 8.0 months. After 1 year of treatment, 22% of patients remained alive and progression-free [26]. A high proportion of patients with P- and A-loop mutation of the ABL domain achieved MHR and MCyR [27]. However, patients with the T315I and F317L gatekeeper mutations do not respond to dasatinib [27, 28]. Dasatinib is approved in the United States for Ph+ ALL patients who have failed to respond to imatinib, and clinical trials evaluating its efficacy in newly diagnosed Ph+ ALL are ongoing.

Combining imatinib with conventional chemotherapy revolutionized the treatment of Ph+ ALL; CR rates now approach 95%, and 3-year OS can exceed 50% (Table 1) [5, 7-12]. Imatinib may be administered either concurrently or sequentially with chemotherapy.

Combination chemotherapy with dasatinib

Dasatinib combined with conventional chemotherapy is also efficacious and safe in Ph+ ALL patients. Combining hyper-CVAD with dasatinib (50 mg bid for the first 14 days of each cycle) led to CR in 93% of patients; after a median follow-up of 10 months, 75% were alive, and 64% remained in CR. A high incidence of T315I ABL mutation was noted among relapsed patients [29]. AFR 07 evaluated dasatinib in combination with the European Working Group on Adult ALL chemotherapy protocols for the treatment of ≥55 year old Ph+ ALL patients [30]. Dasatinib was administered with vincristine and dexamethasone during induction, sequentially with

methotrexate and L-asparaginase alternating with cytarabine during consolidation, and with 6-mercaptopurine, methotrexate, and dexamethasone/vincristine during maintenance. A 95.2% CHR rate was observed, and the rate of serious adverse events was 40%, as expected in this population. Responses appeared to be durable; the level of minimal residual disease (MRD) has continued to decrease with prolonged therapy.

This protocol will cover all age groups, 18 and above.

1.5 Central Nervous System Prophylaxis

The central nervous system (CNS) is a sanctuary site for ALL, and relapses may occur first in the cerebrospinal fluid (CSF). CNS prophylaxis with intrathecal (IT) chemotherapy is routine. Imatinib does not cross the blood-brain barrier. Dasatinib has a potential advantage of penetrating into the CSF, but this has never been analyzed systematically. We therefore propose to measure dasatinib CSF levels at the time of the first intrathecal administration of chemotherapy. Since dasatinib is presumed to reach a maximal CSF level within 2 hours following its oral administration, the first intrathecal chemotherapy will be scheduled accordingly. Further, since we will be collecting the data prospectively, we will continue to administer standard intrathecal and systemic CNS prophylaxis throughout this study similar to the regimen previously used in CALGB C10001.

1.6 Transplantation for Ph+ ALL

AlloSCT in first CR remains the standard of care for Ph+ ALL and the only established therapy that offers a possibility of cure [31]. However, prior treatment with TKIs can increase the feasibility of SCT in a greater proportion of Ph+ ALL patients by increasing remission rates and extending remission durations [4, 32]. In addition, TKIs have increased the proportion of patients experiencing sustained remissions and provides additional time to identify a suitable donor. Reducing BCR-ABL transcript levels after imatinib-based therapy has also resulted in a lower pre-SCT tumor burden [4]. Finally, three studies [8, 12, 32] demonstrated a clear benefit for alloSCT over chemotherapy alone (Table 1). Additional data with longer follow-up are necessary to determine whether alloSCT may still be necessary in Ph+ ALL patients treated with TKI-combination chemotherapy regimens.

The German [12] and our preliminary experience with autologous (auto) SCT in CALGB 10001 [33] suggest that this approach is at least as beneficial as allo-SCT but with less toxicity and therefore we propose to continue and study this treatment modality herein.

1.6.2 Autologous Transplantation for Ph+ ALL

Not all patients have a suitable donor for allo-HCT. Thus autologous HCT, using stem cells collected during the first CR, offers an alternative approach. Using conventional chemotherapy to eradicate residual disease prior to autologous transplantation in ALL resulted in poor outcomes with increased disease relapse in a recent study [34]. Therefore, it was concluded that "there was no evidence that a single autologous transplantation can replace consolidation/maintenance for any risk group." However, using chemotherapy alone to eradicate residual Ph+ disease is suboptimal. We hypothesize that the combination of dasatinib with chemotherapy will achieve a better success rate in cleansing the marrow from residual disease prior to stem cell collection. As shown in Table 1, several groups [10, 35] including CALGB [36], have reported favorable outcomes following autologous transplantation for Ph+ ALL patients <60 years old without suitable allogeneic donors. Specifically, in one study [35], the outcomes of patients undergoing autologous versus allogeneic transplantation were similar. Even though the relapse rate was higher among patients who underwent autologous HCT, the higher TRM associated with allogeneic HCT balanced the final outcomes. We will build on our preliminary results from CALGB 10001

and pursue autologous transplantation for patients ≤70 years old without suitable allogeneic donors in the current study.

We plan to evaluate the role of melphalan as the preparatory regimen for the autologous transplantation. Melphalan has been used before in the preparatory regimen for autologous transplantation in pediatric ALL [37, 38].

1.7 Dasatinib Maintenance

Patients with CML who have had a good clinical response to imatinib are recommended to continue the drug life-long. Discontinuation of imatinib mesylate after allogeneic or autologous HCT continues to present a scientific dilemma for Ph+ ALL. Several studies continued imatinib until disease recurrence [5, 39, 40] while others had a set time [9, 41, 42] (one to two years) of imatinib maintenance. It is difficult to discern a difference between the studies based on patients' outcomes because of the relatively short follow-up. In our clinical trial of imatinib and chemotherapy followed by autologous HCT (CALGB C10001) [36] we have continued imatinib maintenance for at least one year and then until two consecutive quantitative polymerase chain reaction (Q-PCR) tests 3 months apart were negative. However, long-term data from our study are not available yet. Two other studies claimed that molecular relapse did not predict hematologic relapse [9, 40]. We propose herein to continue patients on dasatinib for at least one year and monitor for molecular response and then discontinue dasatinib if two consecutive Q-PCR tests (three months apart) are negative.

1.8 The Rational for the Current Study

We hypothesize that dasatinib and dexamethasone, with minimal additional chemotherapy, will be well tolerated by older patients with newly diagnosed Ph+ ALL and will result in similar leukemia cytoreduction when compared historically to imatinib with either concomitant or sequential cytotoxic chemotherapy. We also hypothesize that a reduced-intensity preparatory regimen of fludarabine + melphalan + alemtuzumab followed by allogeneic HCT from HLA-matched donors will result in low treatment-related mortality and significant improvement in disease-free survival compared to a no transplantation approach for Ph+ ALL patients ≤70 years old. In addition, we hypothesize that autologous CD34+ stem cell collection following dasatinib and dexamethasone treatment will result in similar or better collections of BCR/ABL-negative stem cells (by Q-PCR) as we observed following imatinib and standard dose chemotherapy in CALGB 10001, allowing autologous HCT for patients who lack allogeneic donors. Given that the 3-year progression free survival was 50% for patients enrolled on the CALGB 10001 trial who under went autologous HCT after imatinib treatment, we anticipate that the DFS will be equal or better using the more potent TKI, dasatinib. Finally, we hypothesize that dasatinib will be well tolerated as a maintenance therapy after HCT or chemotherapy and will result in favorable DFS compared with historical experience prior to TKI treatment.

1.9 Inclusion of Women & Minorities

Although there is no evidence to suggest that the outcome will differ by gender or ethnicity and there is insufficient power to detect small or moderate effects, we will, in a secondary analysis, report the results by gender and ethnicity. Both men and women of all races and ethnic groups are eligible for this study.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	2	+	5	=	7
Not Hispanic or Latino	34	+	25	=	59
Ethnic Category: Total of all subjects	36 (A1)	+	30 (B1)	=	66 (C1)
Racial Category					
American Indian or Alaskan Native	1	+	3	=	4
Asian	4	+	1	=	5
Black or African American	4	+	8	=	12
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	27	+	18	=	45
Racial Category: Total of all subjects	36 (A2)	+	30 (B2)	=	66 (C2)
	(A1 = A2)		(B1 = B2)		(C1 = C2)

2.0 OBJECTIVES

2.1 Primary Objective

Estimate the disease-free survival (DFS) and overall survival (OS) profiles in newly diagnosed patients 18 years or older who have Ph+ (BCR/ABL+) ALL receiving sequential dasatinib, followed by allogeneic or autologous HCT or chemotherapy followed by dasatinib maintenance.

2.2 Secondary Objectives

2.2.1 Compare the OS and DFS profiles for each of the three cohorts to those from similar populations from other studies.

2.2.2 Determine the ability of dasatinib to produce or maintain a *BCR/ABL*-negative status, as judged by Q-PCR following sequential dasatinib, chemotherapy, and HCT.

2.2.3 Determine the feasibility of collecting adequate peripheral blood stem cells for autologous HCT following dasatinib therapy, and assess for residual Ph+ (BCR/ABL+) cells by Q-PCR.

2.2.4 Study the safety and efficacy of autologous HCT following therapy with dasatinib.

2.2.5 Study the safety and efficacy of reduced-intensity preparatory regimen followed by an allogeneic HCT following induction therapy with dasatinib.

2.2.6 Study the safety and efficacy of dasatinib maintenance administered after allogeneic or autologous HCT or chemotherapy.

2.2.7 Correlate plasma and CSF levels of dasatinib when given orally during induction.

3.0 ON-STUDY GUIDELINES

This clinical trial can fulfill its objectives only if patients appropriate for the trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Management throughout the full duration of the protocol treatment at a medical facility having ready access to blood product support and adequate staff to care for the severely neutropenic patient with multiple therapy-induced toxicities will maximize patient safety. Physicians should consider the risks and the benefits of any therapy and therefore only enroll patients for which the agents administered are appropriate. Although they will not be considered as formal eligibility (exclusion) criteria, as part of this decision-making process physicians should recognize that the following problems may increase the risk to the patient entering this protocol:

- Any other serious illness which would limit survival to <3 months, or psychiatric condition which would prevent compliance with treatment or informed consent.
- Uncontrolled or severe cardiovascular disease.
- Prior use of the agents administered in this protocol for other non-malignant disease may reduce the likelihood of beneficial outcome and should also be considered prior to enrolling patients.
- Elevations of bilirubin, or creatinine that may suggest impaired hepatic or renal function must be considered as potentially serious obstacles for safe tolerance of the therapy prescribed in this protocol.
- Physicians should be aware that dasatinib is a competitive inhibitor of CYP2C9, CYP2D6, and CYP3A4/5. Studies also show CYP3A4 is the major human p450 enzyme catalyzing biotransformation of dasatinib. Thus, co-administration of drugs which are inducers (e.g., phenytoin) or inhibitors (e.g., itraconazole, voriconazole, posaconazole) of this isoenzyme could decrease or increase dasatinib concentrations. A list of agents that may have potential drug interactions is included in Appendix III.

4.0 ELIGIBILITY CRITERIA

All questions regarding eligibility should be directed to the Alliance Study Chair. Please note that the Study Chair may not grant waivers to eligibility requirements.

4.1 ALL Diagnosis

Unequivocal histologic diagnosis of ALL.

4.2 Hemotopathology

Detection of the t(9;22)(q34;q11) or 3-way variant by metaphase cytogenetics or BCR-ABL positive status by molecular analysis (Q-PCR or FISH) in a CLIA-approved laboratory.

4.3 Prior Therapy Status

No prior therapy except up to one week of corticosteroids and/or hydroxyurea to enable time for the detection of t(9;22)(q34;q11) or BCR/ABL.

4.4 Age Requirement

Age ≥ 18 years with no upper age limit.

4.5 Pregnancy and Nursing Status

Non-pregnant and non-nursing. Treatment under this protocol would expose an unborn child to significant risks. Women and men of reproductive potential should agree to use an effective means of birth control and contraception should continue for three months after the last dose of

dasatinib to allow complete clearance of drug and its principal metabolites from the body. In women of childbearing potential, a pregnancy test will be required at study entry.

4.6 Cardiac Function

- Left ventricular ejection fraction ≥ lower limit of institutional normal
- No myocardial infarction within 6 months
- No ventricular tachyarrhythmia within 6 months
- No major conduction abnormality (unless a cardiac pacemaker is present)

5.0 REGISTRATION

5.1 Registration Requirements for CALGB 10701

5.1.1 Informed Consent

The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts. Human protection committee approval of this protocol and of its consent form are required.

5.1.2 Study Monitoring Teleconferences

A representative from each institution with one of the first **24* patients** enrolled on the trial **ARE REQUIRED** to participate in a teleconference with members of the Alliance Statistics and Data Center and Alliance Protocol Operations Program Office staff.

* Based on the results of the first interim analysis for feasibility and safety, it was decided that the monitoring teleconferences would be extended from 12 patients to 24 patients.

The CALGB 10701 study data coordinator will establish the teleconferences and notify participants. Institutions that do not participate in the teleconferences may be denied future registrations to this trial.

5.2 Registration Procedures for CALGB 10701

5.2.1 CTSU Registration Requirements

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

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 (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU Web site (enter credentials at https://www.ctsu.org; then click on the Register tab) or by calling the PMB at 240-276-6575 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

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 enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org.

Requirements for CALGB-10701 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

5.2.2 Patient Registration

All institutions will use OPEN (Oncology Patient Enrollment Network) for registration of patients to CALGB 10701. All institutions may access OPEN registration at https://open.ctsu.org. Alliance and CTSU registrars will direct all requests for registration to CALGB 10701 to occur through OPEN.

If technical difficulties are experienced with OPEN during normal business hours, please contact the CTSU Help Desk (1-888-823-5925).

To be able to enroll a patient, institution staff must have:

- A valid and active CTEP-IAM account

  This the same user ID and password used for the CTSU website (for more information, see https://www.ctsu.org/public/CTEP-IAM_Factsheet.pdf).
- A 'Registrar' role on in the Alliance or CTSU roster

  Assignment of the Alliance 'Registrar' role is managed through the Alliance Protocol Operations Program Office via submission of a roster update form signed by the Principal Investigator of the member network.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria has been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Site and/or Data Administrators can manage the CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' website. This will allow them to assign staff the 'Registrar' role.

A training video and user guide is available on the CTSU members' website, under the "OPEN" tab and within the OPEN application. Although the OPEN system is user-friendly and has many help features built in, we strongly encourage users to view the training demo for a quick overview of how OPEN works. OPEN has a "Practice Mode" which allows the user to switch from a "working" mode to practice mode to create registrations without updating live data. The user guide is also available to download and/or print as a reference tool. There are help icons within each of the OPEN screens to assist you with navigating the system.

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

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU 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.

5.3 Registration to Optional Substudy CALGB 61004

Within CALGB 10701 there is one embedded substudy. This substudy must be offered to all patients enrolled on CALGB 10701. Although patient may opt not to participate, this substudy is strongly recommended for ALL patients.

If a patient answers "yes" to "*I agree that my specimen(s) may be used for the research described above*" (Question #1) in the model consent, they have consented to participate in the embedded

companion CALGB 61004. Samples for CALGB 61004 should be submitted according to the instructions in Section 6.4. The rationale for performing the correlative substudy is described in Section 6.4.

If a patient has also consented to the optional embedded companion study CALGB 61004, register the patient to CALGB 61004 within OPEN. Pre-registration to 61004 is not available.

5.4 CALGB Registration to CALGB Companion Studies

5.4.1 Registration to REQUIRED CALGB 8461

Enrollment in CALGB 8461 (Cytogenetic Studies in Acute Leukemia) is **required** for CALGB patients in order to achieve the scientific outcomes of this trial. Follow the instructions within CALGB 8461 for collection and submission of specimens (also see Section 6.5).

Patients who register to CALGB 10701 must also register to CALGB 8461. Pre-registration to 8461 is no longer available.

5.4.2 Registration to OPTIONAL CALGB 9665 (prior to February 28, 2014)

Enrollment in the Leukemia Correlative Science Committee study CALGB 9665 (CALGB Leukemia Tissue Bank) is **optional**, but is strongly recommended for all Alliance patients. Pre-registration to CALGB 9665 is available. Follow the instructions within CALGB 9665 for collection and submission of specimens (also see Section 6.5).

If a patient has also consented to the optional companion study CALGB 9665, register the patient to CALGB 9665. Pre-registration to 9665 is not required.

CALGB 9665 was temporarily suspended on February 28, 2014. Therefore, after February 28, 2014, Alliance institutions may not consent or enroll patients on CALGB 9665. Patients already enrolled on CALGB 9665 should continue to submit specimens as required per protocol.

5.5 ECOG-ACRIN Registration to ECOG Companion Study

5.5.1 Registration to REQUIRED E3903

Prior to or at the time of registration to 10701, ECOG patients **must be registered** on and baseline samples submitted per ECOG E3903, "Ancillary laboratory protocol for collecting diagnostic material on patients considered for ECOG treatment trials for leukemia or related hematologic disorders."

The baseline eligibility assessments which will be reported back to the site for CALGB 10701 include the results of the BCR/ABL status as determined by quantitative PCR. The assessments will be performed by the CLIA Certified Immunology Laboratory at Montefiore Medical Center-North Division.

E3903 closed to new patient accrual on August 21, 2014. Therefore, after 8/21/14, ECOG-ACRIN institutions may not consent or enroll patients on E3903. After 8/21/14, baseline eligibility assessments are to be performed by a local CLIA laboratory as per protocol (Section 4.2).

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data submission

Forms should be submitted to the Alliance Statistics and Data Center in compliance with the data submission schedule below. There are two options for submitting forms that use the Teleform barcode and cornerstones:

- The preferred method is to submit the forms electronically using the "Submit to CALGB" button located at the bottom of the last page of each form. Forms submitted electronically should not be submitted by mail.
- The forms may be mailed to the Alliance Statistics and Data Center, RO FF-3-24-CC/NW Clinic, 200 First Street Southwest, Rochester, MN 55905. Please note that the four cornerstones and the form id ("bitmap") must appear on the form. Copies must be 100% of the original form size.

Supporting documentation for studies using Teleform can be mailed along with the Teleform forms.

Form*		Submission Schedule
	C10701 Registration Worksheet	
C-1944	10701 On-Study Form	
C-1961	10701 Molecular Results Form	
C-970	Peripheral Blood & Bone Marrow Report Form	Within 1 month of registration.
C-972	Leukemia Immunophenotyping Form	
C-1963	10701 Prior Therapy Form	
	Pathology Reports†	
	C10701 BCR/ABL1 Transcripts Form	With Update #10, this form was added. This form can be found on the study webpage on the Alliance and CTSU website under "Case Report Forms." Complete this form for all patients, and mail to the Alliance Statistics and Data Center.
	C10701 ABL1 Mutational Analysis Form	With Update #11, this form was added. This form can be found on the study webpage on the Alliance and CTSU website under "Case Report Forms." Complete this form for all patients, and mail/e-mail to the Alliance Statistics and Data Center.
	During Treatment (Course I)	
C-1838	Adverse Event Form**	
C-1945	10701 Treatment Form	
C-1834	Acute Lymphoblastic Leukemia Follow-up Form	
C-664	Infectious Complications Form	At end of Course I.
C-028	Acute Leukemia Flow Sheet	
C-970	Peripheral Blood & Bone Marrow Report Form	
	Pathology Reports‡	
	During Treatment (Course II)	

C-1838	Adverse Event Form**	At end of Course II.
C-1945	10701 Treatment Form	
C-1834	Acute Lymphoblastic Leukemia Follow-up Form	
C-664	Infectious Complications Form	
C-028	Acute Leukemia Flow Sheet	
C-970	Peripheral Blood & Bone Marrow Report Form	
	Pathology Reports‡	

	During Treatment (Course III)	
C-1838	Adverse Event Form**	At end of Course III.
C-1945	10701 Treatment Form	
C-1834	Acute Lymphoblastic Leukemia Follow-up Form	
C-664	Infectious Complications Form	
C-028	Acute Leukemia Flow Sheet	
C-970	Peripheral Blood & Bone Marrow Report Form	
	Pathology Reports‡	
	During Treatment (Course IV)	
C-1838	Adverse Event Form**	At end of Course IV.
C-1945	10701 Treatment Form	
C-1834	Acute Lymphoblastic Leukemia Follow-up Form	
C-664	Infectious Complications Form	
C-028	Acute Leukemia Flow Sheet	
C-970	Peripheral Blood & Bone Marrow Report Form	
C-1833	Serum Methotrexate Adjustment Record Form	
C-1961	10701 Molecular Results Form	
	During Treatment (Course V)	
C-1838	Adverse Event Form**	At end of Course V.
C-1945	10701 Treatment Form	
C-1834	Acute Lymphoblastic Leukemia Follow-up Form	
C-664	Infectious Complications Form	
C-028	Acute Leukemia Flow Sheet (Alternative Chemotherapy Only)	
TR-1	Allogeneic Transplant Flow Sheet (Allo Transplant only)	
TR-2	Autologous Transplant Flow Sheet (Auto Transplant only)	
C-970	Peripheral Blood & Bone Marrow Report Form	
C-1835	Course V Follow-up Form	
C-939	HLA Typing Form	
C-1839	Peripheral Blood Stem Cell Collection Form	
C-1842	Chimerism Analysis Form	
C-1961	10701 Molecular Results Form	
	Pathology Reports ‡	

During Treatment (Course VI) and Post-Treatment Follow-Up		
C-1838 C-1945 C-028	Adverse Event Form** 10701 Treatment Form Acute Leukemia Flow Sheet	Monthly for first year or until protocol treatment ends.
C-1961	10701 Molecular Results Form	At Day +30 post transplant or end of all Course V treatment, at one year post transplant or end of all Course V treatment, and at relapse
C-1834 C-970	Acute Lymphoblastic Leukemia Follow-up Form Peripheral Blood & Bone Marrow Report Form	Every 3 months for two years and at relapse.
C-1961	10701 Molecular Results Form	For allogeneic and autologous transplantation arms, every 3 months for 5 years from study entry, and at relapse. For alternative chemotherapy arm, every month for 1 year, every 3 months for subsequent 2 years, then every 6 months for 5 years from study entry, and at relapse.
	C10701 ABL1 Mutational Analysis Form	At relapse and at refractory disease. With Update #11, this form was added. This form can be found on the study webpage on the Alliance and CTSU website under "Case Report Forms." Complete this form for all patients, and mail/e-mail to the Alliance Statistics and Data Center.
C-400	CALGB Long-Term Follow-up Form	Q6 months until year 5, then annually for a maximum of ten years from study entry.
Other		
C-300	CALGB: Off Treatment Notice	At conclusion of treatment.
C-113	CALGB Notification of Death Form	At time of death.
C-1001	New Malignancy Form	At presentation of another malignancy.
C-1820	Adverse Events Addendum Form	Complete if additional space is needed to report other adverse events.
C-1742	CALGB Confirmation of Lost to Follow-up Form	See form for submission instructions.

* Use the CALGB Remarks Addenda (C-260) if additional comments are necessary or additional writing space is needed.

** Submit AE form until all protocol treatment related events have resolved or until non-protocol treatment begins. If patient death is reported via CTEP-AERS, report grade 5 event on AE form even is patient is off protocol treatment.

† Submit legible copies of all pathology, cytochemistry, immunophenotyping, molecular, and cytogenetic reports documenting diagnosis to the Alliance Biorepository at Ohio State University (OSU) and the Alliance Statistics and Data Center.

‡ Submit legible copies of all pathology, cytochemistry, immunophenotyping, molecular, and cytogenetic reports documenting response, progression or relapse to the Alliance Biorepository at Ohio State University (OSU) and the Alliance Statistics and Data Center.

S-069 and S-070 Medication Calendars are for institutional and patient use only. These forms are not required to be submitted to the Alliance Statistics and Data Center.

Please refer to the Alliance web site to obtain up-to-date data forms for this study.

6.2 Specimen Submission Instructions

Label the tubes with the CALGB study number, patient study ID number, patient initials, the date of collection, source of material, and the sample collection period.

All submitted specimens must be labeled with the protocol number CALGB 10701, OPEN patient registration number, patient's initials, and date and type of specimen collected (e.g., serum, whole blood).

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: http://bioms.wustl.edu/bioms, using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS web page to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: 1-855-55-BIOMS. For assistance in using the application or questions or problems related to specific specimen logging, please contact: 1-855-55-BIOMS.

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

Samples	Sample Collection on CALGB 10701		
	Prior to initiation of remission induction therapy	**During Treatment** Course I, Day 15 (± 1 day)	**Ship to**
Bone marrow smears * (6.3.1)	3 unstained slides		OSU
Whole blood smears (6.3.1)	3 unstained slides		OSU
Bone marrow biopsy (6.3.1)	1 stained section and 4 unstained sections		OSU
Peripheral blood (plasma) [1] (lavender top) (6.4.2)		3 mL	OSU
Cerebrospinal fluid [1] (lavender top) (6.4.2)		3 mL	OSU

* See Section 6.3.4 for patients who have inaspirable bone marrow samples and/or for patients who have had a bone marrow examination (with extra slides available) within the past 8 days and refuse another examination prior to registration.

1 For patients who consent (model consent question #1) to substudy 61004.

6.3 Central Morphology Review (For CTSU and Alliance)

6.3.1 At entry on this study, slides that were obtained prior to any protocol induction treatment must be submitted. Send three (3) air-dried, unstained bone marrow smears (films) and three (3) unstained blood smears (films), one (1) H & E stained biopsy slide, and four (4) unstained biopsy sections for confirmatory cytologic and cytochemical studies. These should be submitted together with the final institutional pathology, cytochemistry, and immunophenotyping reports (if possible).

6.3.2 There must be an adequate amount of marrow in each smear. The above requirements are considered minimal. Contact the Alliance Study Chair with any questions.

6.3.3 Identify each slide with the patient's study ID number and protocol number, pack carefully in protective slide cartons (not cardboard folders). Samples must be logged and shipped via BioMS, see Section 6.2 for instructions. A copy of the shipping manifest produced by BioMS must be printed and placed in the shipment with the specimens. Promptly mail (slides must arrive within one week of sampling) to:

Alliance Biorepository at Ohio State University (OSU)
Department of Pathology
Polaris Innovation Centre
2001 Polaris Parkway
Columbus, OH 43240
Phone: 614-293-7073 Fax: 614-293-7967

Send a copy of your institutional bone marrow aspiration and biopsy report, cytochemistry, cytogenetic, and flow cytometry reports as soon as complete to the Alliance Statistics and Data Center and to the Alliance Biorepository at Ohio State University. This report must include differential cell counts, cytochemistry results, and FAB/WHO classification.

6.3.4 Inaspirable Bone Marrow Cases

Patients who have inaspirable bone marrow samples ("dry tap") can be enrolled if there are adequate numbers of circulating blast cells in the blood to allow complete immunophenotyping, cytogenetic and molecular analysis. One H&E stained biopsy slide and four unstained biopsy sections must be submitted for central morphology review together with six air-dried unstained peripheral blood smears.

A patient who has had an adequate diagnostic bone marrow examination within the past 8 days (with extra slides available) and refuses another aspiration prior to registration can be enrolled on the study if their previous bone marrow slides are submitted for central morphology review and if their absolute lymphoblast count is > 10,000/μL in the peripheral blood. Three unstained prior bone marrow aspirate smears, one H&E stained biopsy slide and four unstained biopsy sections must be submitted for Central Review together with six fresh air-dried unstained peripheral blood smears. Adequate volumes of peripheral blood must be submitted for the companion studies as described in those protocols to meet the objectives of those studies.

6.4 Dasatinib Pharmacokinetic (PK) Substudy CALGB 61004 (For CTSU and Alliance)

6.4.1 Cerebrospinal Fluid and Plasma Specimen Collection (Course I Day 15)

A lumbar puncture will be performed in all patients on Course I Day 15 (± 1 day). In consenting patients (model consent question #1), a CSF and peripheral blood sample will be collected to determine dasatinib cerebrospinal fluid (CSF) and plasma levels. The lumbar

puncture should be performed between 2 and 3 hours after dasatinib administration, and the timing of the dasatinib administration.

6.4.2 Cerebrospinal Fluid and Plasma Specimen Submission

- **Peripheral Blood:** Collect 3 mL of peripheral blood in a 3 mL lavender top tube. After collection, invert specimen gently 8-10 times for complete mixing with the anticoagulant. Place the lavender tube on wet ice for a minimum of 10 minutes. Centrifuge within 30 minutes of collection at 4 degrees for 5 minutes at 2000 x g. Transfer plasma into a labeled, screw-cap, polypropylene plasma drug tube, or equivalent. Specimens should be stored at or below -20°C.

  Label the tube with the patient study ID#, protocol number, date of collection, nominal collection time and cycle, actual sample time, and source of material.

- **CSF:** Collect CSF in a lavender top tube. After collection, invert specimen gently 8-10 times for complete mixing with the anticoagulant. Place the lavender tube on wet ice for a minimum of 10 minutes. Centrifuge within 30 minutes of collection at 4 degrees for 5 minutes at 2000 x g. Transfer into a labeled, screw-cap, polypropylene plasma drug tube, or equivalent. Specimens should be stored at or below -20°C.

  Label the tube with the patient study ID#, protocol number, date of collection, nominal collection time and cycle, actual sample time, and source of material.

It is essential that all specimens are thoroughly frozen prior to packing for shipment and that all tubes are securely capped. All specimens should be shipped on dry ice by overnight express courier. Samples must be logged and shipped via BioMS, see Section 6.2 for instructions. A copy of the shipping manifest produced by BioMS must be printed and placed in the shipment with the specimens. Shipment on Monday through Thursday by overnight service to assure receipt is encouraged. Do not ship specimens on Fridays or Saturdays. Specimens may be shipped to:

Alliance Biorepository at Ohio State University (OSU)
Department of Pathology
Polaris Innovation Center
2001 Polaris Parkway
Columbus, OH 43240
Phone: 614-293-7073
Fax: 614-293-7967
path.calgb@osmu.edu

Plasma and cerebrospinal fluid samples will be de-identified and sent to Dr. Jan Beumer's lab at University of Pittsburgh Cancer Institute for pharmacokinetics analyses.

6.5 CALGB Companion Studies Sample Submission (For Alliance only)

Follow instructions in the protocols below for collection and submission of specimens.

6.5.1 CALGB 8461 (Cytogenetic Studies in Acute Leukemia): Patients are required to be enrolled on CALGB 8461 in order to meet the objectives of this clinical trial. A bone marrow aspirate and/or peripheral blood sample are required at the following intervals:

- At diagnosis;
- At complete remission, if diagnostic specimen is abnormal;
- At relapse.

6.5.2 CALGB 9665 (CALGB Leukemia Tissue Bank) (prior to February 28, 2014): All patients are strongly encouraged to be enrolled on CALGB 9665. A marrow aspirate, whole blood sample, and buccal smear are required at the following intervals:

- At the time of diagnosis;
- At the time of remission (bone marrow and blood sample only);
- At the time of relapse (bone marrow and blood sample only).

6.6 ECOG-ACRIN Companion Studies Sample Submission (For ECOG-ACRIN only)

Follow instructions in E3903 for collection and submission of specimens.

6.6.1 ECOG E3903 (Ancillary laboratory protocol for collecting diagnostic material on patients considered for ECOG treatment trials for leukemia or related hematologic disorders): Patients are required to be enrolled on ECOG E3903. Blood, bone marrow and karyotypes are to be submitted as outlined in E3903. After 8/21/2014, no new patients may be enrolled on E3903 (see Section 5.5.1).

7.0 REQUIRED DATA

Laboratory and clinical parameters during the treatment courses are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this protocol will be cared for by physicians experienced in the treatment and supportive care of patients with acute leukemia and transplantation.

Treatment courses are specified using a roman numeral, followed by a cardinal numeral indicating the number of days from the start of that course (e.g., Day III-28 is the 28th day of Course III).

Guidelines For Pre-Study Testing

To be completed within 8 DAYS prior to study:

All bloodwork; bone marrow examinations; history & physical exam; any X-ray, scan of any type, or ultrasound of uninvolved organs which is not utilized for tumor measurement.

Tests & Observations	Prior to Study	Prior to Each Treatment Course (I-V)	During Each Treatment Course (I-V)	Prior to & During Course VI & Post- Treatment Follow-Up*
History and Progress Notes	X	X	Weekly	X
Physical Examination***	X	X	A	X
Pulse, Blood Pressure, Temperature	X	X	A	
Height	X	X		
Weight/Body Surface Area†	X	X		X
Performance Status	X	X		X
Tumor Measurements**	X	X		X
Drug Toxicity Assessment		X	X	X
Laboratory Studies				
CBC, Differential, Platelets	X	X	Weekly	X
Serum Creatinine, BUN, Electrolytes	X	X	A,L	
PT, PTT	X	G	A	
AST, ALT, Alk. Phos., Bilirubin, LDH	X	X	A	
Uric acid, PO_4	X		A	
Total Protein, Albumin	X		A	
Glucose, Amylase, Fibrinogen			A	
ECHO or MUGA		F, G		
DLCO (PFTs)		G		
Hepatitis A, B, C, HIV serology		G		
EKG	X	G		
u-HCG or Serum HCG	X			
CMV DNA titer		G,M		
Staging				
Central Morphology Review	X			
Chest X-ray, PA & Lateral	X	O		
CSF Cell Count, CSF Protein & Glucose	A		B	
CSF for Dasatinib level			C	
Serum Methotrexate Levels			D	
Cytogenetics	X	E (until CCyR)		Relapse
Chimerism analysis			H	
Institutional Q-PCR for BCR/ABL	X	J	K	N
ABL Mutation Analysis	X			Relapse
Bone Marrow Asp & Bx	X	E		I

*	Monthly for the first year, then every 3 months for 2 years, then every 6 months for 2 years, then yearly for a maximum of 10 years from study entry, or at relapse, whichever occurs first.
**	Note specifically by physical exam the size of the liver, spleen, lymph nodes and, if applicable, mediastinal mass by chest x-ray.
***	Including assessment for symptoms of pulmonary arterial hypertension (PAH). Right heart catheterization can confirm the diagnosis of PAH.
†	Drug doses need not be changed unless the calculated dose changes by ≥ 10%.
A	As clinically indicated using good clinical practice.
B	CSF should be obtained on Days I-15, IV-1, IV-15, IV-29, or if clinically indicated (see Sections 8.7 and Section 8.8).
C	In consenting patients only, CSF + plasma for dasatinib level on day I-15.
D	On Days IV-2, IV-4, IV-16, IV-18, IV-30, IV-32 (see Section 8.4.2).
E	Required at the end of Courses I, II, III, IV, V (patients undergoing autologous transplant will need BM test after Step I and before Step II).
F	Required prior to Day 1 of course IIB and III.
G	Required prior to Course V allogeneic HCT.
H	Institutional chimerism analysis on peripheral blood from donor and recipient prior to registration and from recipient on day +30, +90-+100, +180, +365 and at time of relapse. Perform T-cell chimerism on Day +120.
I	Every 3 months for 2 years and at relapse.
J	Perform institutional Q-PCR on peripheral blood and bone marrow aspirate prior to Course V.
K	For allogeneic transplant during Course V, perform institutional Q-PCR on bone marrow on Day +30 and one year post transplant. For autologous transplant during Course V, perform institutional Q-PCR on each day's PBSC product, on bone marrow aspirate prior to autologous stem cell transplant, on bone marrow aspirate on day +30 post transplant and one year post transplant. For chemotherapy only during Course V, perform institutional Q-PCR on bone marrow one year after initiation of chemotherapy.
L	Daily during the four days of high-dose ara-C during Course V for autologous transplant and non-transplant patients.
M	Patients undergoing allogeneic HCT should be screened weekly for CMV viremia until day +120 (see Section 8.5.1.9).
N	For patients who underwent Allogeneic HCT, institutional Q-PCR should be performed on peripheral blood every 3 months for 5 years from study entry. For patients who underwent Autologous HCT, institutional quantitative RT-PCR should be performed on peripheral blood every 3 months for 5 years from study entry. For patients who received the Alternative Chemotherapy Regimen, perform institutional Q-PCR on peripheral blood monthly for the first year, every 3 months for 2 years, then every 6 months for 5 years from study entry. At time of relapse, perform institutional Q-PCR on peripheral blood or bone marrow aspirate for all patients on study.
O	Required prior to Course V allogeneic HCT. Required within 72 hours of Course IV day 1 methotrexate IV dose to rule out pleural effusion. Repeat chest X-ray prior to each IV methotrexate dose if clinically indicated.

Institutional normal laboratory values must be recorded on flow sheets.

8.0 TREATMENT PLAN

All questions regarding treatment or dose modifications should be directed to the Alliance Study Chair.

Patients must be enrolled on this study without prior enrollment on any other treatment protocol. A lumbar puncture prior to treatment is not required and should not be performed in the absence of significant CNS symptoms or signs. CNS leukemia at time of entry on study will only be treated if symptomatic (see Section 8.7).

Alliance institutions should submit peripheral blood and bone marrow aspirate specimens for the appropriate companion studies CALGB 8461 (required) and CALGB 9665 (in consenting patients). See Section 6.5.

ECOG-ACRIN institutions should submit blood and bone marrow specimens as described in protocol ECOG E3903. As of 8/21/2014, no new patients may be enrolled on E3903. See Section 6.6.

Treatment courses are specified using a roman numeral, followed by a cardinal indicating the number of days from the start of that course (e.g., Day III-28 is the 28th day of Course III).

8.1 Course I: Induction Therapy

8.1.1 Pre-Study Phase

Course I must begin only after confirmation of the presence of t(9;22)(q34; q11) or BCR/ABL. During this pre-study phase, dexamethasone 10 mg/m^2/day orally (or IV) once daily or in divided doses or equivalent corticosteroid regimen can be administered to control the peripheral blast count for a maximum of 7 days (Days -7 – 0). Hydroxyurea also is permitted to control leukocytosis, **although no other ALL-directed therapy is allowed.**

8.1.2 Course I Treatment

8.1.2.1 Dasatinib 140 mg PO daily. H_2 blockers or proton pump inhibitors are prohibited. Use of antacids separated by more than 2 hours from dasatinib should be considered.

8.1.2.2 Dexamethasone 10 mg/m^2/day PO or IV (once daily, or in divided doses) on days I-1 to I-7. Round dose to nearest 0.75 mg.

8.1.2.3 Day I-15 Bone Marrow Examination

A bone marrow aspiration and biopsy must be obtained for all patients on day I-15 to assess initial response. The day of this bone marrow exam can be moved up or back one day to accommodate weekends or holidays.

8.1.2.4 Day I-15 Cerebrospinal Fluid (CSF) Examination

A lumbar puncture will be performed on day I-15. The day of this lumbar puncture can be moved up or back one day to accommodate weekends or holidays. The lumbar puncture (LP) should be performed between 2 to 3 hours after dasatinib administration. CSF obtained on day I-15 should be analyzed by cytocentrifuge exam. Record the cell count and differential cell count and results of cytocentrifuge examination. If the patient has a platelet count <20,000/µL, it is recommended to transfuse platelets during the LP. Please see Section 8.7 for treatment of CNS leukemia.

Additionally, in consenting patients (see model consent question #1), a sample will be collected for dasatinib level and sent to a central reference laboratory (see Section 6.3).

8.2 Course II: Early Intensification Therapy (begins shortly after Day I-15)

The treatment plan for this course will depend on the bone marrow results on day I-15. Until these results are available, patients will continue on dasatinib as a single agent at 140 mg/day. It is recommended that patients continue with dasatinib and onto Course II regardless of counts.

All patients will begin cotrimoxazole DS one tablet PO BID 3 days per week continuously during Course II, or, if allergic to sulfonamides, inhaled aerosolized pentamidine (300 mg once per month) or dapsone 100 mg PO daily.

8.2.1 If ≤ 20% blasts in the Day I-15 marrow (Cohort IIA)

8.2.1.1 **Dasatinib** 140 mg PO daily. H_2 blockers or proton pump inhibitors are prohibited. Use of antacids separated more than 2 hours from dasatinib should be considered.

8.2.1.2 **Dexamethasone** 10 mg/m^2/day PO or IV (once daily, or in divided doses) on days II-1 to II-7. Round dose to nearest 0.75 mg.

8.2.1.3 Day II-22 Bone Marrow Examination

A bone marrow aspiration and biopsy must be obtained for all patients on day II-22 to assess response. Institutions should submit peripheral blood and bone marrow aspirate specimens for relevant Alliance companion studies (CALGB 8461 [required]).

8.2.2 If > 20% blasts in the Day I-15 marrow (Cohort IIB)

8.2.2.1 **Dasatinib** 140 mg PO daily. H_2 blockers or proton pump inhibitors are prohibited. Use of antacids separated more than 2 hours from dasatinib should be considered.

8.2.2.2 **Dexamethasone** 10 mg/m^2/day PO or IV (once daily, or in divided doses) on days II-1 to II-7. Round dose to nearest 0.75 mg.

8.2.2.3 **Daunorubicin** 30 mg/m^2/day IV on days II-1, II-8 and II-15.

8.2.2.4 **Vincristine** 2 mg (flat dose) IV on days II-1, II-8, and II-15. If use of an azole antifungal is necessary, it is recommended that an agent with the least inhibitory affect on CYP3A4 be selected if possible. The following azoles appear in order of strength of inhibition of CYP3A4: voriconazole, itraconazole, posaconazole, and fluconazole. Fluconazole at doses of 200 mg or less is not thought to be a significant inhibitor of CYP3A4. Azole antifungal agents should not be administered within 5 half lives of vincristine. Please note vincristine dose modifications in Section 9.5.5.

8.2.2.5 Day II-22 Bone Marrow Examination

A bone marrow aspiration and biopsy must be obtained for all patients on day II-22 to assess response. Institutions should submit peripheral blood and bone marrow aspirate specimens for relevant Alliance companion studies (CALGB 8461 [required]).

8.3 Course III: Second Induction Therapy (only for patients not yet in CR or CRi)

The treatment plan for this course will depend on the bone marrow results from day II-22 for cohorts IIA and IIB. Until these results are available, patients will continue dasatinib at 140 mg/day.

If patients have achieved hematologic and morphologic complete remission (please see Section 12.1 for definition of complete remission) based on day II-22 bone marrow examination, they

will proceed directly to Course IV **without receiving the second induction therapy in Course III below**. Those patients who have not achieved CR, however, **will** receive Course III below.

All patients will continue cotrimoxazole DS one tablet PO BID 3 days per week continuously during Course III, or, if allergic to sulfonamides, inhaled aerosolized pentamidine (300 mg once per month) or dapsone 100 mg/day.

8.3.1 **Dasatinib** 140 mg PO daily.

8.3.2 **Cyclophosphamide** 1000 mg/m^2 IV on day III-1. Hydrate intravenously and induce diuresis.

8.3.3 **Daunorubicin** 30 mg/m^2/day IV on days III-1 and III-8.

8.3.4 **Vincristine** 2 mg (flat dose) IV on days III-1 and III-8. Concomitant voriconazole or posaconazole are contraindicated due to increased neurotoxicity. If use of an azole antifungal is necessary, it is recommended that an agent with the least inhibitory affect on CYP3A4 be selected if possible. The following azoles appear in order of strength of inhibition of CYP3A4: voriconazole, itraconazole, posaconazole, and fluconazole. Fluconazole at doses of 200 mg or less is not thought to be a significant inhibitor of CYP3A4. Azole antifungal agents should not be administered within 5 half lives of vincristine. Please note vincristine dose modifications in Section 9.5.5.

8.3.5 **Dexamethasone** 10 mg/m^2/day PO or IV (once daily, or in divided doses) on days III-1 to III-7. Round dose to nearest 0.75 mg.

8.3.6 **G-CSF** subcutaneously daily beginning on day III-9 and continuing for at least 7 days and then until neutrophil recovery (≥ 1000/µL) on any one determination after the nadir. Use the nearest vial size for administration: for patients <78 kg use 300 mcg and for patients ≥78 kg use 480 mcg vial. One dose of PEG-filgrastim (6 mg) may be substituted for G-CSF on day III-9.

8.3.7 Day III-29 Bone Marrow Examination

A bone marrow aspiration and biopsy must be obtained for all patients on day III-29 or as soon thereafter as the ANC recovers to >1000/µl to assess response. Alliance institutions should submit peripheral blood and bone marrow aspirate specimens for relevant companion studies (8461 [required]).

8.4 Course IV: CNS Prophylaxis Therapy

Do not begin Course IV therapy until dasatinib has been interrupted for at least 7 days prior to administration of the day 1 IV methotrexate dose.

It is recommended that patients be hospitalized during the high-dose IV methotrexate administration for continuous IV hydration.

The goal of this treatment course is to maintain serum methotrexate concentrations of >1 µM for 30 continuous hours during 3 treatments. **It is recommended that IV vincristine be administered prior to the initiation of the IV methotrexate infusion.** The IT methotrexate should be administered later in the day (at any time during the IV methotrexate infusion) to avoid any possible confusion between the IV vincristine and the IT methotrexate.

All patients will continue cotrimoxazole DS one tablet PO BID 3 days per week until the completion of all therapy, or, if allergic to sulfonamides, inhaled aerosolized pentamidine (300 mg once per month). **Cotrimoxazole should be stopped 3 days before and resumed 3 days after each dose of methotrexate.**

- **Dasatinib** 140 mg PO daily beginning after recovery from the final methotrexate dose (methotrexate level <0.05 µM).
- **IT Methotrexate (IT Mtx)** 15 mg intrathecal once every two weeks on days IV-1, IV-15, and IV-29. Use preservative-free methotrexate. Hydrocortisone 50 mg should be included with the methotrexate. The LP can be done anytime during the 3-hour IV methotrexate infusion on these days, but it is recommended that it be done at the end of the 3-hour IV methotrexate infusion, well after the IV vincristine has been given.
- **Vincristine (VCR)** 2 mg (flat dose) IV once every two weeks on days IV-1, IV-15, and IV-29. If use of an azole antifungal is necessary, it is recommended that an agent with the least inhibitory affect on CYP3A4 be selected if possible. The following azoles appear in order of strength of inhibition of CYP3A4: voriconazole, itraconazole, posaconazole, and fluconazole. Fluconazole at doses of 200 mg or less is not thought to be a significant inhibitor of CYP3A4. Azole antifungal agents should not be administered within 5 half lives of vincristine. Please note vincristine dose modifications in Section 9.5.5.
- **IV Methotrexate (IV Mtx)** 500 mg/m^2 IV in one liter of D_5W or NS over 3 hours once every two weeks days IV-1, IV-15, and IV-29. Prior to beginning IV-Mtx, patients should be pre-hydrated with 500 mL - 1 liter of D_5W plus 100 mEq/L of sodium bicarbonate. Continue vigorous hydration as tolerated over the course of the day to maintain hydration and urine pH >6. Please check with pharmacy to ensure that patients are not receiving any medications (e.g., sulfonamides, salicylates, penicillins, other organic acids, proton pump inhibitors) that may interfere with methotrexate clearance.
- It is strongly recommended that additional hydration (with NS or D_5W containing 100 mEq/L of sodium bicarbonate per liter) be given on days 2, 16 and 30 when patient returns for IV leucovorin. If patients remain on PO leucovorin for a prolonged period of time because of slow methotrexate clearance, then the subsequent dose of methotrexate (scheduled on days IV-15 and IV-29) must be delayed, as necessary, to ensure that no leucovorin has been administered for at least 72 hours prior to beginning the next methotrexate infusion.
- **PO Methotrexate (PO Mtx)** 25 mg/m^2 PO every 6 hours x 4 doses (total) beginning 6 hours after starting each dose of IV Mtx (on days 1 and 2, days 15 and 16, and days 29 and 30). See Section 8.4.2 for dose adjustment levels. Doses should be rounded to the nearest 2.5 mg tablet size.
- **IV Leucovorin (IV Lcv)** 25 mg/m^2 IV 6 hours after the 4th (last) PO Mtx dose (i.e., 30 hours after starting IV Mtx; on days 2, 16, and 30).
- **PO-Leucovorin (PO Lcv)** 5 mg/m^2 PO every 6 hours for a planned 8 doses or until serum methotrexate level <0.05 µM, beginning 12 hours after IV Lcv. (Calculated doses of 7.5 mg to 12.5 mg may be rounded to nearest 10 mg.)

8.4.1 Timing of Chemotherapy

The following is a recommended schedule of chemotherapy administration:

Day IV-1	Monday, 9 AM: IV Vincristine. Monday, 9 AM-12 PM: **IV Mtx 3-hour infusion with hydration. During IV infusion, administer IT Mtx.*** Monday, 3 PM: Begin PO Mtx. Monday, 9 PM: PO Mtx at home.
Day IV-2	Tuesday, 3 AM: PO Mtx at home. Tuesday, 9 AM: PO Mtx at home. Tuesday, 3 PM: Obtain serum Mtx level (see Section 8.4.2). Give IV Lcv.
Day IV-3	Wednesday, 3 AM: PO Lcv at home. Wednesday, 9 AM: PO Lcv at home. Wednesday, 3 PM: PO Lcv at home. Wednesday, 9 PM: PO Lcv at home.
Day IV-4	Thursday, 3 AM: PO Lcv at home. Thursday, 9 AM: PO Lcv at home. Thursday, 3 PM: PO Lcv at home. Thursday, 9 PM: PO Lcv at home. Thursday: Obtain serum Mtx level at any time during the day on Thursday. Stop leucovorin if serum Mtx <0.05 mM.

* It is recommended that patients be hospitalized during the high-dose IV methotrexate administration for continuous IV hydration.

8.4.2 Serum Methotrexate Levels

Serum methotrexate levels should be obtained on days IV-2 (exactly 30 hours after starting the IV Mtx infusion) and IV-4, days IV-16 and IV-18, and days IV-30 and IV-32.

On day IV-15 and day IV-29, the oral methotrexate dose will be adjusted to try to achieve a level between 1-2 mM at 30 hours. The adjustment will be performed on day IV-15 and IV-29 based on the 30-hour serum methotrexate level obtained during the previous week on Days IV-2 or IV-16. Please refer to the tables below for instructions on methotrexate dose adjustments.

Note: All patients should begin PO Mtx at Level 0 (25 mg/m^2 PO every 6 hours x 4). Subsequent adjustments will be made according to the table below. Each adjustment will be made according to the previous week's methotrexate level at 30 hours.

Note: Patients must be off leucovorin for a minimum of 3 days (72 hours) prior to beginning the next dose of methotrexate.

Note: For methotrexate renal toxicity see Section 9.5.4. See Section 16.2 for additional reporting requirements.

The PO methotrexate dose should be adjusted according to the following tables:

30 hour Mtx level (µM) from Day 2 or Day 16	**Dose Adjustment for Day 15 or Day 29**
< 1.0	Increase one dose level from previous week
1 – 2	No adjustment
2.1 - 10	Decrease one dose level from previous week
> 10	No oral methotrexate

Dose Level	Adjusted MTX Dose
2	60 mg/m^2 every 6 hours x 4
1	40 mg/m^2 every 6 hours x 4
0 (Starting Level)	25 mg/m^2 every 6 hours x 4
-1	18 mg/m^2 every 6 hours x 4
-2	13 mg/m^2 every 6 hours x 4

8.4.3 Day IV-43 Bone Marrow Examination

A bone marrow aspiration and biopsy must be obtained for all patients on about day IV-43 to assess response, and perform institutional Q-PCR on peripheral blood and bone marrow aspirate. Alliance institutions should submit peripheral blood and bone marrow aspirate specimens for relevant companion studies (CALGB 8461 [required]).

8.5 Course V

This course includes three different options: allogeneic transplantation for patients ages 18-70 with an HLA-matched donor (see Section 8.5.1); autologous transplantation for patients age 18-70 without an HLA-matched donor or not a candidate for allogeneic transplantation (see Section 8.5.2); and for patients age > 70, or who are not transplant candidates, or without insurance coverage, an alternative chemotherapy regimen without transplantation (see Section 8.5.3).

The treating physician should consult with the Study Chair regarding frail patients who may need to skip Course V and continue on to Course VI.

8.5.1 Course V: Allogeneic Transplantation (for patients ages 18-70 with an HLA-matched donor)

Discontinue dasatinib during Course V (Allogeneic Transplantation) until approximately day V-30.

Patients must be treated at or referred to an Alliance-approved, ECOG-ACRIN-approved, SWOG-approved, or FACT-credentialed allogeneic transplant center to be eligible to receive this portion of the therapy. Course V therapy should begin no later than 10 days following count recovery in Course IV.

To receive allogeneic transplant, patients must have adequate organ function (renal, liver, cardiac, and pulmonary) to meet institutional requirements for allogeneic transplantation.

8.5.1.1 Donor Mobilization

Any consenting healthy individual who fulfills the donor (FAHCT) criteria will be considered for peripheral blood stem cell mobilization and collection. Sibling donors must be matched at 6/6 or 5/6 HLA antigens (HLA A, B and DR). Unrelated donors will be matched for HLA A, B, C and DRB1 antigens by molecular sequencing techniques. Syngeneic donors are acceptable.

- Mobilization of allogeneic peripheral blood stem cells will be performed according to institutional guidelines. Peripheral blood stem cell collection should target an optimal CD34+ cell dose > 5 x 10^6 cells/kg (actual weight) with a maximum of 10 x 10^6 CD34+ cells/kg. Stem cells may be collected at any time prior to transplant.
- In instances where the cells harvested from the donor are <5 x 10^6 CD34+ cells/kg recipient, the clinical investigator may elect to collect a bone marrow backup product.

8.5.1.2 **Fludarabine** 30 mg/m^2/day (actual body weight) IV over 30 minutes on days –7, –6, –5, –4, –3. At a minimum of one hour prior to the first dose, begin IV hydration to induce at least 100 mL/hr urine output. Fludarabine will be administered prior to alemtuzumab.

8.5.1.3 **Alemtuzumab** 20 mg/day (flat dose) IV over 30 minutes on days –7, –6, –5, –4, –3. Alemtuzumab will be given within one hour of completion of fludarabine. Prior to each alemtuzumab infusion, patients will receive acetaminophen 650 mg orally, diphenhydramine 50 mg IV (or equivalent), and methylprednisolone 2 mg/kg IV (or equivalent) to prevent alemtuzumab toxicity. Premedication may be repeated as necessary. Patients who develop infusion-related symptoms, such as fever, or rigors, despite treatment with diphenhydramine, acetaminophen and methylprednisolone, will receive meperidine at investigator discretion.

8.5.1.4 **Melphalan** 140 mg/m^2/day (corrected body weight) IV over 30 minutes on day –2. It is recommended that the patient be hydrated with normal saline (150 mL/hour) starting one hour prior to the melphalan dose and continuing for 24 hours after the melphalan dose.

Corrected weight = ideal weight (see Appendix I) + 25% of the difference between ideal and actual weight. If actual weight is less than ideal, use actual weight rather than corrected weight. The corrected weight should then be used to calculate Body Surface Area (BSA) for dosing.

8.5.1.5 **GVHD Prophylaxis with Tacrolimus for Matched Sibling Donors**

- GVHD prophylaxis should be per institutional guidelines. The following is a recommendation for the use of tacrolimus.
- Tacrolimus 0.05 mg/kg/day on Day -2 through +3 (6 days total) given via continuous IV infusion. The scheduling of tacrolimus administration should be such that a full 48 hours has been given before the donor stem cells are infused.
- Tacrolimus 0.03 mg/kg/day on Day +4 through +14 (11 days total) via continuous IV infusion.
- Tacrolimus 0.03 mg/kg/day on Day +15 through +100 via continuous IV infusion or in divided doses every 12 hours or oral. Oral dose is 3x the last IV dose.
- Tacrolimus blood concentration should be maintained between 10 - 20 ng/mL as a steady state during continuous IV infusion or as trough levels during divided doses.
- Following Day +100, tacrolimus will be tapered according to institutional guidelines.

8.5.1.6 **GVHD Prophylaxis with Tacrolimus for Mismatched (5/6) Related and Matched Unrelated Donors (MUD)**

- GVHD prophylaxis should be per institutional guidelines. The following is a recommendation for the use of tacrolimus.
- Initial tacrolimus dosing will be the same as in Section 8.5.1.5.
- In recipients of mismatched related or unrelated donor transplants, tacrolimus should continue until day +180. Thereafter, tacrolimus will be tapered by 20% per week in the absence of GVHD.

8.5.1.7 **Allogeneic peripheral blood stem cells will be infused on day 0.**

8.5.1.8 G-CSF 5 mcg/kg/day (actual body weight) SC beginning on day +1.

It is recommended that G-CSF be started on day +1. If no ANC recovery has been achieved by Day 14, G-CSF must be administered.

- G-CSF should continue daily until ANC > 1500/µL for 2 consecutive days or 5000/µL for 1 day. G-CSF can be restarted if the ANC falls to < 500/µL.
- G-CSF doses should be rounded as follows: 300 mcg for patients ≤60 kg, 480 mcg for weight 61-95 kg, 600 mcg if weight >95 kg. IV administration of each dose over 15-60 minutes is permissible if patient cannot tolerate subcutaneous injections.

8.5.1.9 Infectious Disease Prophylaxis

- **Antibacterial prophylaxis is required.** For example, levofloxacin 500 mg or gatifloxacin 400 mg orally or institutional equivalent until resolution of neutropenia.
- **Antifungal prophylaxis is required.** For example, posaconazole 200 mg three times daily orally or voriconazole 200 mg two times daily orally (or IV) or institutional equivalent until day +180. Azole antifungal agents should not be administered within 5 half lives of vincristine.
- **Pneumocystis pneumonia prophylaxis is required.** For example, cotrimoxazole double-strength BID twice a week from engraftment until 1 year after transplantation.
- **CMV viremia monitoring and prophylaxis are required.** For example, cytomegalovirus (CMV) positive patients or those who had a CMV-seropositive donor can be given ganciclovir 5 mg/kg from day -8 until day -3, followed by receive acyclovir 10 mg/kg every 8 hours IV/orally until discharge. Then continue acyclovir 800 mg orally three times a day will be continued until day 210. Alternatively, and based on institutional practice, patients can receive valacyclovir 2,000 mg four times daily from discharge until day +210. Patients who are CMV negative and had a CMV-negative donor can follow institutional guidelines.
- Patients should be screened weekly for CMV viremia until day +120 and treated with ganciclovir upon detection of CMV viremia.
- Monitoring for EBV viremia by DNA PCR is strongly encouraged througout the first 100 days.
- Antifungal, antiviral, and *Pneumocystis* prophylaxis and screening for CMV viremia should continue indefinitely for those with active GVHD or those receiving immunosuppressive treatment.
- In institutions that do not provide CMV-negative blood products for CMV-negative donor/recipient pairs, CMV-negative donor/recipient pairs should be screened weekly for CMV viremia.

8.5.1.10 On Day 30 post-transplant in Course V all patients will undergo a bone marrow examination. Perform institutional Q-PCR on bone marrow aspirate on Day +30 and one year post-transplant to assess for minimal residual disease.

8.5.2 Course V: Autologous Transplantation (for patients ages 18-70 without an HLA-matched donor or not a candidate for allo-HCT)

Patients must be treated at or referred to an Alliance-approved, ECOG-ACRIN-approved, SWOG-approved or FACT-credentialed autologous transplant center to be eligible to receive this portion of the therapy. Course V therapy should begin no later than 10 days following count recovery in Course IV.

To receive autologous transplant, patients must have adequate organ function (renal, liver, cardiac, and pulmonary) to meet institutional requirements for autologous transplantation.

Discontinue dasatinib 24 hours prior to the initiation of Course V and restart after completion of stem cell collection (see Section 8.5.2.8).

8.5.2.1 Step I – Peripheral Blood Stem Cell (PBSC) Mobilization and Leukapheresis

Patients will receive therapy as follows:

1) Begin the etoposide continuous IV infusion at hour 0 (Hours 0 - 96, days 1-4);
2) Start the high-dose ara-C (HiDAC) 2-hour IV infusion at hour 0 (every 12 hours x 8 doses on days 1-4);
3) Start the G-CSF on day 14 at a dose of 10 mcg/kg/day SC. G-CSF must be continued until PBSC collection has been completed or WBC >50,000/µL.
4) It is recommended that patients remain in hospital until full hematologic recovery.

8.5.2.2 Etoposide

- **In patients age ≤ 65 years,** etoposide 10 mg/kg/day (corrected weight) via continuous IV infusion over 96 hours (days 1-4). Total dose is 40 mg/kg.

  Corrected weight = ideal weight (see Appendix I) + 25% of the difference between ideal and actual weight. If actual weight is less than ideal, use actual weight rather than corrected weight.

  During etoposide infusion, other IV fluids should be kept to a minimum and blood products should not be given except in an emergency.

- **In patients age > 65 years,** etoposide 5 mg/kg/day (corrected weight) via continuous IV infusion over 96 hours (days 1-4). Total dose is 20 mg/kg.

  Corrected weight = ideal weight (see Appendix I) + 25% of the difference between ideal and actual weight. If actual weight is less than ideal, use actual weight rather than corrected weight.

  During etoposide infusion, other IV fluids should be kept to a minimum and blood products should not be given except in an emergency.

8.5.2.3 HiDAC

In patients ≤ 65 years of age:

- Cytarabine 2000 mg/m^2 in 250 mL D_5W IV over 2 hours every 12 hours x 8 doses (days 1-4).
- Prior to each dose of cytarabine, evaluate for the presence of nystagmus or other signs of cerebellar dysfunction. (Assessments are more accurate if the patient has not recently, i.e., in approximately the last hour, been medicated with anti-emetics.) If these symptoms are present, stop cytarabine and do not resume this drug. Corticosteroid eye drops should be used prophylactically. Please note dose modification in Section 9.6.

- Cytarabine doses should be given while the etoposide continuous infusion is running.
- Actual body weight should be used in Body Surface Area (BSA) calculations for dosing.

In patients > 65 years of age:

- Cytarabine 1000 mg/m^2 in 250 mL D_5W IV over 2 hours every 12 hours x 8 doses (days 1-4).
- Prior to each dose of cytarabine, evaluate for the presence of nystagmus or other signs of cerebellar dysfunction. (Assessments are more accurate if the patient has not recently, i.e., in approximately the last hour, been medicated with anti-emetics.) If these symptoms are present, stop cytarabine and do not resume this drug. Corticosteroid eye drops should be used prophylactically. Please note dose modification in Section 9.6.
- Cytarabine doses should be given while the etoposide continuous infusion is running.
- Actual body weight should be used in Body Surface Area (BSA) calculations for dosing.

8.5.2.4 Prophylactic Anti-Fungal, Anti-Bacterial Antibiotic and Anti-Viral Therapy

Prophylactic anti-fungal and anti-bacterial antibiotic therapy beginning on day 5 of this regimen are required. An institutional equivalent, or any of the following commonly used regimens may be used: ciprofloxacin 500 mg PO BID, amoxicillin/clavulanate (Augmentin) 875 mg PO BID, acyclovir 400 mg PO BID, posaconazole 200 mg PO TID, fluconazole 200 BID or voriconazole 200 mg BID. Such therapy may be discontinued once the ANC is >500/µL, unless otherwise clinically indicated.

8.5.2.5 Granulocyte Colony Stimulating Factor (G-CSF)

G-CSF 10 mcg/kg/day (total dose) subcutaneously in one or two divided doses starting on day 14. Continue until PBSC collection has been completed or WBC >50,000/µL. Do not skip or reduce dose for bone pain.

G-CSF doses should be rounded to the nearest vial size. IV administration of each dose over 15-60 minutes is permissible if patient cannot tolerate subcutaneous injections.

8.5.2.6 Peripheral Blood Stem Cell (PBSC) Collection

- Begin PBSC collections when the WBC >10,000/µL. This usually occurs about day 18 after starting HiDAC/etoposide. Waiting until the WBC >30,000/µL may increase the CD34+ yield.
- Aim for a total of 1-5 collections with a goal of collecting $\geq$ 5 x 10^6 CD34+ cells/kg and not more than 10 x 10^6 CD34+ cells/kg. This would be an adequate collection even if the mononuclear (MNC) collection is <12 x 10^8/kg. In the absence of a reliable measurement of CD34+ cells, the MNC collection should be >12 x 10^8 cells/kg.
- If the CD34+ collection on the first day of apheresis is poor, it is recommended to continue G-CSF, delay apheresis 1-3 days, and resume once the WBC has increased to > 15,000-20,000/µL.

- While 5 x 10^6 CD34+ cells/kg represents an acceptable minimum, infusion of a larger collection may improve engraftment. It is not recommended, however, to continue the leukapheresis for more than 5 aphereses in order to exceed the minimum required collection once that amount of PBSC has been collected.
- If the CD34 collection is inadequate after 5 aphereses, allow a two-week rest period. Bone marrow and peripheral blood criteria for CR must then be redocumented after which an attempt may be made to remobilize PBSC using G-CSF at doses ≥ 10 µg/kg daily. Physician discretion is permitted at this juncture with respect to using higher G-CSF doses and allowing the use of GM-CSF. The remobilization attempt must take place no later than two weeks after bone marrow and peripheral blood criteria for CR have been documented.
- Patients who cannot be mobilized following HiDAC/etoposide because of therapy-related complications may remain on study and receive autologous transplantation following mobilization at a later date using the methods outlined above. Bone marrow and peripheral blood criteria for CR must be met within two weeks of the mobilization.
- Patients unable to undergo PSCT after HiDAC/etoposide may continue as outlined in Section 8.5.3.
- PBSC processing should occur per institutional criteria. Ex vivo "purging" procedures are not permitted.
- An aliquot of each day's stem cell collection (1 x 10^7 cells) must be sent for institutional Q-PCR.

8.5.2.7 Backup Bone Marrow Harvest - This is not a requirement if stem cell collection is adequate.

- Total nucleated cell count collection should be >1 x 10^8/kg.
- Cells will be processed as per institutional criteria.
- An aliquot of each day's stem cell collection (1 x 10^7 cells) must be sent for institutional Q-PCR.

8.5.2.8 Dasatinib

Restart dasatinib at 140 mg PO daily after completion of stem cell collection. Dasatinib must then be continued until 3 days prior to the autologous transplant.

8.5.2.9 Step II - Autologous Peripheral Blood Stem Cell Transplant (PBSCT)

- Peripheral blood stem cell transplantation should take place no earlier than 4 weeks following hospital discharge and after recovery from toxicity related to myelosuppression following mobilization and leukapheresis. The preparative regimen should begin no sooner than 72 hours after the last dose of dasatinib in Section 8.5.2.8.
- Patients must meet institutional criteria for PBSCT and have neither active infection nor need for ongoing antibiotics.
- A bone marrow examination must be performed prior to autologous HCT to assess response. Patients must remain in complete remission as documented by normal bone marrow morphology with < 5% blasts within 2 weeks of transplant therapy, and have stable or improving peripheral blood counts. ANC must be > 500/µL and platelet count > 50,000/µL. Patients with falling blood counts should be observed to exclude relapse as the cause of the change. Perform institutional

Q-PCR on bone marrow aspirate prior to autologous HCT. Procure specimens for relevant companion studies (CALGB 8461 [required]).

8.5.2.10 Melphalan 100 mg/m^2/day (corrected weight) IV over 30 minutes on days -2 and -1. It is recommended that the patient be hydrated with normal saline (150 mL/hour) starting one hour prior to the melphalan dose and continuing for 24 hours after the melphalan dose. Diurese vigorously to keep at baseline weight.

Corrected weight = ideal weight (see Appendix I) + 25% of the difference between ideal and actual weight. If actual weight is less than ideal, use actual weight rather than corrected weight. The corrected weight should then be used to calculate Body Surface Area (BSA) for dosing.

8.5.2.11 Autologous PBSC infusion on Day 0. Peripheral stem cells should be thawed in a 37°C water bath and infused IV immediately without an in-line filter.

8.5.2.12 G-CSF 5 mcg/kg (actual body weight) subcutaneously daily starting on day 0 and continued daily until ANC >1500/µL for 2 days or >5000/µL for one day. G-CSF should be restarted if the ANC falls to <500/µL and continued until the ANC >5000/µL for two days.

G-CSF doses should be rounded off to nearest vial sizes. IV administration of each dose over 15-60 minutes is permissible if patient can not tolerate subcutaneous injections.

8.5.2.13 On Day 30 post-transplant following Course V all patients will undergo a bone marrow examination. Perform institutional Q-PCR on bone marrow aspirate on Day+30 and one year post-transplant.

8.5.3 Course V: Alternative Chemotherapy Regimen without Transplantation (for those patients age > 70, those who are not candidates for any transplant, or those without insurance coverage)

Patients who are age > 70, who are not candidates for transplantation, or those without insurance coverage **should not** be removed from protocol therapy. Rather, they will receive an alternative chemotherapy regimen consisting of etoposide and high-dose ara-c.

Dasatinib is to be discontinued until initiation of Course VI.

Chemotherapy should begin no less than 72 hours and no more than 10 days after the last dose of dasatinib in Course IV.

8.5.3.1 Etoposide

- In patients age ≤ 65 years, **etoposide 10 mg/kg/day (corrected weight) via continuous IV infusion over 96 hours (days 1-4). Total dose is 40 mg/kg.**

  Corrected weight = ideal weight (see Appendix I) + 25% of the difference between ideal and actual weight. If actual weight is less than ideal, use actual weight rather than corrected weight.

  During etoposide infusion, other IV fluids should be kept to a minimum and blood products should not be given except in an emergency.
- In patients age > 65 years, **etoposide 5 mg/kg/day (corrected weight) via continuous IV infusion over 96 hours (days 1-4). Total dose is 20 mg/kg.**

Corrected weight = ideal weight (see Appendix I) + 25% of the difference between ideal and actual weight. If actual weight is less than ideal, use actual weight rather than corrected weight.

During etoposide infusion, other IV fluids should be kept to a minimum and blood products should not be given except in an emergency.

8.5.3.2 HiDAC

- **In patients age ≤ 65 years,** cytarabine 2000 mg/m^2 in 250 mL D_5W IV over 2 hours every 12 hours x 8 doses (days 1-4). Prior to each cytarabine dose, evaluate for the presence of nystagmus or other signs of cerebellar dysfunction. (Assessments are more accurate if the patient has not recently, i.e., in approximately the last hour, been medicated with anti-emetics.) If these symptoms are present, stop cytarabine and do not resume this drug. Corticosteroid eye drops should be used prophylactically. Cytarabine doses should be given while the etoposide continuous infusion is running. Actual body weight should be used in Body Surface Area (BSA) calculations for dosing.
- **In patients age > 65 years,** cytarabine 1000 mg/m^2 in 250 mL D_5W IV over 2 hours every 12 hours x 8 doses (days 1-4). Prior to each cytarabine dose, evaluate for the presence of nystagmus or other signs of cerebellar dysfunction. (Assessments are more accurate if the patient has not recently, i.e., in approximately the last hour, been medicated with anti-emetics.) If these symptoms are present, stop cytarabine and do not resume this drug. Corticosteroid eye drops should be used prophylactically. Cytarabine doses should be given while the etoposide continuous infusion is running. Actual body weight should be used in Body Surface Area (BSA) calculations for dosing.

8.5.3.3 Prophylactic Anti-Fungal, Anti-Bacterial Antibiotic, and Antiviral Therapy

Prophylactic anti-fungal and anti-bacterial antibiotic therapy beginning on day 5 of this regimen are required. A commonly used regimen is ciprofloxacin 500 mg PO BID, amoxicillin/clavulanate (Augmentin) 875 mg PO BID, acyclovir 400 mg PO BID and posaconazole 200 mg PO TID. Such therapy may be discontinued once the ANC is >500/µL, unless otherwise clinically indicated.

8.5.3.4 Granulocyte Colony Stimulating Factor (G-CSF)

G-CSF 5 mcg/kg/day subcutaneously starting on day 14, and continued until WBC >5000/µL for one day or >1500 for two days.

G-CSF doses should be rounded to the nearest vial size. IV administration of each dose over 15-60 minutes is permissible if patient can not tolerate subcutaneous injections.

8.5.3.5 On Day 30 of Course V all patients will undergo a bone marrow examination. Perform institutional Q-PCR on bone marrow aspirate approximately one year after initiating Course V.

8.6 Course VI: Dasatinib Maintenance Therapy

8.6.1 In Patients Who Underwent Allogeneic HCT

Patients who underwent allogeneic HCT will receive dasatinib for at least twelve months after the initial dose of dasatinib. Dasatinib maintenance is to be discontinued when any ONE of the following criteria are met:

(1) Completion of 12 months of maintenance if two consecutive negative RT-PCR assays performed in a local CLIA-approved laboratory three months apart are documented.

(2) After 12 months of maintenance when two consecutive negative RT-PCR assays performed in a local CLIA-approved laboratory three months apart are documented.

(3) At relapse.

Dasatinib maintenance administered as follows:

- **Dasatinib** 50 mg/day PO beginning on about day V-30 post-transplant (if tolerable).
- **Dasatinib** dose should be increased to 100 mg PO once daily after two weeks if tolerated. Report accurately in the flow sheets.
- **Bone marrow examinations** will occur every 3 months for 2 years and at relapse. Institutional Q-PCR should be performed on peripheral blood every 3 months for 5 years from study entry. At time of relapse, MRD assessment on bone marrow aspirate or peripheral blood by institutional Q-PCR should be performed.

8.6.2 In Patients Who Underwent Autologous HCT

Patients who underwent autologous HCT will receive dasatinib for at least twelve months after the initial dose of dasatinib. Dasatinib maintenance is to be discontinued when any ONE of the following criteria are met:

(1) Completion of 12 months of maintenance if two consecutive negative RT-PCR assays performed in a local CLIA-approved laboratory three months apart are documented.

(2) After 12 months of maintenance when two consecutive negative RT-PCR assays performed in a local CLIA-approved laboratory three months apart are documented.

(3) At relapse.

Dasatinib maintenance administered as follows:

- **Dasatinib** 100 mg PO once daily beginning on about day V-30 post-transplant (if tolerable).
- **Bone marrow examinations** will occur every 3 months for 2 years and at relapse. Institutional quantitative RT-PCR should be performed on peripheral blood every 3 months for 5 years from study entry. At time of relapse, MRD assessment on bone marrow aspirate or peripheral blood by institutional Q-PCR should be performed.

8.6.3 In Patients Who Did Not Undergo HCT

Patients who did not undergo HCT will receive dasatinib and chemotherapy for at least twelve months after the initial dose of dasatinib. Dasatinib maintenance is to be discontinued when any ONE of the following criteria are met:

(1) Completion of 12 months of maintenance if two consecutive negative RT-PCR assays performed in a local CLIA-approved laboratory three months apart are documented.

(2) After 12 months of maintenance when two consecutive negative RT-PCR assays performed in a local CLIA-approved laboratory three months apart are documented.

(3) At relapse.

Dasatinib and chemotherapy maintenance administered as follows:

- **Dasatinib** 100 mg PO once daily beginning on day V-30 (30 days after starting etoposide/cytarabine).
- **Vincristine** 2 mg IV every 4 weeks.
- **Dexamethasone** 10 mg/day for 5 days every 4 weeks.
- **6-mercaptopurine** 60 mg/m^2/day PO in the evening. Doses of 6-mercaptopurine may be rounded to the next 25 mg.
- **Methotrexate** 20 mg/m^2 PO once per week. Doses of methotrexate may be rounded to the next 2.5 mg.
- **Bone marrow examinations** will occur every 3 months for 2 years and at relapse. Institutional Q-PCR should be performed on peripheral blood every month for the first year, every 3 months for the following two years, and every six months for 5 years from study entry. At time of relapse, MRD assessment on bone marrow aspirate or peripheral blood by institutional Q-PCR should be performed.

8.7 Treatment for CNS Leukemia

CNS leukemia at time of entry on study or up to the beginning of Course III will only be treated if symptomatic. Give IT methotrexate 15 mg twice weekly (hydrocortisone 50 mg should be included with preservative free methotrexate) for at least 6 doses and until the CSF is clear. Begin cranial radiation therapy (see Section 8.9) for symptomatic patients with CNS leukemia at time of entry (or promptly after day of CNS diagnosis for symptomatic patients diagnosed after entry into this protocol). Concurrent with cranial radiation therapy, continue weekly IT methotrexate (15 mg). Use minimal doses of leucovorin as necessary to prevent mucositis or severe myelosuppression. If CNS remission is achieved, then continue to give intrathecal methotrexate monthly for 12 months.

8.8 CNS Leukemia Developing During Hematologic Remission (CR or PR) While Receiving or Having Completed Protocol Therapy

Continue protocol therapy for patients who experience CNS failure without marrow relapse. Give 15 mg IT methotrexate weekly or twice weekly until CNS is clear of leukemia cells and then monthly for 12 months. Give concurrent cranial radiation (see Section 8.9). These patients continue to receive protocol therapy until bone marrow relapse occurs. Consult with the Alliance Study Chair if CSF leukemia persists, regarding the use of intrathecal cytarabine.

8.9 Cranial Radiation Therapy

Cranial radiation therapy is intended only for patients with CNS leukemia at presentation, symptomatic CNS disease prior to beginning Course III, or for patients who develop symptoms of CNS disease during remission (as described in Sections 8.7 and 8.8). IMRT and proton RT will not be allowed on this study.

8.9.1 Equipment

Modality: Co-60 or X-ray beams with a nominal energy between 4 and 6 MV.

Calibration: The calibrations of therapy units used in this protocol shall be verified by the Radiological Physics Center.

8.9.2 Target Volume

The target volume consists of the entire brain and meninges, including the frontal lobe as well as the posterior halves of the globes of the eyes, with the optic disk and nerve superior

to the vertex and posterior to the occiput. The caudal border shall be below the skull base at the C2 vertebral level (see discussion of field matching in Section 8.9.4).

Localization: The planning target volumes shall be defined by means of a simulator.

8.9.3 Target Dose

Prescription Point: The prescription point in each target volume is at or near the center*. For multi-convergent beams, the prescription point is usually at the intersection of the beam axes.

*Note: This follows the recommendations of ICRU Report 50. If your institution's practice differs, a conversion may be necessary. For instance, if you prescribe to a certain isodose line, adjust this (departmental) prescription so that the (protocol) prescribed dose is given to the (protocol) prescription point.

Dose Definition: The absorbed dose is specified below in centigray (cGy)-to-water.

Tissue Heterogeneity: No corrections for bone attenuation shall be made. Institutions that customarily correct of heterogeneities must calculate monitor units or time of irradiation without this option.

Prescribed dose and fractionation: The total dose to the prescription point shall be 2400 cGy in 12 fractions. The patient shall be treated with one fraction per day of 200 cGy.

Dose Uniformity: The dose variations in each target volume shall be within +7%,-5% of the prescription dose (In accordance with ICRU Report 50, small high-dose volumes can be excluded from the evaluation of the dose uniformity but not small low-dose volumes).

Treatment Interruptions: No corrections shall be made for treatment interruptions less than seven days. For interruptions greater than seven days, please contact the radiation oncology co-chair.

8.9.4 Treatment Technique

Patient Position: The patient shall be treated in the supine position.

Beam Configuration: The cranial volume is treated with two lateral, equally weighted photon beams.

Field Shaping: Field-shaping shall be done with blocks which are at least 5 HVL thick.

Eye Protection: A simple method to minimize lens irradiation, while irradiating the posterior halves of the eyes, is to let the central axes of the horizontal cranial beams go through both orbits. The anterior edges of the beams are defined by an external block or by an independently controlled collimator and meet at a point 1 cm anterior to the frontal lobe meninges. Shielding blocks cover the anterior halves of the eyes and protect the nose and mouth.

Essentially the same geometry can be achieved with the central axes through the center of the head by angling the lateral fields so that the rays through the eyes lie in the same horizontal plane. It is acceptable to use a parallel-opposed beam-pair, without such angling, with shielding blocks that cover the anterior half of the proximal eye. The dose to the contralateral lens will then increase, however.

8.9.5 Dose Calculations and Reporting

Prescription Point: The monitor units or time or irradiation required to deliver the prescribed dose to the prescription points shall be calculated and submitted using the "RT-1 Dosimetry Summary" form.

Dose Uniformity: The maximum and minimum doses in the target volumes shall be calculated and reported on the RT-1 form. These may be extracted from isodose diagrams or calculated separately.

Isodose Distributions: For single beams (electrons or photons) and equally-weighted, parallel-opposed photon beams, isodose distributions are not required. In all other cases, a plot of the dose distribution in the central transverse plane through the target volume shall be submitted. The prescription point and the outlines of the target volume and critical organs shall be shown. Isodose values must be clearly labeled. The effects of shielding blocks shall be included.

8.9.6 Cranial Radiation Therapy Definitions of Deviation of Performance

Prescription Dose:

- **Minor Deviation:** The dose to the prescription point differs from that in the protocol by between ±6% and ± 10%.
- **Major Deviation:** The dose to the prescription point differs from that in the protocol by more than 10%.

Dose Uniformity:

- **Minor Deviation:** The variation in dose in one target of the volumes exceeds +7%/-5%.

8.10 Testicular Radiation: 2400 cGy in 12 Treatment Fractions

Testicular disease at time of entry on study or during therapy without marrow relapse will be treated by radiation and the patient will continue on study therapy. IMRT and proton RT will not be allowed on this study.

8.10.1 Equipment:

Modality: High-energy photon electron beams. The selection of energy is determined by the dose uniformity criterion, and with electrons, the lowest possible energy should be used to spare tissues outside the target volume.

Calibration: The calibrations of therapy machines in this protocol shall be verified by the Radiological Physics Center.

8.10.2 Planning Target Volume: The planning target volume consists of the testes in the scrotal sac. Use margins of at least 1/2 cm.

8.10.3 Target Dose

Prescription Point: The prescription point is at or near the center of the planning target volume.

Note: This follows the recommendations of ICRU Report 50. If your institution's practice differs, a conversion may be necessary. For instance, if you prescribe to a certain isodose line, adjust this (departmental) prescription so that the (protocol) prescribed dose is given to the (protocol) prescription point.

Dose Definition: The absorbed dose is specified as centigray (cGy)-to-water.

Prescribed Dose and Fractionation: The total dose to the prescription point shall be 2400 cGy in 12 fractions. The patient shall be treated with one fraction per day of 200 cGy.

Dose Uniformity: The variations of dose within the planning target volume shall be within +7%, -5% of the dose prescription point (In accordance with ICRU Report 50, small high-dose volumes can be excluded from the evaluation of the dose uniformity but not small low-dose volumes). The uniformity requirement can in general be met with an electron beam of

appropriate energy provided bolus is used, which is the simplest technique. Bolus may also be needed for photon beams to fulfill the dose uniformity requirement.

Treatment Interruptions: No corrections shall be made for treatment interruptions less than seven days. For interruptions greater than seven days, please contact the radiation oncology co-chair.

8.10.4 Treatment Technique

Patient Position: The patient shall be treated in the supine position.

Field-Shaping: Field-shaping can be done with blocks of at least 5 HVL thick.

8.10.5 Normal Tissue Sparing and Dose Specification Points

Perineum: The testes shall be supported posteriorly and, if possible, extended caudally in order to minimize perineal irradiation. The field shall not be angled **towards the perineum.**

Penis: The penis shall be excluded from the field by fixing it to the skin over the symphysis pubis.

Dose Specification Points: To ensure dose uniformity specified in Section 8.10.3, the dose at two points shall be calculated and submitted with the Quality Assurance Documentation.

Point A: 0.5 cm from the anterior surface of the testes.

Point B: 0.5 cm from the posterior surface of the testes.

Note: Points A and B are defined with respect to the surface of the testis itself, and not the bolus material.

8.10.6 Dose Calculations and Reporting

Prescription Point: The monitor units or time of irradiation required to deliver the prescribed dose to the prescription points shall be calculated and submitted using the "RT-1 Dosimetry Summary" form.

Dose Uniformity: The maximum and minimum doses in the target volumes shall be calculated and reported on the "RT-1 Dosimetry Summary" form. These may be extracted from isodose diagrams or calculated separately.

Dose Specification Points: The daily dose to dose specification points shall be calculated and reported on the "RT-2 Radiotherapy Total Dose Record."

8.10.7 Testicular Radiation Therapy Definitions of Deviation of Performance

Prescription Dose:

- **Minor Deviation**: The dose to the prescription point differs from that in the protocol by between ±6% and ± 10%.
- **Major Deviation:** The dose to the prescription point differs from that in the protocol by more than 10%.

Dose Uniformity:

- **Minor Deviation:** The variation in dose in one target of the volumes exceeds +7%/-5%.

8.11 Quality Assurance Documentation

8.11.1 Within one week of the completion of radiotherapy, the following data shall be submitted:

- A copy of the patient's radiotherapy record including prescription, and the daily and cumulative doses to the prescription point and specified dose points.
- Documentation of the treatment field: This may consist of a photograph of the patient in the treatment position, taken in a darkened room with the light field on, to demonstrate that the treatment field completely includes the patient. Alternatively, verification films that show the patient with respect to the radiation field may be submitted.

8.11.2 Submission of Quality Assurance Documentation

- Submit data to: Quality Assurance Review Center
  272 West Exchange Street, Suite 101
  Providence, RI 02903-1025
  Tel: 401-454-4301
  Fax: 401-454-4683
  calgb@qarc.org
- Direct questions regarding the radiotherapy in this study to:

  Jeffrey Bogart, MD
  CALGB 10701 Radiation Oncology Co-Chair
  Tel: 315-464-5276
  bogartj@upstate.ed

  CALGB 10701 Protocol Dosimetrist
  Quality Assurance Review Center
  272 West Exchange Street, Suite 101
  Providence, RI 02903-1025
  Tel: 401-454-4301
  Fax: 401-454-4683
  physics@QARC.org

9.0 DOSE MODIFICATIONS AND MANAGEMENT OF TOXICITY

9.1 Anticipated Toxicity and Management

Should unanticipated circumstances arise that might require minor variances from the prescribed dosing and schedule of protocol therapy in order to ensure safety and allow patients to continue to receive treatment on study, the Alliance Study Chair should be contacted in advance for discussion and approval. If the following signs or symptoms are medically manageable, they are not to be a consideration with respect to the patient's dosing or continuation on study: nausea, mild vomiting, diarrhea, drug-related fever or chills, alopecia.

It is the intent of this protocol to administer the maximum tolerated dose intensity of designated therapy to adults with ALL even though hospitalization, blood transfusions, and parenteral antibiotics may be routinely required. Antibacterial, antiviral, and antifungal prophylaxis and treatment are required.

9.2 Treatment Delays

Doses may be delayed because of marked mucositis, hepatic toxicity, renal toxicity, or infection. Continue treatment, starting at the point where it had been suspended, after toxicity resolves to ≤grade 2 or when infection is eradicated. Document on study report forms.

9.3 Dasatinib Dose Modifications During Courses I - V

Dasatinib Dose Level	Dasatinib Dose
Dose Level 0 (Starting Dose)	140 mg once daily
Dose Level -1	100 mg once daily
Dose Level -2	50 mg once daily

If dose reduction below dose level -2 is required, please contact the Alliance Study Chair regarding further use of dasatinib in subsequent treatment modules.

9.3.1 Dasatinib Dose Modifications for Hepatic Toxicity

- For bilirubin ≥ 3 mg/dL but < 5 mg/dL, decrease dasatinib by one dose level until bilirubin improves to < 3 mg/dL, then resume dasatinib at the previous dose level.
- For bilirubin ≥ 5 mg/dL, interrupt dasatinib until bilirubin improves to < 5 mg/dL, then resume dasatinib with one dose level reduction for the remainder of that course. At the next course, re-escalate to the previous dose level. If bilirubin does not improve to < 5 mg/dL after four weeks, contact the Study Chair.
- For grade 3 or 4 ALT or AST, interrupt dasatinib until ALT/AST improves to ≤ grade 1, then resume dasatinib with one dose level reduction for the remainder of that course. At the next course, re-escalate to the previous dose level.

9.3.2 Other Non-Hematologic Toxicity

- **During Course I, dasatinib will only be modified for non-hematologic grade 3/4 toxicity (as described below).**
- **Grade 2 (Courses II-V)**

  For grade 2 non-hematologic toxicity due to dasatinib that does not resolve despite symptom-oriented therapeutic intervention, interrupt dasatinib until toxicity resolves to ≤ grade 1. Dasatinib may then be resumed at the previous dose. If grade 2 toxicity recurs, interrupt dasatinib until toxicity resolves to ≤ grade 1, then resume dasatinib with one dose level reduction for the remainder of that course. For the next course, re-escalate to the previous dose level.
- **Grade 3/4**

  For ≥ grade 3 non-hematologic toxicity at least possibly due to dasatinib, interrupt dasatinib until toxicity resolves to ≤ grade 1. Then resume dasatinib with a one level dose reduction for the remainder of that course. For the next course, re-escalate to the previous dose level. For recurrent grade 4 non-hematologic toxicity, discontinue dasatinib and contact the Alliance study chair.

9.3.3 Hematologic Toxicity

- **Grade 3 or 4 (Courses II-V)**

  For ANC < 1000/μL or platelet count <50,000/μL, interrupt dasatinib until ANC > 1000/μL and platelet count > 50,000/μL.
  - If toxicity resolves within 2 weeks, then resume dasatinib at previous dose level.
  - If toxicity does not resolve within 2 weeks or recurs, interrupt dasatinib until ANC >1000/μL and platelet count > 50,000/μL, then resume dasatinib with one dose level reduction for the remainder of that course. For the next course, re-escalate to the previous dose level.

- Patients with recurrent cytopenia but no evidence of relapse should be discussed with the Alliance Study Chair with regard to ancillary support with G-CSF during dasatinib therapy. Ph+ ALL lymphoblasts often express G-CSF receptors.

9.4 Dasatinib Dose Modifications During Course VI

9.4.1 In Patients Who Underwent Allogeneic HCT

9.4.1.1 Dasatinib Dose Levels

Dose Level	Dasatinib Dose
Dose Level 0	50 mg once daily
Dose Level +1	100 mg once daily

9.4.1.2 Dasatinib Dose Modifications for Hepatic Toxicity

- For bilirubin > 1.5 mg/dL du eto dasatinib, interrupt dasatinib until bilirubin improves to ≤ 1.5 mg/dL, then resume dasatinib at the previous dose level.
- If bilirubin does not improve to ≤ 1.5 mg/dL after four weeks, contact the Study Chair.
- For ≥ grade 2 ALT or AST due to dasatinib, interrupt dasatinib until ALT/AST improves to ≤ grade 1, then resume dasatinib at the previous dose. If ALT/AST does not improve to ≤ grade 1 after four weeks, contact the Study Chair.
- When tolerated, an attempt should be made to increase the dasatinib dose to 100 mg once daily. Once increased to 100 mg once daily, the dose modifications for patients who underwent autologous HCT or alternative chemotherapy will apply to these patients.

9.4.1.3 Dasatinib Dose Modifications for Other Non-hematologic and Hematologic Toxicity

- For ≥ grade 2 hematologic toxicity or ≥ grade 2 non-hematologic toxicity due to dasatinib, interrupt dasatinib until toxicity resolves to ≤ grade 1, then resume dasatinib at the same dose level.
- When tolerated an attempt should be made to increase the dasatinib dose to 100 mg once daily. Once increased to 100 mg once daily, the dose modifications for patients who underwent autologous HCT/alternative chemotherapy (Section 9.4.2) will apply to these patients.

9.4.2 In Patients Who Underwent Autologous HCT or Alternative Chemotherapy

9.4.2.1 Dasatinib Dose Levels

Dose Level	Dasatinib Dose
Dose Level 0	100 mg once daily
Dose Level -1	50 mg once daily

9.4.2.2 Dasatinib Dose Modifications

Hepatic Toxicity

- For bilirubin >1.5 mg/dL –3 mg/dL due to dasatinib, interrupt dasatinib until bilirubin improves to ≤ 1.5 mg/dL, then resume dasatinib at the previous dose level.

- For recurrent bilirubin >1 mg/dL – 3 mg/dL due to dasatinib, interrupt dasatinib until bilirubin improves to ≤ 1.5 mg/dL, then resume dasatinib with one dose level reduction for the remainder of that cycle (1 cycle = 4 weeks). For the next cycle, re-escalate dasatinib to the previous dose level.
- For bilirubin >3 mg/dL due to dasatinib, interrupt dasatinib until bilirubin improves to ≤ 1.5 mg/dL, then resume dasatinib with one dose level reduction for the remainder of that cycle (1 cycle = 4 weeks). For the next cycle, re-escalate dasatinib to the previous dose level.
- If bilirubin does not improve to ≤ 1.5 mg/dL after four weeks, contact the Study Chair.
- For recurrent bilirubin > 10 mg/dL, discontinue dasatinib and contact the Study Chair.
- For ALT/AST > 2.5–5x ULN due to dasatinib, interrupt dasatinib until ALT/AST improve to ≤2.5x ULN, then resume dasatinib at the previous dose level.
- For recurrent ALT or AST >2.5 – 5x ULN due to dasatinib, interrupt dasatinib until ALT/AST improves to ≤2.5x ULN, then resume dasatinib with one dose level reduction for the remainder of that cycle (1 cycle = 4 weeks). For the next cycle, re-escalate dasatinib to the previous dose level.
- For ALT/AST > 5x ULN due to dasatinib, interrupt dasatinib until ALT/AST improve to ≤2.5x ULN then resume dasatinib with one dose level reduction for the remainder of that cycle (1 cycle = 4 weeks). For the next cycle, re-escalate dasatinib to the previous dose level.
- If ALT/AST does not improve to ≤2.5x ULN after four weeks, contact the Study Chair.
- For recurrent ALT/AST >20x ULN, discontinue dasatinib and contact the Study Chair.

Other Non-Hematologic Toxicity

- For grade 2 non-hematologic toxicity due to dasatinib that does not resolve despite symptom-oriented therapeutic intervention, interrupt dasatinib until toxicity resolves to ≤ grade 1. Dasatinib may then be resumed at the previous dose level. If grade 2 toxicity recurs, interrupt dasatinib until toxicity resolves to ≤ grade 1, then resume dasatinib with a one dose level reduction for the remainder of that cycle (1 cycle = 4 weeks). For the next cycle, re-escalate to the previous dose level.
- For ≥ grade 3 non-hematologic toxicity at least possibly due to dasatinib, interrupt dasatinib until the toxicity resolves to ≤ grade 1. Then resume dasatinib with one level dose reduction for the remainder of that cycle. For the next cycle, re-escalate to the previous dose level. For recurrent grade 4 non-hematologic toxicity discontinue further dasatinib and contact the Alliance study chair.
- If dose modification below dose level -1 is required, please contact the Alliance Study Chair regarding further use of dasatinib in subsequent treatment modules.

Hematologic Toxicity

- For ANC < 1000/μL or platelet count <50,000/μL, interrupt dasatinib until ANC > 1000/μL and platelet count > 50,000/μL. If toxicity resolves within 2 weeks, then resume dasatinib at previous dose level. If toxicity does not resolve within 2 weeks or recurs, interrupt dasatinib until ANC >1000/μL and platelet count >

50,000/μL, then resume dasatinib with one dose level reduction. For the next course, re-escalate the previous dose level.

- Patients with recurrent cytopenia and yet no evidence of relapse should be discussed with the Alliance Study Chair with regard to ancillary support with G-CSF during dasatinib therapy. Ph+ ALL lymphoblasts often express G-CSF receptors.
- If dose modification below dose level -1 is required, please contact the Alliance Study Chair regarding further use of dasatinib in subsequent treatment modules.

9.5 Course IV (CNS Prophylaxis) Dose Modifications

9.5.1 Neutropenic Fever

For neutropenic fever (ANC < 500/μL and temperature ≥ 101°F) delay methotrexate until ANC ≥1000/μL and infection resolves.

9.5.2 Hyperbilirubinemia

Give the following doses:

Bilirubin (mg/dL)	VCR	PO-MTX	High-Dose IV-MTX
<1.5	2 mg (flat dose)	25 mg/m^2	500 mg/m^2
≥1.5 but <3.0	1 mg (flat dose)	25 mg/m^2	500 mg/m^2
≥3.0 but <5.0	0	18.0 mg/m^2	0*
≥5.0	0	0	0*

* Delay treatment for up to two weeks. Contact the Alliance Study Chair if toxicity does not resolve.

9.5.3 Oral Mucositis

For ≥ grade 3 oral mucositis, hold treatment until toxicity resolves to ≤ grade 2. If delay is greater than two weeks, then notify the Alliance Study Chair.

9.5.4 Renal Toxicity

- Patients with elevated serum creatinine (≥1.8 mg/dL) who have met all other criteria for initiation of Course IV treatment should have therapy held for as many as two weeks to allow for normalization of renal function (serum creatinine <1.8 mg/dL). If creatinine remains elevated after two weeks, notify Study Chair.
- Patients who experience nephrotoxicity should discontinue all methotrexate (IV, IT, oral). Substitute IV cytarabine (1000 mg/m^2) for IV methotrexate and IT cytarabine (50 mg total dose) for IT methotrexate. There is no substitute for oral methotrexate; it is simply discontinued.

9.5.5 Neurologic Toxicity

9.5.5.1 Dose Modification for Seizures

- For grade 2 seizures, hold next VCR dose. Reinstitute at previous dose at time of next planned VCR dose. For recurrent grade 2 seizures, please contact the Study Chair.
- For ≥ grade 3 seizures, please contact the Study Chair.

9.5.5.2 Dose Modification for Constipation

For grade 3 or 4 constipation, hold VCR dose, and institute aggressive hydration and laxative treatment. When toxicity resolves to ≤ grade 1, resume VCR at 50% of previous dose. VCR should then be re-escalated to previous dose, as tolerated.

9.5.5.3 Dose Modification for Sensory or Motor Neuropathy from Vincristine

For grade 3 or 4 sensory or motor neuropathy, hold VCR. Upon resolution of toxicity to ≤ grade 1, resume VCR at 50% of previous dose at time of next scheduled dose. Document on study report forms.

9.5.5.4 Dose Modification for Arachnoiditis

If CSF granulocytosis or pleocytosis, increased CSF pressure, fever, or localized signs of arachnoiditis occur following IT Mtx, skip IT Mtx. After resolution of symptoms, intrathecal treatment can be resumed with methotrexate (15 mg) or cytarabine (50 mg) at the point where it had been suspended.

9.5.5.5 Dose Modification for Methotrexate Neurotoxicity

If a patient develops neurological symptoms, including malaise, headaches, somnolence, focal neurologic deficits or seizures following administration of methotrexate, treatment with dextromethorphan may result in rapid improvement of symptoms. Prompt treatment of neurologic symptoms with 45-90 mg dextromethorphan (e.g., as found in 15-30 mL Robitussin DM) every 4-6 hours x 24-48 hours should be considered. For grade 3 or 4 neurotoxicity, hold the methotrexate and discuss the patient with the Study Chair.

9.5.5.6 Dose Modification for Psychosis

If signs or symptoms of psychosis caused by steroids are present, steroid treatment should be discontinued.

9.5.6 Pleural Effusions

Patients with pleural effusions who have met all other criteria for initiation of Course IV treatment should have therapy held for as many as two weeks to allow pleural effusions to resolve. If pleural effusions persist, notify Study Chair.

9.6 Course V High-Dose Ara-C Dose Modifications

9.6.1 Cerebellar Toxicity

Neurologic assessments should be performed before and after each dose of ara-C for cerebellar toxicities. If signs or symptoms of cerebellar toxicity occur during or following ara-C, infusion should be terminated and no further ara-C should be administered. Notify the Study Chair.

9.6.2 Creatinine Elevation

- **In patients ≤ 65 years**

  For creatinine > 1.5 mg/dL and ≤ 2 mg/dL decrease cytarabine to 1000 mg/m^2. For creatinine > 2.0 mg/dL decrease cytarabine to 200 mg/m^2.

- **In patients > 65 years**

  For creatinine > 1.5 mg/dL and ≤ 2 mg/dL decrease cytarabine to 400 mg/m^2. For creatinine > 2.0 mg/dL decrease cytarabine to 200 mg/m^2.

9.7 Dose Modifications for Methotrexate and 6-Mercaptopurine in Course VI

9.7.1 Dose Levels

Dose Level	6-MP	MTX
Dose Level 0	60 mg/m^2	20mg/m^2
Dose Level -1	45 mg/m^2	15 mg/m^2

9.7.2 Dose Modifications for Hematologic Toxicity in Course VI

- For ANC ≤ 1000, skip methotrexate and interrupt 6-MP until ANC improves to > 1000, then resume methotrexate and 6-MP at the previous dose.
- For recurrent ANC ≤ 1000, skip methotrexate and interrupt 6-MP until ANC improves to > 1000, then resume methotrexate and 6-MP with one dose level reduction of each. Re-escalate methotrexate and 6-MP at 2-4 week intervals, as allowed, to maintain ANC > 1000.
- For platelets ≤ 75,000, skip methotrexate and interrupt 6-MP until platelets improve to > 75,000, then resume methotrexate and 6-MP at the previous dose.
- For recurrent platelets ≤ 75,000, skip methotrexate and 6-MP until platelets improve to > 75,000, then resume methotrexate and 6-MP with one dose level reduction of each. Re-escalate methotrexate and 6-MP at 2-4 week intervals, as allowed, to maintain platelets > 75,000.

9.7.3 Dose Modifications for Bilirubin in Course VI

- For bilirubin ≥ 3mg/dL but < 5 mg/dL, decrease methotrexate and 6-MP by one dose level until bilirubin improves to < 3 mg/dL.
- For bilirubin ≥ 5 mg/dL, skip methotrexate and interrupt 6-MP until bilirubin improves to < 5 mg/dL.
- Re-escalate methotrexate and 6-MP at 2-4 intervals, as allowed. If bilirubin does not improve to < 5 mg/dL after 4 weeks, contact the Study Chair.

9.7.4 Dose Modifications for ALT and AST Course VI

- For grade ≥ 3 ALT or AST, skip methotrexate and interrupt 6-MP until ALT/AST improves to ≤ grade 2, then resume methotrexate and 6-MP with one dose level reduction of each.
- Re-escalate methotrexate and 6-MP at 2-4 week intervals, as allowed.
- IF ALT/AST does not improve to ≤ grade 2 after 4 weeks, contact the Study Chair.

9.8 Treatment of GVHD

Acute GVHD generally develops at time of engraftment or within the first three months after transplantation. It is a clinico-pathological syndrome involving the skin, the liver, and the gut. Serial biopsies and observations are used to help establish the diagnosis and severity of GVHD. The clinical appearance of skin GVHD can be mimicked by toxicity of the conditioning regimen and by drug reaction; therefore, documentation by skin biopsy should be performed when possible. Hepatic GVHD cannot be assessed solely on clinical grounds in patients who have concurrent drug toxicity, viral hepatitis, or toxicity caused by the conditioning regimen, and liver biopsy is helpful when possible. Gastrointestinal GVHD can be difficult to distinguish from

infectious enteritis, and endoscopic biopsy should be done whenever possible. Appendix II presents the staging and grading system for acute GVHD.

9.8.1 Acute GVHD

- **Indications for initial treatment of acute GVHD**

  In general, treatment for GVHD should be started when grade 2 GVHD criteria have been met (Appendix II). Grade 2 GVHD is moderately severe disease and usually consists of multiorgan disease. The decision to treat is based on the clinical assessment of the patient's condition, the onset time relative to the day of transplant, and the rapidity with which symptoms progress.

- **Agents to be used for initial treatment of acute GVHD**

  Acute GVHD usually is treated with a corticosteroid-containing regimen. Methylprednisolone can be administered at a dose of at least 1 mg/kg body weight every 12 hours for 10-12 days. Tapering should begin between 10-20 days after starting initial treatment. The tapering of steroids can be determined by the institution guidelines. Record treatment information on flow sheets.

  Patients may be eligible for other agents for the treatment of GVHD per institutional protocols. Salvage regimens may include antithymocyte globulin, anti-T-cell antibodies, or psoralen and ultraviolet A irradiation (PUVA).

9.8.2 Chronic GVHD

- **Diagnosis of chronic GVHD**

  Manifestations of chronic GVHD typically do not occur until one to three months after transplantation. The patients will be diagnosed with either limited or extensive chronic GVHD. Biopsies of the liver are recommended for patients who present with abnormal liver function tests in the absence of overt involvement of the skin, eyes, or mouth. Endoscopy and biopsy are recommended to establish gut involvement.

- **Agents to be used for treatment of chronic GVHD**

  Patients diagnosed with extensive chronic GVHD are often treated for 9-12 months with tacrolimus and prednisone but should be managed according to institutional protocols. Suggested dosages are prednisone 1 mg/kg/day given as an oral dose in the morning. Record treatment information on flow sheets.

10.0 DRUG FORMULATION, AVAILABILITY AND PREPARATION

Qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents in a self-contained, protective environment.

Discard unused portions of injectable chemotherapeutic agents that do not contain a bacteriostatic agent or are prepared with unpreserved diluents (i.e., Sterile Water for Injection USP or 0.9% Sodium Chloride for Injection USP) within eight hours of vial entry to minimize the risk of bacterial contamination.

The total administered dose of chemotherapy may be rounded up or down within a range of 5% of the actual calculated dose.

10.1 Campath-1H (alemtuzumab, Campath)

AVAILABILITY

Campath is provided through the US Campath Distribution Program. It is no longer commercially available (as of September 2012). To request Campath supplies, call 1-877-422-6728. Campath is supplied in 1 mL single-use vials containing 30 mg/mL in 1 mL. Please refer to the agent's package insert for additional information.

STORAGE & STABILITY

Intact vials should be stored, protected from light, under refrigeration. Do not freeze.

Alemtuzumab was physically and chemically stable at room temperature for up to 24 hours after dilution at concentrations between 20 and 4800 mcg/mL in 0.9% sodium chloride and 5% dextrose infusion bags. However, since the product does not contain any preservatives, solutions diluted for infusion must be used within 8 hours of preparation. Infusion solutions may be stored at room temperature or under refrigeration.

PREPARATION

Withdraw the desired volume of alemtuzumab (0.67 mL) and inject into 100 mL of normal saline or 5% dextrose for IV infusion. Gently invert the bag to mix the solution.

ADMINISTRATION

In this study, alemtuzumab will be administered IV over 30 minutes within one hour after fludarabine. Premedicate with 50 mg diphenhydramine IV (or equivalent), 650 mg acetaminophen PO, and 2 mg/kg methylprednisolone (or equivalent) 30 minutes prior to each alemtuzumab dose. Patients who develop infusion-related symptoms, such as fever, or rigors, despite treatment with diphenhydramine, acetaminophen and methylprednisolone, will receive meperidine at the investigator discretion.

TOXICITY

Infusion reactions occur in most patients. They commonly consist of rigors, fever, headache, nausea, vomiting, diarrhea, rash, pruritus, dyspnea and hypotension. Acute infusion reactions may also include chills, abdominal and back pain, bronchospasm, angioedema, tachyarrhythmia, etc.

Autoimmune hemolytic anemia, neutropenia, autoimmune thrombocytopenia, lymphopenia, bacterial and opportunistic infections (e.g., Pneumocystis jiroveci pneumonia, oral candidiasis, herpes zoster, CMV reactivation, cryptococcosis), allergic reactions, fatigue, hypertension, syncope, angina and myocardial infarction, anorexia, nausea, vomiting, diarrhea, constipation, dyspepsia, mucositis, thrombocytopenia, myalgia, bone pain, tremor, tumor lysis syndrome, insomnia, interstitial pneumonitis, pruritus, urticaria, peripheral edema are also seen.

CAUTION: Women of child-bearing age and fertile men must use adequate and effective contraception during treatment with alemtuzumab and for at least 3 months after all therapy in this study is completed. The effects of alemtuzumab on embryogenesis, reproduction, and spermatogenesis are unknown. Breast feeding should be discontinued during this study and for 3 months after study treatment is completed.

10.2 Cyclophosphamide (Cytoxan®; CTX; CPA; Neosar®; Cytoxan Lyophilized®)

AVAILABILITY

Commercially available as a powder for reconstitution in 100 mg, 200 mg, 500 mg, 1 gram, and 2 gram vials.

STORAGE & STABILITY

Intact vials should be stored at room temperature. Reconstituted and diluted solutions are stable for 24 hours at room temperature and 6 days if refrigerated.

PREPARATION

Reconstitute 100 mg, 200 mg, 500 mg, 1 gram and 2 gram vials with 5, 10, 25, 50, or 100 mL of SWI or NS to give a final concentration of 20 mg/mL.

Vigorous shaking, gentle warming may be necessary for non–lyophilized preparation.

Bacteriostatic water for injection (paraben preserved only) may be used; benzyl alcohol derivatives may NOT be used. May be further diluted in 100 - 250 mL of D_5W or NS for IV infusion.

ADMINISTRATION

IV.

TOXICITY

Myelosuppression, hemorrhagic cystitis, SIADH, fatigue, alopecia, anorexia, nausea, vomiting, azoospermia, amenorrhea, cardiotoxicity (myocardial necrosis) - with high doses (such as those used in PBSCT), anaphylaxis (rare).

Please refer to the package insert for a comprehensive list of adverse events.

DRUG INTERACTIONS

Cyclophosphamide undergoes metabolic activation via cytochrome P450 3A4 in the liver and may potentially interact with any drug affecting the same enzyme systems. Inhibitors of 3A4, e.g., itraconazole, could theoretically inhibit activation and inducers of 3A4, e.g., phenytoin, could theoretically enhance activation of cyclophosphamide to active alkylating species. For the most part, such interactions have not yet been documented clinically.

10.3 Cytarabine, Ara-C (Cytosine Arabinoside)

AVAILABILITY

Commercially available as a sterile powder for reconstitution in vials of 100 mg, 500 mg, 1000 mg, and 2000 mg, or a preservative free 20 mg/mL solution in 5 mL, 25 mL, and 50 mL vials, or a 100 mg/mL solution in 20 mL vials.

PREPARATION

Cytarabine powder is reconstituted with sterile water for injection or 0.9% sodium chloride for injection. Solutions reconstituted with bacteriostat should not be used for IV administration of high dose cytarabine (> 1 gm/m^2), as are used in this study. Solutions for parenteral administration should be reconstituted to a concentration of 100 mg/mL. Reconstituted solutions are further diluted in D_5W or 0.9% sodium chloride for IV infusion.

STORAGE & STABILITY

Intact vials should be stored at room temperature. Solutions reconstituted with bacteriostatic diluents are stable for 8 days at room temperature, but solutions without preservatives should be used within 8 hours.

ADMINISTRATION

Cytarabine will be administered intravenously over 2 hours in Course V for patients no undergoing transplant.

TOXICITY

The most common adverse reactions reported with cytarabine ("usual dosage" e.g., ≤ 200 mg/m^2/day) include hematologic, gastrointestinal, dermatologic, and hepatic. Myelosuppression

includes neutropenia, thrombocytopenia and anemia. Cytarabine is considered highly emetogenic. In addition to nausea and vomiting, diarrhea and mucositis are reported in > 10% of patients receiving cytarabine. Alopecia is common. Rash, including hand-foot syndrome, is reported also. Mild jaundice, and elevated transaminase levels also are reported in > 10% of patients. Fever (non-infectious) is also reported among the most common adverse reactions associated with cytarabine.

Less commonly, a "cytarabine syndrome" or "ara-C syndrome" has been reported. The syndrome may be characterized by fever, myalgia, bone pain, rash, malaise, and chest pain.

In addition to the above, the following adverse reactions have been described with high dose (≥ 1 gm/m^2/day) cytarabine. Neurologic toxicity is primarily cerebellar (nystagmus, dysarthria, dysdiadochokinesia, ataxia, abnormal gait) but cerebral toxicity (somnolence, confusion, psychosis, seizures) may also be seen. Ocular toxicity including photophobia and conjunctivitis are described with high dose cytarabine. Steroid ophthalmic solution should be administered, beginning 6-12 hours before cytarabine and continuing for 24 hours after the last "high dose", to prevent conjunctivitis. Pulmonary edema has been rarely reported in association with high dose cytarabine.

Please refer to the package insert for a comprehensive list of adverse events.

10.4 Dasatinib (Sprycel®) (IND #73969, NSC #732517)

AVAILABILITY

Dasatinib (Sprycel®) is available in 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, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, and polyethylene glycol (in the 20 mg tablets and 50 mg tablets).

AGENT ORDERING

NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and 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.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a

"current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

ACCOUNTABILITY

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, Agent-CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as a "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/default.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose 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 investigational 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 prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that 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 investigational 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. 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 Collaborator(s) for Phase 3 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 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:

   Regulatory Affairs Branch, CTEP, DCTD, NCI
   NCI Shady Grove
   Room 5W520, MSC 9740
   9609 Medical Center Drive
   Bethesda, Maryland 20892
   FAX 240-276-7894
   Email: ncicteppubs@mail.nih.gov

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

STORAGE & STABILITY

Store the intact bottles at controlled room temperature (15°C-25°C) and protect from light. Excursions are permitted up to 30°C. Shelf life testing of the intact bottles is on-going.

ADMINISTRATION

Oral. The tablets may be taken with or without a meal. Tablets should not be crushed or cut; they should be swallowed whole. Please refer to the protocol text for dasatinib doses during each course of therapy. During the first month, subjects will be instructed to take dasatinib in the morning. Subsequently, subjects may adjust the time they take dasatinib as long as they take the drug approximately every 24 hours. If a scheduled dose is missed for more than 12 hours or dosing is interrupted for toxicity or for any other reason, these doses should be omitted.

TOXICITY

Common adverse events with dasatinib are myelosuppression, bleeding events, fluid retention and QT prolongation. Treatment with dasatinib is associated with grade 3/4 thrombocytopenia, neutropenia and anemia. Myelosuppression is managed by dose interruption, dose reduction, or discontinuation. Dasatinib can cause platelet dysfunction in vitro and thrombocytopenia in humans. Severe CNS hemorrhage, including fatalities occurred in 1% of patients. Severe GI hemorrhage occurred in 7% of patients and generally required treatment interruptions and transfusions. Other cases of severe hemorrhage occurred in 4% of patients. Most bleeding events were associated with severe thrombocytopenia. Fluid retention was severe in 9% of patients,

including pleural and pericardial effusions reported in 5% and 1%, respectively. Severe ascites and generalized edema were each reported in 1%. Severe pulmonary edema was reported in 1% of patients. Patients who develop symptoms suggestive of pleural effusion (dyspnea or dry cough) should be evaluated by chest x-ray. Severe pleural effusion may require oxygen therapy and thoracentesis. Fluid retention is typically managed by supportive care measures that include diuretics or short courses of steroids. Dasatinib has the potential to prolong cardiac ventricular repolarization (QT interval). Dasatinib should be administered with caution in patients who have or may develop prolongation of QTc, including patients with hypokalemia, hypomagnesemia, or congenital long QT syndrome and patients taking anti-arrhythmic drugs or other medical products that lead to QT prolongation. Hypokalemia or hypomagnesemia should be corrected prior to dasatinib administration.

In October 2011, the FDA issued a Drug Safety Communication describing the risk of pulmonary arterial hypertension (PAH) associated with dasatinib. At least twelve cases of PAH have been confirmed by right heart catheterization (normal pulmonary capillary wedge pressure, but elevated pulmonary artery pressure) with dasatinb considered the most likely cause. The onset of PAH was variable, including the occurrence after more than one year of treatment. Symptoms of PAH include dyspnea, fatigue, hypoxia, and fluid retention. No fatalities were reported, and PAH may be reversible upon discontinuation of dasatinib. Because dasatinib is associated with other adverse events that can cause pulmonary symptoms, it is suggested that these other events (e.g., pleural effusion, pulmonary edema, anemia, lung infiltration) be ruled out prior to performing right heart catheterization.

POTENTIAL DRUG INTERACTIONS

Potent CYP3A4 inducers and inhibitors are prohibited on CALGB 10701. Dasatinib is primarily metabolized by the human CYP3A4 enzyme.

CYP3A4 substrates known to have a narrow therapeutic index should be administered with caution in patients receiving dasatinib.

Systemic antacids (both H2 receptor antagonists and proton pump inhibitors) are prohibited on CALGB 10701.

Dasatinib may prolong the QT/QTc interval. Use caution when administering dasatinib with other potential QTc-prolonging medications.

Due to the possibility of CNS, gastrointestinal, cardiac, and cutaneous hemorrhage, avoid using medications that inhibit platelet function or anticoagulants with dasatinib.

Long-term suppression of gastric acid secretion by use of H2 blockers or proton pump inhibitors (e.g., famotidine and omeprazole) is likely to reduce dasatinib exposure. Therefore, concomitant use of H2 blockers or proton pump inhibitors with dasatinib is not recommended. If antacid therapy is needed, the antacid dose should be administered at least 2 hours prior to or 2 hours after the dose of dasatinib.

Specifically in this study, tacrolimus is metabolized by CYP3A4 and dasatinib may inhibit tacrolimus metabolism. Patients who have undergone allogeneic transplant and are continuing to receive tacrolimus should be carefully monitored for a rise in tacrolimus levels and consequent toxicities, such as renal and hepatic toxicities, as well as myelosuppression.

Examples of substrates, inducers, and inhibitors of CYP3A4 may be found in Appendix III.

10.5 Daunorubicin

AVAILABILITY

Daunorubicin is commercially available (or available as required in non North American countries) as a powder for reconstitution in 20 mg vials, and in vials of solution at a concentration of 5 mg/mL in 20 mg vials. Please refer to the package insert for additional information.

PREPARATION

Reconstitute the 20 mg vial with 4 mL of sterile water for injection to attain a 5 mg/mL concentration.

Storage & Stability

Intact vials should be stored at room temperature. Reconstituted solutions are stable for 48 hours under refrigeration. Daunorubicin contains no preservative and should be used with 24 hours.

ADMINISTRATION

Give IV push or as a short IV infusion through a well-established IV site. AVOID EXTRAVASATION, as severe necrosis may result.

TOXICITY

The most common adverse reactions associated with daunorubicin include hematologic, gastrointestinal, and cardiovascular. Leukopenia and thrombocytopenia are often dose-limiting. Daunorubicin causes nausea and vomiting, but is generally considered moderately emetogenic. Stomatitis is also common. Acute cardiovascular reactions include EKG abnormalities which are usually asymptomatic and self-limiting. Chronic cardiomyopathy manifests as congestive heart failure. Risk factors include age (> 70 years), mediastinal irradiation and cumulative lifetime dose (e.g., > 450 mg/m^2). Dermatologic reactions (alopecia, "radiation recall") are also common.

Less common are red/orange urine (more alarming than of notable consequence to patients) and skin "flare." The flare consists of redness and itching along the distribution of the vessel through which daunorubicin was administered. It is usually self-limiting and of short duration, but should be distinguished from an extravasation reaction.

Extravasation of daunorubicin does not occur very often, but can result in severe skin and tissue necrosis. Cold should be applied to the site of a suspected or actual extravasation of daunorubicin.

10.6 Etoposide (VePesid®)

AVAILABILITY

Etoposide is commercially available in 5 mL, 7.5 mL, 25 mL, and 50 mL vials containing 20 mg/mL.

STORAGE & STABILITY

Unopened vials should be stored at room temperature and protected from light. Solutions of 0.2 or 0.4 mg/mL are stable for 96 and 24 hours, respectively, at room temperature under normal light.

PREPARATION

The dose of etoposide is usually diluted with D_5W or Normal Saline for Injection to a final concentration of no more than 0.4 mg/mL. If the volume required to prepare etoposide to ensure stability for a desired amount of time is too large, then drug should be given undiluted.

ADMINISTRATION

Etoposide will be administered via continuous intravenous infusion over 96 hours (mobilization for autologous transplant, and alternative chemotherapy in patients not undergoing transplant).

NOTE: DO NOT ADMINISTER CLOUDY OR PRECIPITATED DRUG.

TOXICITY

Myelosuppression, anorexia, nausea, vomiting (mildly emetogenic), alopecia, peripheral neuropathy, hypersensitivity reactions (chills, fever, bronchospasm, dyspnea, hypotension).

Please refer to the package insert for a comprehensive list of adverse events.

10.7 Fludarabine (Fludara®)

AVAILABILITY

Fludarabine is commercially available as a white, lyophilized powder. Each vial contains 50 mg of fludarabine phosphate, 50 mg of mannitol and sodium hydroxide to adjust pH.

STORAGE & STABILITY

Intact vials should be stored under refrigeration. Reconstituted vials are stable for 16 days at room temperature or under refrigeration. Solutions diluted in D_5W or NS are stable for 48 hours at room temperature or under refrigeration. Solutions of fludarabine phosphate contain no preservatives and should be used within 24 hours of reconstitution.

PREPARATION

Fludarabine should be reconstituted with 2 mL SWI. Each mL of the resulting solution will contain 25 mg of fludarabine, 25 mg of mannitol, and sodium hydroxide to adjust the pH to 7-8.5. The product should be further diluted for intravenous administration in 5% Dextrose for Injection, USP, or in 0.9% Sodium Chloride, USP.

ADMINISTRATION

Fludarabine will be administered IV over a period of 30 minutes. In this study, fludarabine will be administered prior to alemtuzumab for patients undergoing allo transplant in Course V.

TOXICITY

Myelosuppression (dose limiting toxicity), fever, mild nausea and/or vomiting, skin rashes, myalgia, fatigue, autoimmune hemolytic anemia (may be life threatening), peripheral neuropathy and pulmonary toxicity (both pneumonia and pulmonary hypersensitivity reactions have been reported; fatal pulmonary toxicity has been described, especially when fludarabine was used in combination with pentostatin). Severe fatal CNS toxicity presenting with loss of vision and progressive deterioration of mental status as encountered almost exclusively after very high doses of fludarabine. Such toxicity has only been rarely demonstrated at the 25-30 mg/m^2 dosage of fludarabine monophosphate. Very rarely described complications include transfusion-associated graft versus host disease, thrombotic thrombocytopenic purpura, and liver failure. Tumor lysis syndrome has been observed, especially in patients with advanced bulky disease. Opportunistic infections (protozoan, viral, fungal, and bacterial) have been observed.

10.8 Melphalan Hydrochloride (Alkeran®)

AVAILABILITY

Melphalan for IV use is commercially available in 50 mg vials. The product is a lyophilized powder with 20 mg povidone per vial. Also provided is 10 mL of diluent for use in reconstitution. The diluent contains 0.2 gm sodium citrate, 6 mL propylene glycol, 0.5 mL 95% ethanol, and sterile water.

STORAGE & STABILITY

Intact vials should be stored at room temperature (15-30ºC) and protected from light. Reconstituted solutions are chemically and physically stable for at least 90 minutes at room temperature. Solutions further diluted in 0.9% sodium chloride to a concentration of 0.1 mg/mL to 0.45 mg/mL are stable for at least 60 minutes. Solutions diluted to 1 mg/mL are reported to be physically stable for at least 4 hours at room temperature-chemical stability of this dilution is not known. Because of the relative instability of melphalan solutions, it is recommended that administration of the diluted solution be completed within 60 minutes of reconstitution. Reconstituted solutions should not be refrigerated.

PREPARATION

Melphalan should be prepared immediately before intended use. Each vial is reconstituted with 10 mL of the supplied diluent to yield a concentration of 5 mg/mL. The reconstituted solution may be diluted with 0.9% sodium chloride to a concentration of 0.1 mg/mL to 0.45 mg/mL. Alternatively, when the required concentration necessitates an unacceptable volume of fluid, the reconstituted solution may be administered undiluted.

ADMINISTRATION

Melphalan will be administered IV in patients undergoing autologous transplant in Course V.

TOXICITY

The major toxicity of melphalan is bone marrow suppression, usually lasting four to eight weeks. Other toxicities include venoocclusive disease, nausea, vomiting, and mucositis. Less common toxicities include pulmonary fibrosis, alopecia, and allergic reactions.

10.9 Methotrexate (Methotrexate Sodium; Amethopterin; MTX)

AVAILABILITY

Commercially available in 2.5 mg tablets, or 2 mL, 4 mL, 8 mL, 10 mL vials, containing 25 mg/mL, with or without preservative; and powder for reconstitution in 20 mg, 25 mg, 50 mg, 100 mg, 250 mg, or 1,000 mg vials.

STORAGE & STABILITY

Intact vials and tablets should be stored at room temperature and protected from light. Solutions for intrathecal use should be administered within 8 hours. Hydrocortisone and methotrexate may be mixed in the same syringe for IT administration. Solutions for IV administration are stable for 8 days, but for this study, they should be used sooner, since they do not contain preservative.

PREPARATION

IT: Reconstitute to a concentration of 1-5 mg/mL with an appropriate sterile, preservative-free medium.

IV: The 1 gm vial should be reconstituted with 19.4 mL of preservative free SWFI, saline or D_5W to a concentration of 50 mg/mL. Solutions should be further diluted in D_5W or NS for IV infusion.

ADMINISTRATION

Oral: Course IV.

IT: 15 mg mixed with 50 mg hydrocortisone (Course IV).

IV: Infusion over 3 hours; administer after IV hydration and urinary alkalinization (Course IV).

TOXICITY

Hematologic including leukopenia (1.5%), thrombocytopenia (5%) (nadir 5–12 days; recovery 15–27 days), anemia (nadir 6–13 days), pancytopenia (1.5%); gingivitis, glossitis, pharyngitis,

stomatitis, enteritis; nausea/vomiting, anorexia, diarrhea; hematemesis, melena; acute and chronic hepatotoxicity: reversible transaminase increase within 1–3 days after administration, hepatic fibrosis and cirrhosis with long term therapy; pulmonary toxicity including pneumonitis; pruritus, photosensitivity; CNS: seizures, dizziness, confusion; nephropathy: azotemia, renal failure; when administered IT may cause headache, back pain, rigidity.

Please refer to the package insert for a comprehensive list of adverse events.

DRUG INTERACTIONS

Sulfonamides, salicylates, penicillins, other organic acids, and proton pump inhibitors may interfere with renal elimination of methotrexate which can lead to enhanced toxicity.

10.10 Vincristine sulfate (VCR, Oncovin)

AVAILABILITY

Commercially available in 1, 2, and 5 mg vials containing 1 mg/mL.

Storage & Stability

Intact vials should be stored under refrigeration and protected from light.

PREPARATION

The desired volume (2 mL) should be withdrawn and injected into 0.9% NaCl for IV infusion, or administered as a bolus injection. Care must be taken to avoid inadvertent IT injection. The 2 mL volume may be further diluted to 30 mL with 0.9% NaCl in a syringe for bolus IV injection.

ADMINISTRATION

Note: The maximum single dose of vincristine IV bolus injection, prior to starting IV methotrexate infusion in this study is 2 mg.

Administer intravenously only. **Intrathecal administration is fatal.** Vincristine preparations must be wrapped and labeled with the following warnings: "**Fatal if given intrathecally.** For IV use only."

Vincristine is a vesicant which if extravasated can cause tissue necrosis. Inject over 1 minute through a freely flowing IV line or direct IV push after ensuring good blood return.

TOXICITY

Neurotoxicity including peripheral mixed sensorimotor neuropathy, loss of deep tendon reflexes, peripheral numbness, tingling and pain is the major and dose-limiting toxicity. May also see foot drop, cranial palsy, atrophy, ataxia, difficulty walking, jaw pain, and headaches. Also hoarseness and vocal cord paresis, optic or extraocular neuropathy and peripheral neuritis and neuralgia. Autonomic nervous system effects include severe constipation, abdominal cramps and ileus. Urinary retention, bladder atony, incontinence, orthostatic hypotension and myoclonal jerks may also occur. CNS effects may include mental status changes, seizures, progressive encephalopathy and coma. Rarely SIADH has been seen.

Please refer to the package insert for a comprehensive list of adverse events.

DRUG INTERACTIONS

Vincristine is metabolized by CYP3A4/3A5. Inhibitors of CYP3A4/3A5 can result in increased vincristine neurotoxicity. Multiple reports describe increases neurotoxicity (e.g., constipation) in patients receiving concurrent azole antifungals, especially itraconazole.

10.11 Dexamethasone (Decadron®)

AVAILABILITY

Dexamethasone is commercially available in 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, and 6 mg tablets, and in vials for injection at a concentration of 4 mg/mL or 10 mg/mL. Please refer to the agent's package insert for additional information.

STORAGE & STABILITY

Dexamethasone tablets and vials should be stored at room temperature.

ADMINISTRATION

Dexamethasone will be administered orally or by IV.

TOXICITY

Short-term use of dexamethasone (e.g., ≤ 4 weeks) may be associated with gastrointestinal side effects (dyspepsia, ulceration); insomnia, nervousness, and occasionally, psychosis; and hyperglycemia. Immunosuppression with increasing risk of infection also is seen. More prolonged use may be associated with, in addition to the above, muscle weakness and muscle wasting; osteoporosis and factures; hirsutism, acnea, skin atrophy, and easy bruising; sodium and water retention; adrenal suppression can occur with long term use necessitating tapering rather than abrupt discontinuation and the need for steroid coverage during stress. Occasionally a withdrawal syndrome manifest by muscle aches and pains is seen upon discontinuation, even following short-term use.

10.12 6-Mercaptopurine (6-MP, Purinethol, mercaptopurine)

AVAILABILITY

Commercially available as a scored 50 mg tablet.

Please refer to the FDA-approved package insert for 6-mercaptopurine for product information and a comprehensive list of adverse events.

STORAGE & STABILITY

Store at room temperature and protected from light.

ADMINISTRATION

Oral. Round daily dose to the nearest 25 mg (half tablet). Adjust daily doses so that the correct total dose is given each week of therapy. Note that absorption of 6-MP from the GI tract is variable and incomplete with a bioavailability of approximately 50%. Absorption is improved if given one-half hour before or 1 hour after meals. Concurrent milk products can decrease absorption and 6-MP effect is enhanced if given at bedtime on an empty stomach.

Patients with severe myelosuppression should have their thiopurine methyltransferase (TPMT) status and/or their thiopurine metabolite concentrations evaluated, so that the dose of 6-MP can be reduced in patients with a TPMT defect. Patients with the rare homozygous deficient TPMT phenotype may tolerate only 1/10 to 1/20th the average 6-MP dose. TPMT testing and thiopurine metabolite measurements are commercially available.

TOXICITY

Myelosuppression, primarily leukopenia and thrombocytopenia; GI toxicities include stomatitis, diarrhea, abdominal pain, nausea and vomiting; anorexia; hepatotoxicity, rash, and fever.

DRUG INTERACTIONS

Allopurinol - Do NOT give with mercaptopurine unless specifically allowed on protocol. Allopurinol, a xanthine oxidase inhibitor, will enhance the toxicity of 6-MP by inhibiting the

oxidative metabolism of 6-MP. If 6-MP is given with allopurinol the dose should be reduced to 25% to 33% of the planned dose of 6-MP initially with subsequent dosage based on patient response and toxicity.

10.13 Filgrastim (G-CSF: Granulocyte Colony-Stimulating Factor; Neupogen; recombinant-methionyl human granulocyte-colony stimulating factor; r-methHuG-CSF; filgrastim-sndz, Zarxio(R))

AVAILABILITY

G-CSF is commercially available in 1 mL and 1.6 mL vials containing 300 mcg or 480 mcg, and in pre-filled syringes containing 300 mcg/0.5 mL and 480 mcg/0.8 mL.

Storage & Stability

Intact vials and prefilled syringes should be stored under refrigeration. Do not allow the drug to freeze.

PREPARATION

The desired dose (rounded as described in the protocol) is withdrawn from a vial, or already available in a pre-filled syringe for injection. Filgrastim may be diluted in D_5W to a concentration ≥15 µg/mL for IV administration

ADMINISTRATION

The daily dose should be injected subcutaneously in one or two sites. If subcutaneous administration is not possible, filgrastim may be administered as a short IV infusion over 15-60 minutes.

TOXICITY

The most common adverse event associated with G-CSF is bone pain. Bone pain is usually reported as mild or moderate, and, if necessary, may be treated with non-opioid or opioid analgesics.

Please refer to the package insert for a comprehensive list of adverse events.

10.14 PEG-filgrastim

Please refer to the FDA-approved package insert for pegfilgrastim for product information and a comprehensive list of adverse events.

AVAILABILITY

Pegfilgrastim is commercially available as a preservative-free solution containing 6 mg/0.6 mL (concentration 10 mg/mL) of pegfilgrastim in a prefilled single-dose syringe.

STORAGE & STABILITY

Intact syringes should be stored under refrigeration and protected from light. Pegfilgrastim syringes are reportedly stable at room temperature for up to 48 hours prior to injection, if protected from light. Syringes that are frozen intentionally may be allowed to thaw in the refrigerator. Pegfilgrastim syringes that have been frozen a second time should be discarded.

ADMINISTRATION

Pegfilgrastim should be injected subcutaneously at a dose of 6 mg (0.6 mL). Pegfilgrastim will be administered only one time per course, 24 to 72 hours after completion of chemotherapy. If pegfilgrastim is given, the patient should not receive additional filgrastim.

TOXICITIES

The most common side effect associated with pegfilgrastim is bone pain. Bone pain is usually reported as mild or moderate, and, if necessary, may be treated with non-opioid or opioid analgesics.

Other reported side effects include reversible elevations in LDH, alkaline phosphatase and uric acid. These laboratory abnormalities are not usually of clinical significance and do not usually require any intervention.

10.15 Leucovorin Calcium (Citrovorum Factor, Folinic Acid, 5–Formyl Tetrahydrofolate)

AVAILABILITY

Leucovorin calcium is commercially available as a powder for reconstitution in 50 mg, 100 mg 200 mg, 350 mg, and 500 mg vials, and as a solution for injection in 500 mg vials (10 mg/mL). Leucovorin calcium is also available in 5 mg, 10 mg, 15 mg, and 25 mg tablets.

STORAGE & STABILITY

Intact vials and tablets should be stored at room temperature and protected from light. Reconstituted solutions prepared with bacteriostatic water are stable for at least 7 days at room temperature.

PREPARATION

Leucovorin powder may be reconstituted with SWFI or bacteriostatic water for injection.

ADMINISTRATION

The first dose of leucovorin will be given as a bolus IV injection or short IV infusion in D_5W or 0.9% NaCl. Subsequent doses will be administered orally. If oral administration is precluded, the subsequent doses can be given IV.

TOXICITY

The only adverse reaction is rare reports of allergic reactions to parenteral injections of leucovorin. However, these are extremely uncommon.

Please refer to the package insert for a comprehensive list of adverse events.

10.16 Co-trimoxazole (Trimethoprim-sulfamethoxazole, Bactrim®, Septra®, Cotrim, Sulfatrim)

AVAILABILITY

Commercially available as a single strength scored tablet containing 80 mg trimethoprim and 400 mg sulfamethoxazole, a double strength scored tablet containing 160 mg trimethoprim and 800 mg sulfamethoxazole, or an oral suspension containing 40 mg/5 mL of trimethoprim and 200 mg/5 mL of sulfamethoxazole.

STORAGE & STABILITY

Tablets and suspension should be stored at room temperature in airtight, light-resistant package.

ADMINISTRATION

Oral.

TOXICITY

Allergic reactions include epidermal necrolysis, exfoliative dermatitis, serum sickness, and Stevens-Johnson Syndrome (rare) and more commonly, mild to moderate skin rashes (erythematous, maculopapular, morbilliform and/or pruritic). GI: nausea, vomiting anorexia. Hematologic: myelosuppression, hemolysis (with G-6-PD deficiency). Miscellaneous: elevated liver function tests, fever, chills, renal toxicity, and rarely pulmonary infiltrates with cough and shortness of breath.

Please refer to the package insert for a comprehensive list of adverse events.

INTERACTIONS

Folate - Co-trimoxazole can enhance folate deficiency which can contribute to megaloblastic anemia or myelosuppression. Leucovorin may be given for serious bone marrow suppression to reverse this effect.

Warfarin - Co-trimoxazole may prolong prothrombin time by inhibiting metabolic clearance of warfarin. Monitor PT/INR and evidence of bleeding when these agents are used together.

10.17 Pentamidine Isethionate (NebuPent® - oral inhalation solution)

AVAILABILITY

Commercially available as a powder for reconstitution containing 300 mg of pentamidine isethionate for use with Respirgard® nebulizer.

PREPARATION

Reconstitute with 6 mL of SWFI. Place entire contents of vial in nebulizer reservoir for administration.

COMPATIBILITY

Saline will cause the drug to precipitate in the vial. Do not mix with any other drugs for inhalation.

STORAGE & STABILITY

Intact vials should be stored at room temperature. Reconstituted solutions are stable for 48 hours at room temperature. Use immediately upon preparation is recommended due to lack of preservatives in the solution.

ADMINISTRATION

Administer aerosolized pentamidine over 30 to 45 minutes. Pentamidine administration in this study is intended for PCP prophylaxis in patients unable to tolerate cotrimoxazole.

TOXICITIES

Cough (38%) and bronchospasm are the most common side effects associated with inhalation of pentamidine. Other effects associated with inhalation include pharyngitis, fatigue, chest pain. Other systemic effects which are also much less likely with inhalational therapy include hypotension, dizziness, maculopapular pruritic rash, hypoglycemia, hyperglycemia, gastrointestinal side effects, and increased liver function tests.

Please refer to the package insert for a comprehensive list of adverse events.

10.18 Tacrolimus (Prograf®)

AVAILABILITY

Tacrolimus is commercially available as an injection (5 mg/mL) and as oral capsules (0.5 mg, 1 mg, or 5 mg).

STORAGE & STABILITY

Store tacrolimus capsules and injection at controlled room temperature, 15-30°C (59-86°F).

PREPARATION

Tacrolimus injection must be diluted prior to IV infusion with 0.9% sodium chloride or 5% dextrose injection to a concentration of 0.004 to 0.02 mg/mL. Solutions should be prepared in non-PVC plastic or glass. Tacrolimus injection and diluted solutions of the drug should be

inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

ADMINISTRATION

Oral therapy should be started as soon as possible as per protocol and 12 hours after stopping intravenous therapy. Oral doses will be administered twice a day. IV tacrolimus may be administered as a continuous infusion or in divided doses every 12 hours.

TOXICITY

Most of the adverse event information described below comes from studies of tacrolimus in solid organ transplantation. In patients receiving tacrolimus, 5% to 47% experienced anemia, 8% to 32% experienced leukocytosis, and 14% to 24% experienced thrombocytopenia. Mild to moderate hypertension was reported in 38% to 50% of patients receiving tacrolimus. Chest pain was reported in 19%. Antihypertensive therapy may be required. The most common adverse effects of tacrolimus have involved the central nervous system, and include headache (37% to 64%), tremors (48% to 56%), insomnia (32% to 64%), paresthesia (17% to 40%); and dizziness (19%). Tremor and headache may respond to dosage reduction. Agitation, anxiety, confusion, seizures, depression, hallucinations, myoclonus, neuropathy, psychosis, incoordination, and abnormal dreams have been reported in 3% to 15% of tacrolimus-treated patients. Hyperkalemia (13% to 45%), hypokalemia (13% to 29%) hypophosphatemia (49%) and hypomagnesemia (16% to 48%) have been associated with tacrolimus therapy. In addition, hirsutism occurs only rarely with tacrolimus. Gastrointestinal adverse effects of tacrolimus have included nausea (32% to 46%), vomiting (14% to 29%), anorexia (7% to 34%), constipation (23% to 35%) and diarrhea (37% to 72%). Nephrotoxicity was reported in 36% to 40% and 52% of liver and kidney transplant patients receiving tacrolimus. Overt nephrotoxicity is usually seen early after transplantation and is characterized by an increased serum creatinine and a decrease in urine output. Hematuria has been reported in greater than 3% of tacrolimus-treated patients. Abnormal liver function tests have been reported in 6% to 36% of patients; ascites was reported in 7-27% of these patients.

Other miscellaneous effects that have occurred in clinical trials include pain (24% to 63%), fever (19% to 48%), back pain (17% to 30%), and peripheral edema (12% to 36%). The incidence of hyperglycemia is 17% and may require therapy with insulin. Other less frequently occurring effects (greater than 3%) include peritonitis, and photosensitivity reactions. Anaphylaxis has been reported in a few patients receiving intravenous tacrolimus.

DRUG INTERACTIONS

Tacrolimus is metabolized by cytochrome P450 3A4. Drugs that are inhibitors (e.g., itraconazole) or inducers (e.g., phenytoin) of 3A4 might increase or decrease tacrolimus concentrations respectively. This could result in increased or decreased effect of tacrolimus. Tacrolimus dose will be adjusted based on blood levels.

11.0 ANCILLARY THERAPY

Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate.

Treatment with hormones (other than the required dexamethasone) or other chemotherapeutic agents may not be administered except for steroids given for adrenal failure; and hormones administered for non-disease-related conditions (e.g., insulin for diabetes).

Palliative radiation therapy may not be administered except for whole-brain irradiation for documented CNS disease or testicular radiation for documented testicular involvement. Do not hold protocol chemotherapy during CNS irradiation.

11.1 Alliance Policy Concerning the Use of Growth Factors

The following guidelines are applicable unless otherwise specified in the protocol.

11.1.1 Epoetin (EPO)

Use of epoetin (epoetin, darbepoetin, EPO) in this protocol is permissible but not recommended. A baseline serum Epo level should be measured first.

11.1.2 Filgrastim (G-CSF), PEG-filgrastim, and sargramostim (GM-CSF)

1. Filgrastim (G-CSF) or PEG-filgrastim should be used as indicated in Course V.
2. For the treatment of febrile neutropenia the use of CSFs should not be routinely instituted as an adjunct to appropriate antibiotic therapy. However, the use of CSFs may be indicated in patients who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome) or fungal infection, as per the ASCO guidelines. Investigators should therefore use their own discretion in using the CSFs in this setting. The use of CSF (PEG-filgrastim, filgrastim or sargramostim) must be documented and reported on flow sheets.
3. When PEG-filgrastim, filgrastim or sargramostim are used, they must be obtained from commercial sources.

12.0 CRITERIA FOR RESPONSE, PROGRESSION, AND RELAPSE [43]

The assessment of response after treatment for acute leukemia requires a physical examination, complete blood count, platelet count, differential count, and bone marrow aspiration and biopsy. Extramedullary sites known to be involved by leukemia prior to treatment (e.g., mediastinal lymphadenopathy or CSF) must be reexamined as well. Immunophenotyping, cytochemistry, and cytogenetic analyses are supportive data for clinical assessment.

Investigators are cautioned that the bone marrow cytology and peripheral blood differential count in patients who are recovering from chemotherapy or who have received hematopoietic growth factors or cytokines may be shifted to immaturity, reflecting regenerating hematopoiesis; this should not be misinterpreted as residual or recurrent leukemia. Whenever the initial morphological result is ambiguous, a second bone marrow examination should be performed ≥ one week later, and confirmatory data should be gathered from cytogenetic analyses, immunophenotyping, or cytochemistry.

12.1 Complete Remission (CR)

A CR requires the following: an absolute neutrophil count (segs and bands) >1000/µL, no circulating blasts, platelets >100,000/µL; adequate bone marrow cellularity with trilineage hematopoiesis, and <5% marrow leukemia blast cells. All previous extramedullary manifestations of disease must be absent (e.g., lymphadenopathy, splenomegaly, skin or gum infiltration, testicular masses, or CNS involvement).

12.2 Complete Cytogenetic Remission (CCyR)

No clonal abnormal metaphase cells in ≥ 20 bone marrow karyotypes.

12.3 Complete Molecular Remission

No evidence of BCR/ABL transcripts in a Q-PCR assay with a sensitivity of 1:1000 or greater, typically performed on blood.

12.4 Major Molecular Remission

Ratio of BCR/ABL transcript to ABL transcript is ≤ 0.1% in a Q-PCR assay with a sensitivity of 1:1000 or greater, typically performed on blood.

12.5 Complete Remission with Incomplete Recovery of Counts (CRi)

CRi is identical to criteria for CR except for recovery of platelets <100,000/μL or recovery of ANC <1000/μL. Patients must be transfusion independent.

12.6 Partial Remission (PR)

A PR requires all of the CR criteria except that the marrow may still contain 5-25% leukemia blast cells. An absolute neutrophil count (segs and bands) > 1000/μL, no circulating blasts, and platelets > 100,000/μL are required as for a CR.

12.7 Refractory Disease

Failure to achieve a CR or PR with persistence of leukemia cells after treatment.

12.8 Progressive Disease

An increase of at least 25% in the absolute number of circulating or bone marrow leukemic blasts, or development of extramedullary disease.

12.9 Relapsed Disease

The reappearance of unequivocal leukemia blast cells in the blood or the bone marrow (>5%) or in the CNS (positive cytospin examination of CSF) or in any other extramedullary site after a CR; or progression to >25% leukemia blasts cells in the marrow after a PR.

13.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

13.1 Duration of Treatment

Day on Study	Clinical Status*†	Action
II-22	M_0, M_1	Proceed to course IV.
	M_2, M_3	Continue treatment (course III).
	relapse	Remove from protocol therapy.
III-29	M_0, M_1	Continue treatment.
	M_2, M_3, relapse	Remove from protocol therapy.
IV-43	M_0, M_1	Continue treatment.
	M_2, M_3, relapse	Remove from protocol therapy.
V-30	M_0, M_1	Continue treatment.
	M_2, M_3, relapse	Remove from protocol therapy.

* If marrow cellularity is inadequate for diagnosis, repeat weekly until determination can be made.

† Please see Appendix V for definitions of clinical status (i.e., M_0, M_1, etc.).

13.2 Relapse

Patients who achieve complete remission (M_0, M_1) will continue on protocol therapy until the appearance of hematologic relapse as defined by the reappearance of unequivocal leukemia blast cells in the blood or the bone marrow (>5%) or in the CNS (positive cytospin examination of CSF) or in any other extramedullary site after a CR; or progression to >25% leukemia blasts cells in the marrow after a PR. Cytogenetics, FISH, or Q-PCR may be useful to identify recurrent Ph+ ALL cells.

At the time of documented relapse, institutions should submit bone marrow or peripheral blood for institutional Q-PCR.

13.3 Extraordinary Medical Circumstances:

If, at any time the constraints of this protocol are detrimental to the patient's health or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy in patient records.
- Submit C-300 (Off Treatment Notice) and follow the data submission requirements, including submission of appropriate follow-up forms at time of relapse and death, as well as C-300, and C-113, as detailed in Sections 6.1 (Data Submission) and 7.0 (Required Data).
- Notify the Study Chair.
- Continue to follow the patient for relapse, second malignancies, and survival endpoints.

14.0 STATISTICAL CONSIDERATIONS

14.1 Statistical Objectives

The primary objective of this study is the construction of a historical database to provide leukemia investigators relevant baseline data useful for the design of follow-up studies in this rare patient population. Consequently, the primary statistical objectives of this protocol primarily relate to estimation rather than inference. More specifically, the primary statistical objective of this study is the estimation of the disease-free survival (DFS) at the three-year

landmark for the combined as well as each of the three individual patient cohorts. Disease-free survival (DFS) is measured from the date of first induction CR to relapse, or death due to any cause, with patients last known to be alive and disease-free censored at the date of last contact. The analysis population will consist of all eligible patients who receive at least one dose of dasatinib. The manuscripts reporting the results will report the effect of excluding any patients on the results.

A secondary clinical endpoint of this study is achievement of *BCR-ABL* negativity. The corresponding statistical endpoint of this study is the probability of being *BCR-ABL* negative in the bone marrow and peripheral blood in a CLIA-approved clinical laboratory at the completion of the CNS prophylaxis course (Course IV). Patients who discontinue the protocol-specified treatment before completing the CNS prophylaxis course on this study will be counted as non-responders (i.e., be qualified as not having reached *BCR-ABL* negative status). Another secondary clinical endpoint of this study will be the feasibility of maintenance therapy in this patient population. This analysis will be restricted to those patients achieving CR. For both secondary endpoints, the proportions will be estimated based on the combined and individual cohorts.

Other clinical endpoints of interest include overall survival, disease-free survival and response. All time-to-event distributions will be estimated using the Kaplan-Meier estimator. Proportions will be estimated using point as well as interval estimators. All interval estimators will be constructed using the finite sample size sampling distribution at the unadjusted two-sided level of 0.05.

For each endpoint, whenever scientifically plausible, the cohorts may be compared in an exploratory fashion. To this end, a three sample log-rank test will be used for time-to-event profiles and a randomized test for contingency will be used for binary outcomes. These tests will be conducted at the unadjusted 0.05 level.

14.2 Accrual Plan

We plan to evaluate 60 patients. Any eligible patient who receives at least one dose of dasatinib will be deemed evaluable in the sense of being included in the primary analyses. We may have to register up to 66 patients to meet this goal. As the projected accrual rate is 2 patients per month, the projected accrual period is 33 months. Given that the last patient may need to be followed for up to three years, the total projected study period is expected to last up to 69 (=33+36) months.

14.3 Study Monitoring

We will formally monitor, by virtue of using statistical decision rules, the following feasibility and safety endpoints for all treated patients. Each decision rule is designed so as to have high probability of early crossing if the probability of the realization of the event of concern is about an unacceptable threshold and a low probability of early crossing if the event probability is below an acceptable threshold.

1. Hematologic toxicity preventing administration of dasatinib at 70 mg BID during Courses I-IV. A drop-out rate exceeding 0.4 will be considered unacceptable. A drop-out rate of 0.2 will be considered acceptable. The decision rule and its operating characteristics are shown in Tables 1 and 5, respectively.
2. Dasatinib-related pleural effusion necessitating drainage (thoracentesis). A toxicity rate exceeding 0.3 will be considered unacceptable. A drop-out rate of 0.1 will be deemed acceptable. The decision rule and its operating characteristics are shown in Tables 2 and 6, respectively.

3. Dasatinib-related pericardial effusion necessitating drainage (pericardiocentesis). A toxicity rate exceeding 0.15 will be considered unacceptable. The decision rule and operating characteristics are shown in Tables 3 and 7, respectively.
4. Treatment-related mortality (TRM). A TRM rate exceeding 0.4 will be considered unacceptable. The decision rule and its operating characteristics are shown in Tables 4 and 8, respectively.

We will monitor the first 12, 24, 36, 48 and 60 patients. Monitoring will begin after the 12th patient completes Course V. If any of the bounds are crossed, we will initiate a review of the study to determine whether the study needs to be amended (for example, changing eligibility requirements or modifying the treatment regimens) or closed. In addition to the statistical decision rules, we will monitor the first twelve patients by holding regular teleconferences to be attended by the study investigators or their representatives, as well as the Alliance Protocol Operations Program Office and Alliance Statistics and Data Center. The first six patients will be monitored on a bi-weekly basis while the next six will be monitored on a monthly basis. Based on the results of the first interim analysis for feasibility and safety, we may decide to extend the teleconferences for the next 12 patients. These rules are primarily intended to help the study team to formally monitor the study from a safety and feasibility standpoint.

k	**1**	**2**	**3**	**4**	**5**
n_k	12	12	12	12	12
N_k	12	24	36	48	60
r_k	4	7	11	14	16

Table 1: Monitoring design for assessing the inability to administer dasatinib at 70 mg BID due to hematologic toxicity. The stage is denoted by k. The number of patients accrued during and up to stage k are denoted by n_k and N_k respectively. The critical value at stage k is denoted by r_k.

k	**1**	**2**	**3**	**4**	**5**
n_k	12	12	12	12	12
N_k	12	24	36	48	60
r_k	4	5	7	8	9

Table 2: Monitoring design for assessing pleural effusion necessitating drainage (thoracentesis). The stage is denoted by k. The number of patients accrued during and up to stage k are denoted by n_k and N_k respectively. The critical value at stage k is denoted by r_k.

k	**1**	**2**	**3**	**4**	**5**
n_k	12	12	12	12	12
N_k	12	24	36	48	60
r_k	2	3	4	5	6

Table 3: Monitoring design for assessing pericardial effusion necessitating drainage (pericardiocentesis). The stage is denoted by k. The number of patients accrued during and up to stage k are denoted by n_k and N_k respectively. The critical value at stage k is denoted by r_k.

k	**1**	**2**	**3**	**4**	**5**
n_k	12	12	12	12	12
N_k	12	24	36	48	60
r_k	4	7	11	14	16

Table 4: Monitoring design for assessing treatment related mortality. The stage is denoted by k. The number of patients accrued during and up to stage k are denoted by n_k and N_k respectively. The critical value at stage k is denoted by r_k.

p	p_1	p_2	p_3	p_4	p_5	Early Exit Probability	Exit Probability
0.20	0.205	0.073	0.012	0.012	0.027	0.303	0.330
0.30	0.507	0.177	0.045	0.051	0.073	0.780	0.852
0.40	0.775	0.152	0.031	0.023	0.014	0.980	0.994

Table 5: The operating characteristics for the monitoring rule illustrated in Table 1. The probability of not being able to administer dasatinib at 70 mg BID due to hematologic toxicity is denoted by p. The first exit probability at stage k is denoted by p_k. An "exit" would initiate a safety assessment. The probability of early exit is equal to $p_1+...+p_4$. The exit probability is equal to $p_1+...+p_5$.

p	p_1	p_2	p_3	p_4	p_5	Early Exit Probability	Exit Probability
0.10	0.026	0.065	0.021	0.038	0.044	0.150	0.195
0.20	0.205	0.344	0.120	0.137	0.088	0.806	0.894
0.30	0.507	0.385	0.067	0.032	0.007	0.991	0.998

Table 6: The operating characteristics for the monitoring rule illustrated in Table 2. The probability of experiencing an episode of pleural effusion necessitating drainage (thoracentesis) is denoted by p. The first exit probability at stage k is denoted by p_k. An "exit" would initiate a safety assessment. The probability of early exit is equal to $p_1+...+p_4$. The exit probability is equal to $p_1+...+p_5$.

P	p_1	p_2	p_3	p_4	p_5	Early Exit Probability	Exit Probability
0.05	0.118	0.051	0.028	0.017	0.011	0.215	0.226
0.10	0.341	0.160	0.096	0.065	0.048	0.662	0.710
0.15	0.557	0.205	0.098	0.053	0.031	0.913	0.944

Table 7: The operating characteristics for the monitoring rule illustrated in Table 3. The probability experiencing an episode of pericardial effusion necessitating drainage (pericardiocentesis). of not being able to administer dasatinib at 70 mg BID due to hematologic toxicity is denoted by p. The first exit probability at stage k is denoted by p_k. An "exit" would initiate a safety assessment. The probability of early exit is equal to $p_1+...+p_4$. The exit probability is equal to $p_1+...+p_5$.

P	p_1	p_2	p_3	p_4	p_5	Early Exit Probability	Exit Probability
0.20	0.205	0.073	0.012	0.012	0.027	0.303	0.330
0.30	0.507	0.177	0.045	0.051	0.073	0.780	0.852
0.40	0.775	0.152	0.031	0.023	0.014	0.980	0.994

Table 8: The operating characteristics for the monitoring rule illustrated in Table 4. The probability of experiencing a treatment-related mortality is denoted by p. The first exit probability at stage k is denoted by p_k. An "exit" would initiate a safety assessment. The probability of early exit is equal to $p_1+...+p_4$. The exit probability is equal to $p_1+...+p_5$.

14.4 CDUS

This study will be monitored by the Complete Clinical Data System (CDUS) Version 3.0. The Alliance Statistics and Data Center will submit quarterly reports to CTEP by electronic means using the Clinical Data Update System (CDUS).

15.0 WRITING COMMITTEE

A Writing Committee will be responsible for the publication of a manuscript that will describe the results of this study in a peer-reviewed journal. The members of this Writing Committee will be the co-authors of this manuscript, Dr. Wieduwilt, the Study Chair, will be the primary author; the CALGB 10701 Statistician will be the second author; and the Leukemia Committee Chair of the Alliance will be the senior (last) author.

The other members of the Writing Committee will be determined according to the level of participation in the study as measured by the patient accrual from each group. The number of investigators on the Writing Committee from each of the participating cooperative groups (Alliance, ECOG-ACRIN, and SWOG) will be based on the following accrual formula. Each Group enrolling 1-5% of the total number of patients accrued will nominate one member of the Writing Committee. Each group will be entitled to an additional member of the Writing Committee for each additional 10% of the overall accrual. For example, if a group enrolled 15% of the study patients, that group would have 2 co-authors on the Committee; if 25% of the study patients were enrolled, that group would have 3 co-authors. The Alliance will be assigned additional members of the Writing Committee only after that group accrues >15% of the total study patients. It will be the responsibility of each cooperative group to name the individual clinical or laboratory investigators to fill their allotted positions. By this method, it is anticipated that the final Writing Committee will include approximately 8-10 of the clinical and/or laboratory investigators who have been most involved in the design, conduct, and analysis of this study.

16.0 ADVERSE EVENT REPORTING (AER)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 to determine the severity of the reaction for adverse event reporting. All reactions determined to be "reportable" in an expedited manner must be reported using the CTEP Adverse Event Reporting System (CTEP-AERS). Reporting of cases of secondary AML/MDS/ALL is to be performed using CTEP-AERS. New primary malignancies should be reported using Study Form C-1001.

Expedited AE reporting for this study must use CTEP-AERS, accessed via the CTEP Web site (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov). These requirements are briefly outlined in the tables below.

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

16.1 CALGB 10701 Adverse Event Reporting Requirements

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

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

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

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

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

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

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions (see below).
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

16.2 Additional Instructions or Exclusion to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent Under a CTEP IND or non-CTEP IND:

- CALGB 10701 is conducted under a CTEP-held IND for dasatinib. Therefore, the reporting requirements for investigational agents under a CTEP-held IND should be followed for all enrolled patients.
- All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.
- A discussion of adverse events associated with agents used in this trial can be found in Section 10.0 (Drug Formulation, Availability, and Preparation). For the purposes of expedited adverse event reporting, the CAEPR for dasatinib may be found in Section 16.3. **Note**: that the ASAEL column of the CAEPR has been replaced with the specific protocol exceptions to expedited reporting (SPEER) list. This list now includes "expected" severity grades in addition to event terms."
- Grade 3/4 myelosuppression and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results. All other grade 3, 4, or 5 adverse events that precipitate hospitalization or prolong an existing hospitalization must be reported via CTEP-AERS.
- Grade 3/4 nausea or vomiting and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results. All other grade 3, 4, or 5 adverse events that precipitate hospitalization or prolong an existing hospitalization must be reported via CTEP-AERS.
- Grade 3/4 febrile neutropenia and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results. All other grade 3, 4, or 5 adverse events that precipitate hospitalization or prolong an existing hospitalization must be reported via CTEP-AERS.
- Grade 3/4 infection and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results. All other grade 3, 4, or 5 adverse events that precipitate hospitalization or prolong an existing hospitalization must be reported via CTEP-AERS.
- CTEP-AERS report should be submitted for creatinine level that doubles within a 24-hour period.

- CTEP-AERS report should be submitted if Course IV day 4, 18, or 32 serum methotrexate level is >0.05 µM.
- CTEP-AERS reports should be submitted electronically to the Alliance Protocol Operations Program Office (https://eapps-ctep.nci.nih.gov/ctepaers/).
- The reporting of adverse events described in the table above is in addition to and does not supplant the reporting of adverse events as part of the reporting of the results of the clinical trial, e.g., study summary forms, or cooperative group data reporting forms (see Section 6.1 for required forms).

16.3 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Dasatinib (BMS-354825, NSC 732517)

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 2937 patients.* Below is the CAEPR for Dasatinib (BMS-354825, Sprycel).

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 2.6, September 1, 2015[1]

Adverse Events with Possible Relationship to Dasatinib (BMS-354825, Sprycel) (CTCAE 4.0 Term) [n= 2937]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
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		***Abdominal pain (Gr 2)***
	Anal mucositis		
	Constipation		
Diarrhea			***Diarrhea (Gr 3)***
	Dyspepsia		
	Gastrointestinal hemorrhage[2]		
	Mucositis oral		

Adverse Events with Possible Relationship to Dasatinib (BMS-354825, Sprycel) (CTCAE 4.0 Term) [n= 2937]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
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 site conditions - Other (generalized edema)		
	General disorders and administration site conditions - Other (superficial edema)		***General disorders and administration site conditions - Other (superficial edema) (Gr 2)***
	Non-cardiac chest pain		
	Pain		
INFECTIONS AND INFESTATIONS			
	Infection[3]		***Infection[5] (Gr 3)***
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
		Electrocardiogram QT corrected interval prolonged	
Neutrophil count decreased			***Neutrophil count decreased (Gr 3)***
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		***Hypophosphatemia (Gr 3)***
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
Myalgia			***Myalgia (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		
Headache			***Headache (Gr 3)***
		Intracranial hemorrhage	
		Leukoencephalopathy	
		Reversible posterior leukoencephalopathy syndrome	

Adverse Events with Possible Relationship to Dasatinib (BMS-354825, Sprycel) (CTCAE 4.0 Term) [n= 2937]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
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		
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]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:

CARDIAC DISORDERS - Acute coronary syndrome; 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; Conjunctivitis; Dry eye; Eye disorders - Other (optic nerve neuritis)
GASTROINTESTINAL DISORDERS - Ascites; Colitis; Dry mouth; Dysphagia; Enterocolitis; Esophagitis; Flatulence; Gastritis; Gastrointestinal disorders - Other (anal fissure); Gastrointestinal disorders - Other (hematemesis); Gastrointestinal disorders - Other (mouth ulceration); Gastrointestinal disorders - Other (oral soft tissue disorder); Gastrointestinal disorders - Other (oropharyngeal pain); Gastrointestinal disorders - Other (tongue eruption); Gastrointestinal ulcer[4]; 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
INFECTIONS AND INFESTATIONS - Infections and infestations - Other (herpes virus infection)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising
INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; Cardiac troponin T increased; CD4 lymphocytes decreased; CPK increased; Creatinine increased; GGT increased; Investigations - Other (bone densitometry); Investigations - Other (EKG T-wave inversion); Investigations - Other (pancytopenia); 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; Musculoskeletal and connective tissue disorder - Other (epiphyses delayed fusion); Musculoskeletal and connective tissue disorder - Other (muscle spasm); Musculoskeletal and connective tissue disorder - Other (muscle stiffness); Musculoskeletal and connective tissue disorder - Other (nuchal rigidity); Musculoskeletal and connective tissue disorder - Other (rhabdomyolysis); Musculoskeletal and connective tissue disorder - Other (tendonitis); Myositis; Osteoporosis; Pain in extremity
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 - Gynecomastia; Irregular menstruation
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Bronchospasm; Epistaxis; Hypoxia; Pulmonary edema; Sore throat
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Bullous dermatitis; Dry skin; Hyperhidrosis; Nail loss; Pain of skin; Palmar-plantar erythrodysesthesia syndrome; Periorbital edema; Photosensitivity; Purpura; Skin and subcutaneous tissue disorders - Other (acute febrile neutrophilic dermatosis); Skin and subcutaneous tissue disorders - Other (hair color changes); 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.

16.4 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Alemtuzumab (NSC 715969)

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 Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with bold

and italicized text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the CTEP, NCI Guidelines for Adverse Event Reporting Requirements:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events

Frequency is provided based on 346 patients. Below is the CAEPR for alemtuzumab.

Version 2.1, March 23, 2010[1]

Adverse Events with Possible Relationship to Alemtuzumab (CTCAE 4.0 Term) [n= 346]			**EXPECTED AEs FOR CTEP-AERS REPORTING Agent Specific Adverse Event List (ASAEL)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	***Expected***
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia***
		Blood and lymphatic system disorders - Other (bone marrow aplasia)	
	Disseminated intravascular coagulation		
	Febrile neutropenia		***Febrile neutropenia***
		Hemolysis	
CARDIAC DISORDERS			
	Atrial fibrillation		
	Cardiac arrest		
		Left ventricular systolic dysfunction	
	Myocardial infarction		
	Sinus tachycardia		
	Ventricular arrhythmia		
	Ventricular tachycardia		
ENDOCRINE DISORDERS			
	Hyperthyroidism		
	Hypothyroidism		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		
	Diarrhea		
	Dyspepsia		
	Mucositis oral		
Nausea			***Nausea***
	Small intestinal mucositis		
Vomiting			***Vomiting***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Chills			***Chills***
	Edema limbs		
Fatigue			***Fatigue***
Fever			***Fever***
	Flu like symptoms		***Flu like symptoms***
	Injection site reaction		***Injection site reaction***

	Non-cardiac chest pain		
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		***Allergic reaction***
	Autoimmune disorder		
	Cytokine release syndrome		***Cytokine release syndrome***
	Serum sickness		
INFECTIONS AND INFESTATIONS			
	Infection[2]		***Infection[2]***
Infections and infestations – Other (Opportunistic infection with ≥Grade 2 Lymphopenia)			
INVESTIGATIONS			
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		
Lymphocyte count decreased			***Lymphocyte count decreased***
Neutrophil count decreased			***Neutrophil count decreased***
Platelet count decreased			***Platelet count decreased***
	White blood cell decreased		***White blood cell decreased***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia***
	Hypoalbuminemia		***Hypoalbuminemia***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthritis		
	Back pain		
	Generalized muscle weakness		
	Myalgia		***Myalgia***
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness***
	Dysgeusia		***Dysgeusia***
	Headache		***Headache***
	Peripheral sensory neuropathy		
PSYCHIATRIC DISORDERS			
	Insomnia		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Allergic rhinitis		***Allergic rhinitis***
	Bronchospasm		
	Cough		***Cough***
	Dyspnea		***Dyspnea***
	Hypoxia		***Hypoxia***
	Pneumonitis		
	Pulmonary edema		
	Stridor		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Pruritus		***Pruritus***
	Purpura		
	Rash acneiform[3]		
	Urticaria		***Urticaria***
VASCULAR DISORDERS			
	Flushing		***Flushing***
	Hypertension		
	Hypotension		***Hypotension***

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

[3] Also may include desquamation.

[4] 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.

[5] Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

[6] 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

Also reported on alemtuzumab trials but with the relationship to alemtuzumab still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (lymphadenopathy)
CARDIAC DISORDERS - Pericarditis
EAR AND LABYRINTH DISORDERS - Hearing impaired; Tinnitus
ENDOCRINE DISORDERS - Endocrine disorders - Other (aggravated diabetes mellitus)
EYE DISORDERS - Optic nerve disorder
GASTROINTESTINAL DISORDERS - Ascites; Colitis; Gastrointestinal hemorrhage[4]; Gastrointestinal perforation[5]; Gastrointestinal ulcer[6]; Pancreatitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Gait disturbance; General disorders and administration site conditions - Other (Goodpasture's syndrome); General disorders and administration site conditions - Other (Guillain-Barre syndrome); General disorders and administration site conditions - Other (Hemophagocytic syndrome); General disorders and administration site conditions - Other (Syndrome of Inappropriate Antidiuretic Hormone Secretion [SIADH])
INVESTIGATIONS - Blood bilirubin increased; Creatinine increased
METABOLISM AND NUTRITION DISORDERS - Acidosis; Dehydration; Hypercalcemia; Hyperglycemia; Hypocalcemia; Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Joint range of motion decreased; Musculoskeletal and connective tissue disorder - Other (muscle atrophy); Myositis
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Treatment related secondary malignancy
NERVOUS SYSTEM DISORDERS - Intracranial hemorrhage; Ischemia cerebrovascular; Leukoencephalopathy; Seizure; Syncope
PSYCHIATRIC DISORDERS - Agitation; Depression; Personality change; Psychosis
RENAL AND URINARY DISORDERS - Acute kidney injury; Renal and urinary disorders - Other (toxic nephropathy); Urinary frequency; Urinary retention; Urinary tract obstruction
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Erectile dysfunction; Reproductive system and breast disorders - Other (cervical dysplasia); Reproductive system and breast disorders - Other (ovarian failure)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Bronchial obstruction; Bronchopulmonary hemorrhage; Pulmonary fibrosis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythema multiforme
VASCULAR DISORDERS - Vascular disorders - Other (increased capillary fragility); Vascular disorders - Other (splenic infarction)

Note: Alemtuzumab 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.

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APPENDIX I: IDEAL BODY WEIGHT TABLE

	Height (Feet/Inch)	Small Frame (kg)	Medium Frame (kg)	Large Frame (kg)
MEN				
	5’2”	54	59	64
	5’3”	56	60	65
	5’4”	57	62	67
	5’5”	59	63	69
	5’6”	60	65	71
	5’7”	62	67	73
	5’8”	64	69	75
	5’9”	66	71	77
	5’10”	68	73	79
	5’11”	70	75	81
	6’0”	72	77	84
	6’1”	74	79	86
	6’2”	76	82	88
	6’3”	78	84	90
	6’4”	79	86	93
WOMEN				
	4’10”	45	49	54
	4’11”	46	50	55
	5’0”	47	51	57
	5’1”	49	53	58
	5’2”	50	54	59
	5’3”	51	55	61
	5’4”	53	57	63
	5’5”	54	59	64
	5’6”	56	61	66
	5’7”	58	63	68
	5’8”	59	65	70
	5’9”	61	67	72
	5’10”	64	69	74
	5’11”	65	70	76
	6’0”	67	72	79

APPENDIX II: GRAFT VERSUS HOST DISEASE GRADING

To assess graft versus host disease (GVHD), use the scale below rather than the NCI CTCAE.

I. Keystone Convention for Grading GVHD [44]

Organ Grade	Skin*	Bilirubin (mg/dL)	Gut Changes (diarrhea [mL/day])
1	Rash < 25%	2.0 - < 3.0	> 500 - 999 or biopsy-proven upper GI involvement
2	Rash 25-50%	3.1 - 6	≥ 1000 - < 1499
3	Rash > 50%	6.1 - 15	≥ 1500
4	Generalized erythroderma with bullae	> 15	Severe abdominal pain with or without ileus

Organ Grade (see table above)			
Skin	**Hepatic**	**Gut Changes**	**OVERALL GRADE**
1 or 2	0	0	1
1, 2, 3	1	1	2
2 or 3	2 or 3	2 or 3	3
Grade 4 toxicity in any organ system is considered overall Grade 4.			

* Use "rule of nines" to determine body surface area

II. Clinical Grading of Chronic GVHD

A. Limited Chronic GVHD:

1. Localized skin involvement,

and/or

2. Hepatic dysfunction due to chronic GVHD.

B. Extensive Chronic GVHD:

1. Generalized skin involvement,

or

2. Localized skin involvement and/or hepatic dysfunction due to chronic GVHD

Plus

3a. Liver histology showing chronic aggressive hepatitis, bridging necrosis, or cirrhosis, **or**

3b. Involvement of eye (Schirmer's test with less than 5 mm wetting), **or**

3c. Involvement of minor salivary glands or oral mucosa demonstrated on labial biopsy, **or**

3d. Involvement of any other target organ.

APPENDIX III: EXAMPLES OF SUBSTRATES, INDUCERS AND INHIBITORS OF CYP3A4

CYP3A4 Substrates

Albuterol	Dihydroergotamine	Isradipine	Quinidine
Alfentanil	Diltiazem	Itraconazole	Rabeprazole
Alprazolam	Disopyramide	Ketamine	Ranolazine
Amiodarone	Docetaxel	Ketoconazole	Repaglinide
Amlodipine	Doxepin	Lansoprazole	Rifabutin
Amprenavir	Doxorubicin	Letrozole	Ritonavir
Aprepitant	Doxycycline	Levonorgestrel	Salmeterol
Aripiprazole	Efavirenz	Lidocaine	Saquinavir
Atazanavir	Eletriptan	Losartan	Sibutramine
Atorvastatin	Enalapril	Lovastatin	Sildenafil
Benzphetamine	Eplerenone	Medroxyprogesterone	Simvastatin
Bisoprolol	Ergoloid mesylates	Mefloquine	Sirolimus
Bortezomib	Ergonovine	Mestranol	Spiramycin
Bosentan	Ergotamine	Methadone	Sufentanil
Bromazepam	Erythromycin	Methylergonovine	Sunitinib
Bromocriptine	Escitalopram	Methysergide	Tacrolimus
Budesonide	Estradiol	Miconazole	Tamoxifen
Buprenorphine	Estrogens, conj., synthetic	Midazolam	Tamsulosin
Buspirone	Estrogens, conj., equine	Miglustat	Telithromycin
Busulfan	Estrogens, conj., esterified	Mirtazapine	Teniposide
Carbamazepine	Estrone	Modafinil	Tetracycline
Cerivastatin	Estropipate	Montelukast	Theophylline
Chlordiazepoxide	Ethinyl estradiol	Moricizine	Tiagabine
Chloroquine	Ethosuximide	Nateglinide	Ticlopidine
Chlorpheniramine	Etoposide	Nefazodone	Tipranavir
Cilostazol	Exemestane	Nelfinavir	Tolterodine
Cisapride	Felbamate	Nevirapine	Toremifene
Citalopram	Felodipine	Nicardipine	Trazodone
Clarithromycin	Fentanyl	Nifedipine	Triazolam
Clobazam	Flurazepam	Nimodipine	Trimethoprim
Clonazepam	Flutamide	Nisoldipine	Trimipramine
Clorazepate	Fluticasone	Norethindrone	Troleandomycin
Cocaine	Fosamprenavir	Norgestrel	Vardenafil
Colchicine	Gefitinib	Ondansetron	Venlafaxine
Conivaptan	Haloperidol	Paclitaxel	Verapamil
Cyclophosphamide	Ifosfamide	Pergolide	Vinblastine
Cyclosporine	Imatinib	Phencyclidine	Vincristine
Dantrolene	Indinavir	Pimozide	Vinorelbine
Dapsone	Irinotecan	Pipotiazine	Zolpidem
Dasatinib (1)	Isosorbide	Primaquine	Zonisamide
Delavirdine	Isosorbide dinitrate	Progesterone	Zopiclone
Diazepam	Isosorbide mononitrate	Quetiapine	

CYP3A4 Inhibitors

Acetominophen	Diclofenac	Lomustine	Primaquine
Acetazolamide	Dihydroergotamine	Losartan	Progesterone
Amiodarone	Diltiazem	Lovastatin	Propofol
Amlodipine	Disulfiram	Mefloquine	Propoxyphene
Amprenavir	Docetaxel	Mestranol	Quinidine
Anastrozole	Doxorubicin	Methadone	Quinine
Aprepitant	Doxycycline	Methimazole	Quinupristin
Atazanavir	Drospirenone	Methoxsalen	Rabeprazole
Atorvastatin	Efavirenz	Methylprednisolone	Ranolazine
Azelastine	Enoxacin	Metronidazole	Risperidone
Azithromycin	Entacapone	Miconazole	Ritonavir
Betamethasone	Ergotamine	Midazolam	Saquinavir
Bortezomib	Erythromycin	Mifepristone	Selegiline
Bromocriptine	Ethinyl estradiol	Mirtazapine	Sertraline
Caffeine	Etoposide	Mitoxantrone	Sildenafil
Cerivastatin	Felodipine	Modafinil	Sirolimus
Chloramphenicol	Fentanyl	Nefazodone	Sulconazole
Chlorzoxazone	Fluconazole	Nelfinavir	Tacrolimus
Cimetidine	Fluoxetine	Nevirapine	Tamoxifen
Ciprofloxacin	Fluvastatin	Nicardipine	Telithromycin
Cisapride	Fluvoxamine	Nifedipine	Teniposide
Clarithromycin	Fosamprenavir	Nisoldipine	Testosterone
Clemastine	Glyburide	Nizatidine	Tetracycline
Clofazimine	Grapefruit juice (2)	Norfloxacin	Ticlopidine
Clotrimazole	Haloperidol	Olanzapine	Tranylcypromine
Clozapine	Hydralazine	Omeprazole	Trazodone
Cocaine	Ifosfamide	Orphenadrine	Troleandomycin
Conivaptan	Imatinib	Oxybutynin	Valproic acid
Cyclophosphamide	Indinavir	Paroxetine	Venlafaxine
Cyclosporine	Irbesartan	Pentamidine	Verapamil
Danazol	Isoniazid	Pergolide	Vinblastine
Dasatinib (1)	Isradipine	Phencyclidine	Vincristine
Delavirdine	Itraconazole	Pilocarpine	Vinorelbine
Desipramine	Ketoconazole	Pimozide	Voriconazole
Dexmedetomidine	Lansoprazole	Pravastatin	Zafirlukast
Diazepam	Lidocaine	Prednisolone	Ziprasidone

CYP3A4 Inducers

Aminoglutethimide	Nevirapine	Phenytoin	Rifapentine
Carbamazepine	Oxcarbazepine	Primidone	St. John's wort (3)
Fosphenytoin	Pentobarbital	Rifabutin	
Nafcillin	Phenobarbital	Rifampin	

When drugs classified as 'substrates' are co-administered with *(Study Agent)*, there is the potential for higher concentrations of the 'substrate'. When *(Study Agent)* is co-administered with compounds classified as 'inhibitors', increased plasma concentrations of *(Study Agent)* is the potential outcome. The co-administration of 'inducers' would potentially lower plasma *(Study Agent)* concentrations.

Note: Adapted from Cytochrome P450 Enzymes: Substrates, Inhibitors, and Inducers. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 15TH ed. Hudson, OH; LexiComp Inc. 2007: 1899-1912.
Only major substrates and effective inducers are listed.
Additional information for drug interactions with cytochrome P450 isoenzymes can be found at http://medicine.iupui.edu/flockhart/.

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Updated on May 1, 2007

APPENDIX IV: PATIENT INSTRUCTION SHEET

Course IV Drug Administration Schedule

After Course III if there is no evidence of persistent leukemia in your bone marrow, that is, your bone marrow shows a remission from leukemia, you will receive a course of treatment, referred to as "Course IV" to try to further prevent recurrence of your leukemia. This treatment is specifically designed to decrease the risk of leukemia recurring in the brain and spinal cord (the central nervous system), known sites of recurrence in patients with your disease. After you have recovered sufficiently from Course III the following chemotherapy drugs will be given during the next month of therapy:

The following is meant to serve as a schedule of when chemotherapy drugs are to be given during Course IV.

	For Example	Actual Date & Time:	Instructions
Day 1	Monday at 9 AM:		Vincristine in clinic.
	Monday at 9 AM-12 PM:		Intravenous (IV) Methotrexate in clinic. During IV Methotrexate, Intrathecal Methotrexate will be given in clinic.
	Monday at 3 PM:		Begin Oral Methotrexate.
	Monday at 9 PM:		Oral Methotrexate at home.
Day 2	Tuesday at 3 AM:		Oral Methotrexate at home.
	Tuesday at 9 AM:		Oral Methotrexate at home.
	Tuesday at 3 PM:		Return to clinic for blood sample. Intravenous Leucovorin in clinic.
Day 3	Wednesday at 3 AM:		Oral Leucovorin at home.
	Wednesday at 9 AM:		Oral Leucovorin at home.
	Wednesday at 3 PM:		Oral Leucovorin at home.
	Wednesday at 9 PM:		Oral Leucovorin at home.
Day 4	Thursday at 3 AM:		Oral Leucovorin at home.
	Thursday at 9 AM:		Oral Leucovorin at home.
	Thursday at 3 PM:		Oral Leucovorin at home.
	Thursday at 9 PM:		Oral Leucovorin at home.
	Thursday:		Return to clinic for blood sample at any time during the day on Thursday. Oral Leucovorin will be stopped depending on results of blood sample.

In addition to the drugs discussed above, an oral antibiotic, known as Bactrim® will be taken. One Bactrim tablet will be taken twice daily for three days every week to prevent Pneumocystis pneumonia. If you are allergic to this medication, a different antibiotic (pentamidine) can be prescribed.

Bactrim should be stopped 3 days before and resumed 3 days after each dose of methotrexate.

APPENDIX V A: CRITERIA FOR EVALUATING ACUTE LEUKEMIA

(Excerpted from the June 1974 Modification of the December 1969 Criteria)

Category M-Bone Marrow

Specify Marrow Cellularity

Marrow cellularity is to be defined as follows (for purposes of judging toxicity and response):

0 Aplastic (severely hypocellular) bone marrow
1+ Hypocellular bone marrow
2+ Normocellular bone marrow
3+ Hypercellular bone marrow
4+ Packed (intensely hypercellular bone marrow)

It is recognized that assessment of marrow cellularity based on aspiration alone is not always accurate. Where the aspirates are normocellular, further investigation of cellularity is not indicated. When the pretreatment marrow is hypocellular or when decisions concerning further therapy hinge on whether or not hypocellular aspirate is truly representative, marrow biopsy should be done.

	TYPE OF LEUKEMIA			
	Acute Lymphocytic		Acute Myelocytic	
Rating	Blast Cells (%)*	Lymphocytes & Blast Cells (%)	Blast Cells (%)**	Blast Cells & Promyelocytes (%)
M_0	0 - 5.0	0 - 40.0	0 - 5.0	0 - 10.0
M_1	0 - 5.0	0 - 40.0	0 - 5.0	0 -10.0
M_2	5.1 - 25.0	40.1 - 70.0	5.1 - 25.0	10.1 - 30.0
M_{2x}	0 - 25.0	< 70.0	0 - 25.0	0 - 30.0
M_3	25.0 - 50.0	> 70.0	25.0 - 50.0	30.1 - 55.0
M_4	> 50.0		> 50.0	> 55.0

* The term "blast cell" includes any cell which cannot be classified as a more mature normal element, and includes "leukemic cells," pathologic lymphocytes, and stem cells.

** The term "blast cell" includes any cell which cannot be classified as a more mature normal element, and includes "leukemic cells," nucleolated granulated cells, and monocytoid leukemic cells. It does not include pathologic erythroid cells.

APPENDIX V B: CRITERIA FOR EVALUATING ACUTE LEUKEMIA

(Excerpted from the June 1974 Modification of the December 1969 Criteria)

Category H-Hemogram

Rating	Hemoglobin M	Hemoglobin F	Neutrophilic Granulocytes/µl**	Blasts* %	Platelets/µl
H_0	≥ 14	≥ 13	≥ 3,500	0	≥ 200,000
H_1	≥ 12	≥ 11	≥ 2,000†	0	100 - 199,000
H_2	≥ 9.0		≥ 500	≤ 5	50 - 99,000
H_3	7.0 - 8.9		≥ 500	5.1 - 20	25 - 49,000
H_4	< 7.0		< 500	> 20	< 25,000

* In acute lymphocytic leukemia, the term blast cell includes any cell which cannot be classified as a more mature normal element and includes "leukemic cells," "pathologic lymphocytes," and stem cells.

In acute myelocytic leukemia, the term blast cell includes any cell which cannot be classified as a more mature normal element and includes "leukemic cells," nucleolated cells, monocytoid leukemic cells and promyelocytes.

** Term here includes segmented polys, stabs, and metamyelocytes.

† And at least 50% of total number of leukocytes.

Overall "H" rating is to be determined by the worst subcategory present; i.e., hemogram cannot be considered H_0 if any subcategory worse than 0, cannot be H_1 if any subcategory worse than 1, etc.

Ratings indicating improvement in an "H" category must not be ascribable to transfusion of any blood elements.

Mononuclear cells must not exceed 5000 cells/cm^2 (7000 for patients <4 years) for an H_0, H_1 rating.

The appearance of 1 or 2% blast cells on an isolated count does not preclude an H_1 rating but cannot be allowed in an H_0 rating.