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TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS
FROM: Sandi Jo Fredette, Protocol Coordinator (E-mail: sfredette@swog.org)
RE: **S0805**, "Phase II Study of Combination of Hyper-CVAD and Dasatinib with or without allogeneic stem cell transplant in Patients with Philadelphia (Ph) Chromosome Positive and/or Bcr-Abl Positive Acute Lymphoblastic Leukemia (ALL) (A BMT Study)." Study Chairs: Drs. F. Ravandi, S.M. O'Brien, S.J. Forman, C.S. Ha, and J.P. Radich.

REVISION #15

Study Chair: Farhad Ravandi, M.D.
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IRB Review Requirements

- () Full board review required. Reason:
 - () Initial activation (should your institution choose to participate)
 - () Increased risk to patient
 - () Complete study redesign
 - () Addition of tissue banking requirements
 - () Study closure due to new risk information
- () Expedited review allowed
- () No review required

REVISION #15

1. The Version Date of the protocol and Model Consent Form have been updated.
2. Pages 4-5, Table of Contents: The page numbers after Page 105 have been updated.
3. Throughout the protocol, NCI's Adverse Event Expedited Reporting System (AdEERS) has been updated to CTEP's Adverse Event Reporting System (CTEP-AERS). This change takes place in Sections 3.1 (Page 11), 8.6 (Page 72) and 16.1 (Pages 101-104). Associated web links on these pages have also been updated.
4. Throughout the protocol, references to the Physician's Desk Reference (PDF) have been removed. This change takes place in Sections 3.0 (Page 11), 3.2c (Page 19), 3.3c (Page 20), 3.4c (Page 21), 3.5c (Page 22), 3.6c (Page 25), 3.7c (Page 26), 3.8c (Page 27), 3.9c (Page 28), 3.12c (Page 35), 3.13c (Page 40), 3.14c (Page 43) and 3.15c (Page 44) .

5. Page 66, Section 7.7c.4: "Study Coordinator" has been updated to "Study Chair".
6. Page 73, Section 9.1: A missing X has been added in the cycle 1 column of the CNS prophylaxis row.
7. Page 100, Section 16.0: A new standard confidentiality statement has been added.
8. Page 102, Table 16.1 and Section 16.1e: The table and related information below it have been updated to the current standard
9. Pages 104-105, Sections 16.1h and 16.1i: The information for reporting secondary AML/ALL/MDS has been updated to the current standard in Section 16.1h. Section 16.1i has been add to include reporting requirements for pregnancy, fetal death and neonatal death. This addition has caused the addition of a new Page 105. Subsequent pages have been renumbered accordingly.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
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CLOSED EFFECTIVE 10/21/2013

PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY

S0805
Activated September 1, 2009

SWOG

PHASE II STUDY OF COMBINATION OF HYPER-CVAD AND DASATINIB (NSC-732517) WITH OR WITHOUT ALLOGENEIC STEM CELL TRANSPLANT IN PATIENTS WITH PHILADELPHIA (Ph) CHROMOSOME POSITIVE AND/OR BCR-ABL POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) (A BMT STUDY)

PARTICIPANTS: REGISTRATION STEPS 1, 2 AND 4: ALL SWOG MEMBER, CCOP, AFFILIATE MEDICAL ONCOLOGISTS AND PATHOLOGISTS, BMT CTN; CTSU
REGISTRATION STEP 3: ALL SWOG APPROVED ALLOGENEIC BONE MARROW TRANSPLANT FACILITIES
(See <https://swog.org/Members/download/miscellaneous/BMTFacilList.pdf>); BMT CTN APPROVED BONE MARROW TRANSPLANT FACILITIES (see [Appendix 18.10](#)); ECOG APPROVED BONE MARROW TRANSPLANT FACILITIES (see <http://ecog.org/ecoginst/transplant.html>); CALGB APPROVED BONE MARROW TRANSPLANT FACILITIES (see www.ctsu.org)

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AGENTS:

NIC Supplied Investigational Agents:
BMS-354825 (Dasatinib[®], Sprycel[™])
(NSC-732517) (IND-73969)

IND Exempt Agents:
Cyclophosphamide (Cytoxan[®]) (NSC-26271)
Cytosine Arabinoside (Ara-C, Cytarabine, Cytosar U) (NSC-63878)
Dexamethasone (Decadron) (NSC-34521)
Doxorubicin (Adriamycin) (NSC-123127)
Filgrastim (r-metHuG-CSF, Amgen[®])
(NSC-614629)
Leucovorin Calcium (NSC-3590)
Mesna (NSC-113891)
Methotrexate (NSC-740)
Methylprednisolone (NSC-19987)
Pegfilgrastim (Neulasta[™]) (NSC-725961)
Prednisone (NSC-10023)
Sirolimus (rapamycin, Rapamune[®])
(NSC-226080)
Tacrolimus (FK-506, Fujimycin, Prograf)
(NSC-717865)
Vincristine (NSC-67574)

9.0	STUDY CALENDAR	72
9.1	Induction/Consolidation Therapy - Registration Step 1	73
9.2	Maintenance Therapy - Registration Step 2	75
9.3	Allogeneic Stem Cell Transplant - Registration Step 3.....	77
9.4	Single-Agent Dasatinib Therapy - Registration Step 4	78
10.0	CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS	80
10.1	Complete remission (CR).....	80
10.2	Complete remission (Cri)	80
10.3	Partial remission (PR)	80
10.4	Treatment Failures	80
10.5	Relapse from CR or CRi	81
10.6	Relapse-free Survival (RFS)	81
10.7	Continuous Complete Remission (CCR) at 18 months	81
10.8	Overall survival (OS).....	81
10.9	Toxicity Criteria	81
10.10	Performance Status:.....	82
11.0	STATISTICAL CONSIDERATIONS	82
11.1	Primary Chemotherapy Objective	82
11.2	Secondary Analysis.....	83
11.3	Prognostic Significance.....	83
11.4	Eligibility	83
11.5	Distributions	83
11.6	Expected Accrual	84
11.7	Data and Safety Monitoring Committee	84
12.0	DISCIPLINE REVIEW	84
12.1	Quality Assurance Documentation.....	84
13.0	REGISTRATION GUIDELINES	86
13.1	Registration Timing	86
13.2	Investigator/Site Registration	86
13.3	OPEN Registration Requirements	86
13.4	Registration Procedures.....	88
13.5	Exceptions to SWOG registration policies will not be permitted.....	88
14.0	DATA SUBMISSION SCHEDULE	89
14.1	Data Submission Requirement	89
14.2	Master Forms	89
14.3	Data Submission Procedures	89
14.4	BMT CTN, ECOG and CALGB Institutions	90
14.5	Data Submission Overview and Timepoints	90
15.0	SPECIAL INSTRUCTIONS	93
15.1	Southwest Oncology Group and Blood and Marrow Transplant Clinical Trials Network and Other Sites Not Affiliated with ECOG or CALGB:	93
15.2	Eastern Cooperative Oncology Group.....	94
15.3	Cancer and Leukemia Group B	97
16.0	ETHICAL AND REGULATORY CONSIDERATIONS	99
16.1	Adverse Event Reporting Requirements.....	101
17.0	BIBLIOGRAPHY	106
18.0	APPENDIX	108
18.1	Determination of Expedited Adverse Event Reporting Requirements.....	109
18.2	Patient Transplant Conditioning Regimens.....	111
18.3	Total Body Irradiation Guidelines	113
18.4	Graft Versus Host Disease (GVHD) Prophylaxis.....	115
18.5	Sample Tapering Schedules for Sirolimus and Tacrolimus	117
18.6	Recommended BMT Leucovorin Rescue Schema	118
18.7	Guidelines for Simultaneous Use of Sirolimus and Oral Voriconazole.....	119
18.8	Intake Calendar	121

18.9 Drug Order Form Templates 122
18.10 Blood and Marrow Transplant Clinical Trials Network (BMT CTN) Approved Transplant
Facilities 133
18.11 Drugs Known to be Metabolized by CYP450 Isoenzymes 2D6 and 3A4 134
18.12 Acute GVHD Staging and Grading (adapted from BMT CTN Technical Manual of
Procedures Version 2.0 dated September 16, 2005) 138

CLOSED EFFECTIVE 10/01/2013

3.0 DRUG INFORMATION

Investigator's Brochures

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

For this study, cyclophosphamide, cytarabine, dexamethasone, doxorubicin, filgrastim, leucovorin, mesna, methotrexate, methylprednisolone, pegfilgrastim, prednisone, sirolimus, tacrolimus and vincristine are commercially available; therefore, Investigator Brochures are not applicable to these drugs. Information about commercial drugs is publicly available in the prescribing information and other resources.

For this study, dasatinib is investigational and is being provided under an IND held by the National Cancer Institute. The Investigator's Brochures may be obtained by contacting the NCI's Pharmaceutical Management Branch (PMB) at 240/276-6575.

3.1 BMS-354825 (Dasatinib®, Sprycel™) (NSC-732517) (IND-73969)

a. DESCRIPTION

Chemical name: N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide, monohydrate

Other names: Dasatinib®, Sprycel™

Molecular Formula: C₂₂H₂₆ClN₇O₂S·H₂O

Molecular Weight: monohydrate 506.02, anhydrous free base: 488.01

Approximate Solubility: BMS-354825 is slightly soluble in ethanol (USP), methanol, polyethylene glycol 400, and propylene glycol. It is very slightly soluble in acetone and acetonitrile, practically insoluble in corn oil, and insoluble in water.

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

b. TOXICOLOGY

The following is a description of major adverse events associated with BMS-354825 therapy. A list of Comprehensive Adverse Events and Potential Risks (CAEPR) in NCI-CTCAE Version 4.0 terms is listed below.

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

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted

administration, the anesthesiologist should be alerted. Adrenal insufficiency may be worsened with cyclophosphamide. Cyclophosphamide is excreted in breast milk, and it is advised that mothers discontinue nursing during cyclophosphamide administration. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

c. PHARMACOLOGY

Kinetics: Cyclophosphamide is activated principally in the liver by a mixed function microsomal oxidase system. PO administration is well absorbed, with bioavailability greater than 75%. Five to twenty-five percent of unchanged drug is excreted in the urine. Several active and inactive metabolites have been identified with variable plasma protein binding. There appears to be no evidence of clinical toxicity in patients with renal failure, although elevated levels of metabolites have been observed.

Formulation: Cyclophosphamide is supplied in 100 mg, 200 mg, 500 mg, 1 gram and 2 gram vials as a white powder. The drug should be reconstituted with Sterile Water for Injection, USP, and may be diluted in either normal saline or D5W.

Storage and Stability: Although the reconstituted cyclophosphamide is stable for six days under refrigeration, it contains no preservatives and therefore should be used within 6 hours.

Administration: For this study cyclophosphamide should be diluted in about 150-300 cc of normal saline or D5W and infused by IV over 3 hours. An added dose of IV fluids may help prevent bladder toxicity.

Supplier: Cyclophosphamide is commercially available and should be purchased by a third party. This drug will not be supplied by the NCI.

Please refer to the package insert for complete information.

3.3 Cytosine Arabinoside (Ara-C)(Cytarabine)(Cytosar U)(NSC-63878)

a. DESCRIPTION

AraC is chemically 4-amino-1-S-D-arabino-furanosyl-2(1H)-primidinone. AraC is metabolized to its active form, ara-CTP. The ara-CTP functions as an inhibitor of DNA polymerase. Ara-C exhibits cell phase specificity, killing cells undergoing DNA synthesis (S phase) and may also block cells from progressing to S phase from G1. Extensive chromosomal damage, including chromatid breaks, occurs. AraC appears to be most effective in tumors with high growth fraction.

b. TOXICOLOGY

Human Toxicology: Side effects of AraC include myelosuppression, nausea, vomiting, diarrhea, anorexia, anal ulceration, stomatitis, rash, headache, fever, myalgia, malaise, bone pain, chest pain, hepatic and renal dysfunction, and alopecia. Central nervous system toxicity, i.e., significant cerebral and cerebellar, dysfunction, progression to coma, has been seen with high doses. Severe cardiomyopathy has been reported with high dose AraC in combination with cyclophosphamide. Progressive ascending paralysis has occurred in two patients receiving IV and intrathecal ara-C. Marked keratoconjunctivitis has also occurred with high doses.

The most frequently reported reactions after intrathecal administration were nausea, vomiting and fever. Paraplegia and meningitis has been reported with intrathecal administration. AraC given intrathecally may cause systemic toxicity and careful monitoring of the hemopoietic system is indicated. If used intrathecally or if high dose therapy is used, do not use a diluent containing benzyl alcohol.

AraC can cause fetal harm when administered to a pregnant woman, however, there are no adequate and well controlled studies in pregnant women.

c. PHARMACOLOGY

Kinetics: AraC is metabolized by deoxycytidine kinase and related kinases to nucleotide triphosphate, which is an active inhibitor of DNA polymerase. Deoxycytidine prevents or delays cytotoxic activity. The active form is converted to nontoxic uracil derivatives by pyrimidine nucleoside deaminases. The balance of kinase and deaminase levels appears to be an important factor in sensitivity/resistance of the cell to AraC. After IV injection, plasma disappearance of ara-C is biphasic. Initial half-life is 10 minutes, delayed half-life is 1 - 3 hours. After 24 hours, 80% is excreted in the urine as its inactive metabolite, AraI. After a single IV administration of AraC, levels in CSF are low. With intrathecal administration, half-life is 2 hours. There is little conversion to AraU because of low CSF levels of diaminase. Drug interaction of AraC has been reported with digoxin, gentamycin and fluorocytosine.

Formulation: AraC is supplied as a sterile powder in 100 mg and 500 mg vials for injection. AraC is also available in 1 and 2 gram vials. The drug should be reconstituted with sterile water for injection.

Storage and Stability: The sterile powder should be stored at room temperature 15° - 30°C (59° - 86°). The resulting solution has a stability of 48 hours if stored at ROOM TEMPERATURE. Do not use if even a slight haze develops. The reconstituted solution may be further diluted in 5% Dextrose or sodium chloride injection.

Administration: For this study AraC is administered by IV infusion over 2 hours.

Supplier: AraC is commercially available and therefore should be purchased by a third party. This drug will NOT be supplied by the NCI.

Please refer to the package insert for complete information.

3.4 Dexamethasone (Decadron) (NSC-34521)

a. DESCRIPTION

Dexamethasone (Decadron) is a synthetic adrenocortical steroid and is readily absorbed from the gastrointestinal tract. Chemically, dexamethasone is 9-fluoro-11b, 17, 21-trihydroxy-16a-methyl-pregna-1, 4-diene-3, 20-dione.

b. TOXICOLOGY

Human Toxicology: Possible adverse effects associated with the use of dexamethasone are: fluid and electrolyte disturbances, congestive heart failure in susceptible persons, hypertension, euphoria, personality changes, insomnia, exacerbation of infection (e.g., tuberculosis), exacerbation or symptoms of

diabetes, psychosis, muscle weakness, osteoporosis, vertebral compression fractures, pancreatitis, esophagitis, peptic ulcer, dermatologic disturbances, convulsions, vertigo and headache, endocrine abnormalities, ophthalmic changes, and metabolic changes. Some patients have experienced itching and other allergic, anaphylactic or other hypersensitivity reactions. Withdrawal from prolonged therapy may result in symptoms including fever, myalgia and arthralgia. Phenytoin phenobarbital and ephedrine enhance metabolic clearance of corticosteroids.

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

c. PHARMACOLOGY

Kinetics: Natural and synthetic glucocorticoids are readily and completely absorbed from the GI tract. Dexamethasone is insoluble in water. Glucocorticoids have salt-retaining properties, although dexamethasone nearly completely lacks this property. Dexamethasone may suppress the body's response to viral and bacterial infections. Equivalent doses are as follows:

Dexamethasone	Methyl-prednisolone and Triamcinolone	Prednisolone and Prednisone	Hydrocortisone	Cortisone
0.75 mg	4 mg	5 mg	20 mg	25 mg

Formulation: Dexamethasone is available in seven potencies (0.25 mg, 0.5 mg, 0.75 mg, 1.5 mg, 2 mg, 4 mg, and 6 mg) tablet form.

Storage and Stability: Dexamethasone is to be stored at room temperature.

Administration: For this study dexamethasone may be administered orally or by IV.

Supplier: Dexamethasone is commercially available and therefore is to be purchased by a third party. This drug will not be supplied by the NCI.

Please refer to the package insert for complete information.

3.5 Doxorubicin (Adriamycin) (NSC-123127)

a. DESCRIPTION

Mechanism of Action: Doxorubicin is a cytotoxic anthracycline antibiotic different from daunorubicin by the presence of a hydroxyl group in the C-14 position. Doxorubicin is produced by fermentation from *S. Peucetius* var. *caesius*. Its mechanism of action is thought to be the binding of nucleic acids, preventing DNA and possibly RNA synthesis.

b. TOXICOLOGY

Human Toxicology: Studies with doxorubicin have shown that the major toxic effects of this drug are alopecia, which is often total but always reversible; nausea and vomiting, which develops shortly after drug administration, occasionally persisting for 2 - 3 days; fever on the day of administration; and phlebitis at the site of the drug's injection. Extravasation of the drug will lead to soft tissue necrosis. Phlebosclerosis, cellulitis, vesication and erythematous streaking have also been seen. Mucositis may be seen 5 - 10 days after administration. Ulceration and necrosis of the colon, particularly the cecum, with bleeding and severe infection have been reported with concomitant administration of cytarabine. Anorexia and diarrhea have also been observed. Hyperpigmentation of nailbeds and dermal creases, onycholysis and recall of skin reaction from prior radiotherapy may occur. Cardiac toxicity manifested as acute left ventricular failure, congestive heart failure, arrhythmia or severe cardiomyopathy has been reported, but appears to occur predominantly in patients who receive total doses in excess of 550 mg/M². Myelosuppression, predominantly neutropenia, is common with nadir occurring approximately two weeks after a single injection; lesser degrees of anemia and thrombocytopenia have been reported. Rapid recovery of the blood counts approximately two and a half weeks after a single injection generally permits an every three week schedule. Patients with obstructive liver disease have more severe myelosuppression due to impaired drug excretion. Thus, patients with hepatic dysfunction may need to have reduced dosage or to be excluded from therapy. Renal excretion of doxorubicin is minimal, but enough to color the urine red; thus impaired renal function does not appear to increase the toxicity of doxorubicin. Other side effects include fever, chills, facial flushing, itching, anaphylaxis, conjunctivitis and lacrimation. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

c. PHARMACOLOGY

Kinetics: Intravenous administration is followed by a rapid plasma clearance with significant tissue binding. Urinary excretion is negligible; biliary excretion accounts for 40 to 50% of the administered dose being recovered in the bile or the feces in 7 days. The drug does not cross the blood-brain barrier.

Formulation: Doxorubicin is supplied in 10, 20 and 50 mg single-use vials, and 150 mg multidose vials as a red-orange, lyophilized powder which has a storage stability of at least two years - see expiration date on vial. Doxorubicin should be reconstituted with 5, 10, 25 and 75 ml respectively, of Sodium Chloride Injection, USP (0.9%) to give a final concentration of 2 mg/ml.

Storage and Stability: The reconstituted doxorubicin is stable for 24 hours at room temperature and 48 hours under refrigeration (2°-8°C). It should be protected from exposure to sunlight. Discard any unused solution from the vials. Bacteriostatic diluents with preservatives are NOT recommended as they might possibly worsen the reaction to extravasated drug.

Administration: Doxorubicin may be further diluted in 5% dextrose or sodium chloride injection and should be administered slowly into tubing of a freely flowing intravenous infusion over 24 hours with great care taken to avoid extravasation.

Supplier: This drug is commercially available for purchase by a third party. This drug will not be supplied by the NCI.

Please refer to the package insert for complete information.

c. PHARMACOLOGY

Formulation: Filgrastim (Neupogen®) is supplied as a sterile, clear, colorless preservative-free liquid for parenteral administration. Filgrastim is available in single use vials and prefilled syringes. The single use vials contain either 300 mcg or 480 mcg filgrastim at a fill volume of 1 mL or 1.6 mL, respectively. The single use prefilled syringes contain either 300 mcg or 480 mcg filgrastim at a fill volume of 0.5 mL or 0.8 mL, respectively. See table below for product composition of each single use vial or prefilled syringe.

	300 mcg/ 1 mL vial	480 mcg/ 1.6 mL vial	300 mcg/ 0.5 mL syringe	480 mcg/ 0.8 mL syringe
Filgrastim	300 mcg	480 mcg	300 mcg	480 mcg
Acetate	0.59 mg	0.94 mg	0.295 mg	0.472 mg
Sorbitol	50 mg	80 mg	25 mg	40 mg
Tween® 80	0.004%	0.004%	0.004%	0.004%
Sodium	0.035 mg	0.056 mg	0.0175 mg	0.028 mg
Water for injection USP q.s. ad	1 mL	1.6 mL	0.5 mL	0.8 mL

Dilution: If required, filgrastim may be diluted in 5% dextrose. Filgrastim diluted to concentrations between 5 and 15 mcg/mL should be protected from adsorption to plastic materials by addition of albumin (human) to a final concentration of 2 mg/mL. When diluted in 5% dextrose or 5% dextrose plus albumin (human), filgrastim is compatible with glass bottles, PVC and polyolefin IV bags, and polypropylene syringes. Dilution of filgrastim to a final concentration of less than 5 mcg/mL is not recommended at any time. **Do not dilute with saline at any time; product may precipitate.**

Storage and Stability: Filgrastim should be stored in the refrigerator at 2-8°C (36-46°F). Do not freeze. Avoid shaking. Prior to injection, filgrastim may be allowed to reach room temperature for a maximum of 24 hours. Any vial or prefilled syringe left at room temperature for greater than 24 hours should be discarded. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit; if particulates or discoloration are observed, the container should not be used.

Administration: Filgrastim is administered by subcutaneous bolus injection.

Supplier: Filgrastim is commercially available, and should therefore be purchased by a third party. This drug will NOT be supplied by the NCI.

Please refer to the package insert for complete information.

3.7 Leucovorin Calcium (NSC-3590)

a. DESCRIPTION

Leucovorin is a mixture of the diastereoisomers of 5-formyl derivative of tetrahydrofolic acid. The active component is the (-)-L-isomer known as Citrovorum factor. It is useful as an antidote to drugs which act as folic acid antagonists, e.g., methotrexate.

b. TOXICOLOGY

Human Toxicology: Allergic sensitization (including anaphylactoid reactions and urticaria) to leucovorin has been reported. In large doses, leucovorin may counteract the antiepileptic effect of phenobarbitol, phenytoin and primidone and increase the frequency of seizures in susceptible children. Leucovorin may enhance the toxicity of fluorouracil. Deaths from severe enterocolitis, diarrhea, and dehydration have been reported in elderly patients receiving weekly leucovorin and fluorouracil. Concomitant granulocytopenia and fever were also present in some of the patients.

c. PHARMACOLOGY

Kinetics: Leucovorin is rapidly absorbed from the gastrointestinal tract after oral administration and enters the general body pool of reduced folates. Serum folate half-disappearance time is around 3.5 hours. Oral tablets yielded areas under the serum folate concentration-time curves (AUCs) that were 12% greater than equal amounts of leucovorin given intramuscularly and equal to the same amounts given intravenously. After IV administration, peak concentration was at 10 minutes. Terminal half-life of its active metabolite, 5-methyl derivative, was 6.2 hours. IM administration revealed similar terminal half-life.

Formulation: Leucovorin is provided in vials containing cryodesiccated/leucovorin calcium powder which is reconstituted in sterile diluent.

Storage and Stability: Store dry powder, reconstituted solution and tablets at controlled room temperature. Protect from light. When reconstituted with Bacteriostatic Water for Injection, the resulting solution must be used within seven days. If reconstituted with Sterile Water for Injection, use immediately and discard any unused portion. Because of the benzyl alcohol contained in Bacteriostatic Water for Injection, when doses greater than 10 mg/m² are administered, Sterile Water for Injection should be used.

Administration: For this study, leucovorin will be administered by IV.

Supplier: Leucovorin is commercially available, and should therefore be purchased by a third party. This drug will NOT be supplied by the NCI.

PLEASE REFER TO THE PACKAGE INSERT FOR COMPLETE INFORMATION.

3.8 Mesna (NSC-113891)

a. DESCRIPTION

Sodium-2-mercaptoethanesulfonate (Mesnex). The active ingredient is a synthetic sulfhydryl compound. It is considered a detoxifying agent inhibiting the hemorrhagic cystitis induced by ifosfamide.

b. TOXICOLOGY

Human Toxicity: Mesna may cause local venous irritation. Other toxicities include: headache, nausea, vomiting, fatigue, diarrhea, hypotension, allergy, limb pain, and bad taste in mouth. A false positive test for urinary ketones may arise in patients treated with mesna; a red-violet color develops which, with addition of glacial acetic acid, returns to violet.

c. PHARMACOLOGY

Kinetics: This sulfhydryl compound, is highly useful in regional detoxification of the oxazaphosphorine derivatives, including cyclophosphamide and ifosfamide (IFF). Following a single dose of oxazaphosphorine derivatives to the rat, urinary bladder damage was observed within 24 hours. Administration of the sulfhydryl simultaneously with the cytostatics resulted in prevention of cystitis in accordance with the dosage employed. The urotoxic dosage of IFF (68.1 mg/kg) was protected against by treatment with 21.5 mg/kg of the sulfhydryl. Inactive as the dimesna form in the circulation, mesna is reactivated in the kidney. Thus, mesna does not appear to interfere with the antitumor effect of ifosfamide. Because mesna has a short half life (\approx 2 hours) and IFF a considerably longer half life of 7 hours, mesna must be continued after IFF is discontinued.

Formulation: Injection 100 mg/ml. Each ml of solution contains disodium edetate, 0.25 mg and sodium hydroxide to adjust to pH 6.5 to 8.5 in water for injection. The product is supplied in 10 ml multidose vials.

Storage: Store intact vials at controlled room temperature (15 to 30°C). Diluted solutions are chemically and physically stable for at least 24 hours at 25°C.

Stability: Mesna bears an expiration date. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. When exposed to oxygen, mesna is oxidized to dimesna.

Administration: For this study mesna will be given by IV continuous infusion over 24 hours.

Supplier: Mesna is commercially available and should be purchased through a third party. This drug will no longer be supplied by the NCI.

Please refer to the package insert for complete information.

3.9 Methotrexate (NSC-740)

a. DESCRIPTION

Methotrexate is an antimetabolite and has as its principal mechanism of action the competitive inhibition of dihydrofolate reductase.

b. TOXICOLOGY

Human Toxicology: Adverse reactions include mucositis (gingivitis, pharyngitis, stomatitis, enteritis, hematemesis, melena and ulceration), nausea, vomiting, diarrhea, anorexia, myelosuppression, skin rashes, itching, hives, photosensitivity, pigmentation changes, alopecia, ecchymosis, acne, telangiectasia, furunculosis, malaise, fatigue, chills, fever, dizziness, headache, blurred vision, decreased resistance to infection, impaired renal function (including cystitis, azotemia, hematuria and acute renal failure), hepatotoxicity (including elevated transaminase, fibrosis and cirrhosis), and pulmonary toxicity (including death from interstitial pneumonitis and chronic interstitial obstructive pulmonary disease). Pulmonary symptoms (especially a dry, nonproductive cough) may require interruption of treatment and special investigation. Central nervous system toxicities have included headache, drowsiness, blurred vision, aphasia, hemiparesis, paresis, convulsions, transient subtle cognitive dysfunction, mood alteration and unusual cranial sensations.

Leukoencephalopathy may occur in patients who have had cranial irradiation. Toxicity is directly related to duration of blood levels. Because the drug is excreted in the urine, impaired renal function is usually a contraindication to its use. Calcium leucovorin must be administered after high-dose methotrexate to prevent life threatening toxicity. Other potential toxicities include reproductive dysfunctions (defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, vaginal discharge, infertility), opportunistic infection, loss of libido, myalgia, arthralgia, diabetes, osteoporosis, tinnitus, eye discomfort, epistaxis, sweating and sudden death. A few cases of anaphylactoid reactions have been reported. Patients with a known hypersensitivity to methotrexate should not receive the drug. Fetal death and/or congenital anomalies have been reported. Women of childbearing potential should be cautioned. Unexpectedly severe (sometimes fatal) marrow suppression and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high doses) along with some non-steroidal anti-inflammatory drugs. METHOTREXATE FORMULATIONS AND DILUENTS CONTAINING PRESERVATIVES MUST NOT BE USED FOR INTRATHECAL OR HIGH-DOSE METHOTREXATE THERAPY.

c. PHARMACOLOGY

Kinetics: Oral absorption appears to be dose dependent. The absorption of doses greater than 80 mg/M² is significantly less than lower doses. Methotrexate in serum is approximately fifty percent protein-bound. It does not penetrate the blood-brain barrier. Terminal half-life is 3 - 10 hours for doses less than 30 mg/m² and 8 - 15 hours with higher doses. With intravenous administration, 80 - 90% of unchanged methotrexate is excreted in the urine within 24 hours. Ten percent or less is excreted in the bile.

Formulation: Methotrexate is available as the sodium salt for parenteral use in 50 mg and 1 g vials as the lyophilized powder. Liquid methotrexate sodium injection products.

Storage and Stability: Methotrexate should be stored as the dry powder at room temperature (15 - 25° C) and protected from light.

Administration: For this study methotrexate will be given by IV over 22 hours. Methotrexate should be reconstituted immediately prior to use with an appropriate preservative-free medium such as Sodium Chloride Injection, USP. It may be further diluted in 5% Dextrose in Water, USP. For intraventricular use, follow manufacturer's guidelines for reconstitution to a concentration of 25 mg/ml.

Supplier: This drug is commercially available for purchase by a third party. This drug will not be supplied by the NCI.

Please refer to the package insert for complete information.

3.10 Methylprednisolone (NSC-19987)

a. DESCRIPTION

Methylprednisolone and its derivatives, methylprednisolone sodium succinate and methylprednisolone acetate, are synthetic glucocorticoids used orally or parenterally as antiinflammatory or immunosuppressive agents. These drugs have very little mineralocorticoid activity and are therefore not used to manage adrenal insufficiency unless a more potent mineralocorticoid is administered concomitantly.

experienced itching and other allergic, anaphylactic or other hypersensitivity reactions. Withdrawal from prolonged therapy may result in symptoms including fever, myalgia and arthralgia. Phenytoin, phenobarbital, and ephedrine enhance metabolic clearance of corticosteroids.

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

c. PHARMACOLOGY

Kinetics: Natural and synthetic glucocorticoids are readily and completely absorbed from the GI tract. Prednisone is very slightly soluble in water. Glucocorticoids have salt-retaining properties. The anti-inflammatory property of this drug is its ability to modify the body's immune system. On the other hand, glucocorticoids suppress the body's response to viral as well as bacterial infections. Equivalent doses are as follows:

Dexamethasone	Methyl-prednisolone Cortisone and Triamcinolone	Prednisolone and Prednisone	Hydrocortisone	
0.75 mg	4 mg	5 mg	20 mg	25 mg

Formulation: Prednisone is available in 2.5 mg, 5 mg, 10 mg, 20 mg and 50 mg tablets.

Storage and Stability: Prednisone should be stored at room temperature.

Administration: Prednisone is administered orally.

Supplier: Prednisone is commercially available and should be purchased by third party. Prednisone will not be supplied by the NCI.

Please refer to the package insert for complete information.

3.13 Sirolimus (rapamycin)(Rapamune®) (NSC-226080)

a. DESCRIPTION

Chemistry: Sirolimus is an immunosuppressive agent. Sirolimus is a macrocyclic lactone produced by *Sreptomyces hygroscopicus*. Its molecular formula is C₅₁H₇₉NO₁₃ and its molecular weight is 914.2.

Sirolimus is a white to off-white powder and is insoluble in water, but freely soluble in benzyl alcohol, chloroform, acetone, and acetonitrile.

Supplier: Rapamune is commercially available and should be obtained through a third party. This drug will not be supplied by the NCI.

Please refer to the package insert for complete information.

3.14 Tacrolimus (Protopic[®]) (FK506) (Prograf) (Fujimycin)

a. DESCRIPTION

Chemistry: Tacrolimus is an immunosuppressant agent. Its molecular formula is $C_{44}H_{69}NO_{12}H_2O$ and its molecular weight is 822.03. Tacrolimus appears as white crystals or crystalline powder. It is practically insoluble in water, freely soluble in ethanol, and very soluble in methanol and chloroform.

b. TOXICOLOGY

Adverse Reactions: $\geq 15\%$

Cardiovascular: Chest pain, hypertension, pericardial effusion (heart transplant)
CNS: Dizziness, headache, insomnia, tremor (headache and tremor are associated with high whole blood concentrations and may respond to decreased dosage (15-55%))
Dermatologic: Pruritus, rash
Endocrine & metabolic: Diabetes mellitus, hyperglycemia, hyperkalemia (8-45%) (Since tacrolimus may cause hyperkalemia, potassium-sparing diuretics should be avoided), hypokalemia hyperlipemia, hypomagnesemia, hypophosphatemia
GI: Abdominal pain, constipation, diarrhea, dyspepsia, nausea, vomiting
Genitourinary: Urinary tract infection
Hematologic: Anemia, leukocytosis, leukopenia, thrombocytopenia
Hepatic: Ascites
Neuromuscular & skeletal: Arthralgia, back pain, paresthesia, tremor, weakness
Renal: Abnormal kidney function (nephrotoxicity (36-59%), BUN increased, creatinine increased, oliguria, urinary tract infection
Respiratory: Atelectasis, bronchitis, dyspnea, increased cough, pleural effusion
Miscellaneous: CMV infection, infection < 15%
Cardiovascular: Abnormal ECG (QRS or ST segment abnormal), angina pectoris, cardiopulmonary failure, deep thrombophlebitis, heart rate decreased, hemorrhage, hemorrhagic stroke, hypovolemia, hypotension, generalized edema, peripheral vascular disorder, phlebitis, postural hypotension, tachycardia, thrombosis, vasodilation
CNS: Abnormal dreams, abnormal thinking, agitation, amnesia, anxiety, chills, confusion, depression, elevated mood, emotional lability, encephalopathy, hallucinations, nervousness, paralysis, psychosis, quadriparesis, seizure, somnolence
Dermatologic: Acne, alopecia, cellulitis, exfoliative dermatitis, fungal dermatitis, hirsutism, increased diaphoresis, photosensitivity reaction, skin discoloration, skin disorder, skin ulcer
GI: Anorexia, appetite increased, cramps, duodenitis, dysphagia, enlarged abdomen, esophagitis (including ulcerative), flatulence, gastritis, gastroesophagitis, GI perforation/hemorrhage, ileus, oral moniliasis, pancreatic pseudocyst, rectal disorder, stomatitis, weight gain

Protein binding: 99%

Metabolism: Extensively hepatic via CYP 3A4 to eight possible metabolites (major metabolite, 31-demethyl tacrolimus, shows same activity as tacrolimus in vitro)

Bioavailability: Oral: Adults: 7-28%, Children: 10-52%

Half-life elimination: Variable, 21-61 hours in healthy volunteers

Time to peak: 0.5-4 hours

Excretion: Feces (~92%), feces/urine (< 1% as unchanged drug)

Formulation: Tacrolimus is available as a sterile solution (tacrolimus injection) containing the equivalent of 5 mg anhydrous tacrolimus in 1 mL for administration by intravenous infusion only. Each mL contains polyoxyl 60 hydrogenated castor oil (HCO-60), 200 mg, and dehydrated alcohol, USP, 80.0% v/v. Tacrolimus injection must be diluted with 0.9% Sodium Chloride Injection or 5% Dextrose Injection before use. Tacrolimus injection must be diluted with 0.9% Sodium Chloride Injection or 5% Dextrose Injection to a concentration between 0.004 mg/mL and 0.02 mg/mL prior to use.

Storage and Stability: Diluted infusion solution should be stored in glass or polyethylene containers and should be discarded after 24 hours. The diluted infusion solution should not be stored in a PVC container due to decreased stability and the potential for extraction of phthalates. In situations where more dilute solutions are utilized (e.g., pediatric dosing, etc.), PVC-free tubing should likewise be used to minimize the potential for significant drug adsorption onto the tubing. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Due to the chemical instability of tacrolimus in alkaline media, tacrolimus injection should not be mixed or co-infused with solutions of pH 9 or greater (e.g., ganciclovir or acyclovir).

Administration: For this protocol, tacrolimus will be administered by IV.

Supplier: Tacrolimus is commercially available and should be obtained through a third party. This drug will not be supplied by the NCI.

Please refer to the package insert for complete information.

3.15 Vincristine (Oncovin) (NSC-67574)

a. DESCRIPTION

Chemistry: Vincristine is one of the so-called vinca-alkaloids and is extracted from the plant cantharanthus roseus (vinca rosea).

Biochemistry: This drug appears to produce the arrest of mitosis in animal cells by interfering with microtubule function.

b. TOXICOLOGY

Human Toxicology: The primary toxic effects of vincristine are neurological with paresthesia, weakness, muscle wasting, motor difficulties including difficulty walking and slapping gait, loss of deep tendon reflexes, sensory loss, neuritic pain, paralytic ileus, bladder atony, and constipation. Rarely, it produces myelosuppression. Other side effects may include alopecia, allergic reactions, (including rare anaphylaxis, rash and edema), jaw pain, hypertension,

hypotension, nausea, vomiting, diarrhea, fever, headache, oral ulceration, optic atrophy with blindness, ptosis, diplopia and photophobia. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

c. PHARMACOLOGY

Kinetics: After IV administration, a triphasic serum decay pattern follows with half-lives of 5 minutes, 2-3 hours, and 85 hours. The range of terminal half-life is 19-155 hours. Excretion is 80% in the feces and 10-20 % in the urine.

The liver is the major excretory organ in humans and animals, and biliary obstruction causes increased toxicity in man.

Formulation: 1 mg/1 ml, 2 mg/2 ml, and 5 mg/5 ml vials containing solution.

Storage and Stability: It should be stored under refrigeration. Vincristine is available with and without preservatives so the time-frame for use once the vial has been entered varies. The intact vials have a labeled expiration date. Protect from light. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Administration: For this study, vincristine should be administered intravenously through a freely-running IV over 30 minutes or as an IV push. If it extravasates, it produces a severe local reaction with skin slough. **FATAL IF GIVEN INTRATHECALLY, FOR INTRAVENOUS USE ONLY.**

Supplier: Vincristine is commercially available, and should be purchased through a third party. This drug will NOT be supplied by the NCI.

Please refer to the package insert for complete information.

4.0 DIAGNOSTIC AND STAGING CRITERIA

4.1 Diagnostic Criteria

a. Definitions:

1. Bone marrow cellularity: The volume of hematopoietic nucleated cells, expressed as a percentage of marrow volume minus the volume of fibrosis.
2. Blasts: Blasts characteristic of L1, L2, or L3 are included in the calculation of blast percentages. (8, 9)
3. Marrow Blast Percentage: Bone marrow blast percentage is calculated as the percentage of blasts among all nucleated marrow cells except mature lymphocytes and plasma cells.

b. Acute Lymphoblastic Leukemia (ALL) is defined by the following:

The differential diagnosis of ALL is based on the presence of FAB L1, L2, or L3 morphology with negative staining for myeloperoxidase or Sudan Black (myeloid pattern), negative staining for non-specific esterase (myeloid pattern), and the presence of lymphoid-associated antigens. (10, 11) In the setting of relapsed or

Disease Assessment: Specimen submission is required prior to registration to Step 4 and at time of relapse. Please note that specimen submission for MRD testing is also required at any time a bone marrow exam is performed for any reason during protocol therapy.

7.7. Concomitant Medications (during chemotherapy)

- a. Anti-emetic therapy is allowed with each course of Induction, Consolidation and Intensification chemotherapy as outlined in the protocol (see [Sections 7.3a](#), [7.3b](#) and [7.4b](#)).
- b. Either G-CSF or pegfilgrastim will be administered with each course after the completion of chemotherapy as outlined in the protocol.
- c. Total number of prophylactic intrathecal treatments for newly diagnosed patients will be as follows (2 intrathecal of methotrexate on Day 2 \pm 2 days and cytarabine Day 7 \pm 2 days with each course of Induction/Consolidation chemotherapy until total number reached):
 1. Indeterminate or high-risk disease (defined as Serum lactate dehydrogenase (LDH) > 1400 U/L; or Proliferative index %S + G2M \geq 14%; or De novo LDH and/or proliferative index unknown): 8 intrathecal
 2. Low-risk disease (defined as having none of the above features indicating intermediate or high risk for CNS relapse): 6 intrathecal
 3. If the patient has been previously treated, and has had prior intrathecal therapy, or prior CNS disease, discuss management of CNS with the Study Chair.
 4. If active CNS disease: Consider methotrexate alternating with cytarabine twice weekly until CSF clear; then once weekly for 4 weeks, then back to prophylactic schedule. Consider XRT to the base of the skull, particularly with cranial nerve root involvement (cranial nerve palsies). Alternative methods of treating CNS disease are allowed, after discussion with the Study Chair, if appropriate for the patient. Modifications to the regimen thought to be necessary for administration of XRT are allowed after discussion with the Study Chair.
 5. It is recommended to administer the 6 or 8 doses of intrathecal therapy as indicated by risk (discussed above) even if the patient terminates the Induction/Consolidation cycles early (e.g. due to toxicity or transplant). A minimum of 6 IT treatments are needed if the patient does proceed to a TBI allogeneic stem cell transplant. If a patient with high risk for CNS relapse, does not proceed to allogeneic stem cell transplant, a minimum of 8 IT doses should be administered even if the full 8 induction/consolidation cycles are not possible (e.g. due to toxicity). Administration of IT therapy later in the course of treatment (for example during maintenance) is allowed, only if in the best interest of patient and after discussion with the Study Chair.
- d. Monitoring uric acid levels at diagnosis and throughout treatment to evaluate for tumor lysis syndrome is mandatory. Management of tumor lysis syndrome will be based on established guidelines.
- e. Short-acting antacid agents may be taken, but it is recommended that these not be taken from 2 hours before to 2 hours after dosing of dasatinib.

8.5 Dose Modification Contacts

For treatment or dose modification questions, please contact Dr. Farhad Ravandi at 713/745-0394 or Dr. Susan O'Brien at 713/792-7543.

8.6 Adverse Event Reporting

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

9.0 STUDY CALENDAR

CLOSED EFFECTIVE 10/01/2013

9.1 Induction/Consolidation Therapy - Registration Step 1

1 Course = 14-21 days

											#	¥
REQUIRED STUDIES	PRE TX	C 1	C 2	C 3	C 4	C 5	C 6	C 7	C 8	C 9	Rel	F/U
PHYSICAL												
History & Physical Exam	X											X
Weight & Performance Status	X											
Baseline Abnormalities	X											
Toxicity Notation		X	X	X	X	X	X	X	X	X	X	
Intake Calendar							X					
LABORATORY												
CBC, Differential, Platelets \$	X	2x/wk	X	X	X	X	X	X	X	X	X	X
Total Bilirubin ^	X	2x/wk	X	X	X	X	X	X	X	X	X	
SGOT and/or SGPT ^	X	2x/wk	X	X	X	X	X	X	X	X	X	
Serum Creatinine ^	X	2x/wk	X	X	X	X	X	X	X	X	X	
Uric Acid † ‡	X											
Bone Marrow Aspirate/Biopsy %	X	X	X	X			X		X			
Pregnancy Test	X											
Biopsy for Testicular Involvement f †	X											
Lumbar puncture		X β										
FISH and/or PCR ≡	X											
HLA Typing for Recipient and Donors Σ		X										
X-RAYS AND SCANS												
Chest X-Ray Δ †	X		X		X		X		X			
ECHO/MUGA √ †	X											
TREATMENT #												
Mesna		X		X		X		X		X		
Cyclophosphamide		X		X		X		X		X		
Doxorubicin		X		X		X		X		X		
Vincristine		X		X		X		X		X		
Dexamethasone		X		X		X		X		X		
Dasatinib		X	X	X	X	X	X	X	X	X		
G-CSF ϕ		X	X	X	X	X	X	X	X	X		
Pegfilgrastim ϕ		X	X	X	X	X	X	X	X	X		
CNS Prophylaxis (IT cytarabine/MTX)		X	X	X	X	X	X	X	X	X		
Methotrexate (Intravenous)			X		X		X		X			
Methylprednisolone			X		X		X		X			
Cytarabine (Intravenous)			X		X		X		X			
Leucovorin			X		X		X		X			
SPECIMEN SUBMISSION ψ												
Bone Marrow Asp/Biopsy and PB for Banking ψ	X			X			X		X		X	
Bone Marrow for Cytogenetics Π	X											

Click here to see [footnotes](#).

- b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
 - c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to the Collaborator(s) for Phase III studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to the Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/media presentation should be sent to:

E-mail: ncicteppubbs@mail.nih.gov

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

Monitoring

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

Confidentiality

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

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in [Section 14.0](#).) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol. See also [Appendix 18.1](#) for general and background information about expedited reporting.

b. Reporting methods

This study requires that expedited adverse event reporting use CTEP's Adverse Event Reporting System (CTEP-AERS). The NCI's guidelines for CTEP-AERS can be found at <http://ctep.cancer.gov>. An CTEP-AERS report must be submitted to the Southwest Oncology Group Operations Office electronically via the CTEP-AERS Web-based application located at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

In the rare occurrence when Internet connectivity is disrupted, a 24-hour notification is to be made to CTEP by telephone at 240/276-6565. An electronic report **MUST** be submitted immediately upon re-establishment of internet connection. Please note that all paper CTEP-AERS forms have been removed from the CTEP website and will NO LONGER be accepted.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to [Table 16.1](#)) via CTEP-AERS.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event specified in [Table 16.1](#) or [16.2](#), as applicable.

d. Other recipients of adverse event reports

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

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

e. Expedited reporting for investigational agents

Expedited reporting is required if the patient has received at least one dose of the investigational agent(s) as part of the trial. Reporting requirements are provided in [Table 16.1](#). The investigational agent(s) used in this study is dasatinib. If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1: Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a Non-CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention¹ Dasatinib.

<p>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)</p> <p>An adverse event is considered serious if it results in ANY of the following outcomes:</p> <ol style="list-style-type: none"> 1) Death 2) A life-threatening adverse event 3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for \geq 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). 				
<p>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.</p>				
Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization \geq 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization \geq 24 hrs	Not required		10 Calendar Days	
<p>NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR or [Section 16.1f.]</p> <p>Expedited AE reporting timelines are defined as:</p> <ul style="list-style-type: none"> o "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. o "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE. 				
<p>¹Serious 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:</p> <p>Expedited 24-hour notification followed by complete report within 5 calendar days for:</p> <ul style="list-style-type: none"> • All Grade 4, and Grade 5 AEs <p>Expedited 10 calendar day reports for:</p> <ul style="list-style-type: none"> • Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization • Grade 3 adverse events 				
<p>May 5, 2011</p>				

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

1) **Group-specific instructions.**

Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent by fax to 210-614-0006. Note, however, that any documents checked in the Additional Information section of the CTEP-AERS report must be submitted to CTEP per the instructions on that CTEP-AERS web page.

The Operations Office will notify drug companies as required.

For this study, the adverse events listed below do not require expedited reporting via CTEP-AERS:

- Grade 4 myelosuppression

g. **Expedited reporting for commercial agents**

Commercial reporting requirements are provided in [Table 16.2](#). The commercial agent(s) used in this study are cyclophosphamide, cytosine arabinoside, dexamethasone, doxorubicin, filgrastim, leucovorin, mesna, methotrexate, methylprednisolone, prednisone, vincristine. If there is any question about the reportability of an adverse event, please telephone or email the SAE Program at the Operations Office, 210-614-8808 or adr@swog.org, before preparing the report.

Table 16.2. Expedited reporting requirements for adverse events experienced by patients who have received only the commercial drug(s) listed in [16.1g](#) above.

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

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

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

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

h. **Reporting Secondary Malignancies, including AML/ALL/MDS**

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

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

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

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

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

For more information see:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

2. Supporting documentation should be submitted to CTEP in accordance with instructions provided by the CTEP-AERS system. A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 days by fax to 210-614-0006 or mail to the address below:

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

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

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

i. **Reporting Pregnancy, Fetal Death, and Death Neonatal**

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

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

2. **Fetal Death** Fetal Death defined in CTCAE as “A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation” should be reported expeditiously as **Grade 4 “pregnancy, puerperium and perinatal conditions – Other (pregnancy loss)”** under the **Pregnancy, puerperium and perinatal conditions SOC**.
3. **Death Neonatal** Neonatal death, defined in CTCAE as “A disorder characterized by cessation of life occurring during the first 28 days of life” that is felt by the investigator to be at least possibly due to the investigational agent/intervention should be reported expeditiously.

A neonatal death should be reported expeditiously as **Grade 4 “General disorders and administration – Other (neonatal loss)”** under the **General disorders and administration SOC**.

*Fetal death and neonatal death should **NOT** be reported as a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.*

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

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

CLOSED

Informed Consent Model for S0805

*NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document that are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the Southwest Oncology Group Operations Office for approval before a patient may be registered to this study.

Please particularly note that the questions related to banking of specimens for future study are in bolded type and may not be changed in any way without prior approval from the Southwest Oncology Group Operations Office.

Readability Statistics:

Flesch Reading Ease 55.7 (targeted above 55)

Flesch-Kincaid Grade Level 9.6 (targeted below 8.5)

- Instructions and examples for informed consent authors are in *[italics]*.
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- The term "study doctor" has been used throughout the model because the local investigator for a cancer treatment trial is a physician. If this model is used for a trial in which the local investigator is not a physician, another appropriate term should be used instead of "study doctor".
- The dates of protocol updates in the header and in the text of the consent is for reference to this model only and should not be included in the informed consent form given to the prospective research participant.
- The local informed consent must state which parties may inspect the research records. This includes the NCI, the drug manufacturer for investigational studies, any companies or grantors that are providing study support (these will be listed in the protocol's model informed consent form) and the Southwest Oncology Group.

The "Southwest Oncology Group" must be listed as one of the parties that may inspect the research records in all protocol consent forms for which patient registration is being credited to the Southwest Oncology Group. This includes consent forms for studies where all patients are registered directly through the Southwest Oncology Group Data Operations Office, all intergroup studies for