NRG ONCOLOGY

RTOG 0627

PHASE II TRIAL OF DASATINIB IN PATIENTS WITH RECURRENT GLIOBLASTOMA MULTIFORME

NCI Supplied Agent: Dasatinib (BMS-354825) (NSC 732517; IND 73969)

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GBM, treated with radiation and temozolomide

CT or MRI documenting recurrent/progressive GBM

Dasatinib daily*

CT or MRI every 2 months

* See Section 7.3.1 for intrapatient dose-escalation schedule.

Patient Population: (See Section 3.0 for Eligibility) (4/14/09)
Patients with GBM who have progressive/recurrent disease despite treatment with radiotherapy and temozolomide. Patients accrued to stage 1 (closed to accrual) or stage 1B (opened to accrual May 5, 2009) require overexpression/activity in at least two of the following SRC, KIT, PDGFR, and EPHA2. Patients accrued to stage 2 (cohort closed; not currently applicable) do not require overexpression/activity.

Required Sample Size: 84 (Stage 1: 29; Stage 1B: 29 (maximum); Stage 2: 26 (maximum) (5/6/09)
RTOG Institution #  
RTOG 0627  
ELIGIBILITY CHECKLIST (5/18/07)  
Case #  

__________ (Y)  1. Is there histologic proof of a diagnosis of GBM or gliosarcoma?

__________ (Y/N)  2. Did the patient participate in RTOG 0525?

______ (Y)  If no, has the patient consented to submission of tissue for central pathology review?

__________ (Y)  3. Is the patient ≥ 18 years of age?

__________ (Y)  4. Is the Karnofsky performance status ≥ 60?

__________ (Y)  5. Were a history and physical including height and weight done within 10 days prior to registration?

__________ (Y)  6. Was an MRI or CT of the brain with and without contrast done within 10 days prior to registration?

__________ (Y)  7. Was a CBC/differential obtained within 10 days prior to registration and was bone marrow function within the parameters of Section 3.1 of the protocol?

__________ (Y)  8. Were required liver function studies done within 10 days prior to registration and were the results within the parameters of Section 3.1 of the protocol?

__________ (Y)  9. Were renal function studies done within 10 days prior to registration and are the results within the parameters of Section 3.1 of the protocol?

__________ (Y)  10. Has the patient under gone prior treatment with radiotherapy and temozolomide for GBM?

______ (N)  Has the patient received any other prior treatment?

__________ (Y)  11. For patients with measurable disease, is there unequivocal radiographic evidence of tumor progression on MRI or CT scans?

__________ (Y)  12. If the patient has recently undergone surgery for recurrent/progressive disease, has he or she fully recovered from the effects of the surgery?

__________ (Y)  13. If there is no measurable disease present post-resection are all of the following conditions met as applicable?:

- Progression of disease led to the surgery
- Gliadel wafers were not placed during the most recent surgery
- Neither convection enhanced delivery nor catheters for infusion of chemotherapy were used during the most recent surgery
- Radioactive seeds were not placed during the most recent surgery
- The histology of the most recent surgery documented recurrent/persistent/progressive malignant glioma

(continued on next page)
14. Has the patient signed a study-specific informed consent form prior to study entry?

15. Is there history of prior malignancy?
   ___(Y) If yes, does it meet the eligibility criterion in Section 3.2?

16. Was radiotherapy given within 4 weeks prior to registration or temozolomide given within 14 days prior to registration?

17. Has the patient recovered from adverse events from prior radiotherapy and temozolomide?

18. Will the patient be receiving other investigational agents?

19. Does the patient have any of the severe, active comorbidities defined in Section 3.2 of the protocol?

20. Is there a history of allergic reactions attributed to compounds of similar chemical or biological composition to dasatinib?

21. Is the patient currently taking any of the prohibited substances listed in Appendix IV?

22. Has the patient been taking enzyme-inducing antiepileptic drugs (EIAEDS)?
   ___(Y) If yes, have or will EIAEDS be discontinued 2 weeks prior to start of dasatinib?

23. Is the patient taking systemic H2 blockers or proton pump inhibitors?

24. Is the patient using antithrombotic and/or antiplatelet agents as defined in Section 3.2 of the protocol?

25. Is the patient using ibuprofen or other NSAIDs?

26. Does the patient have any condition that impairs his or her ability to swallow and retain dasatinib tablets as defined in Section 3.2 of the protocol?

27. Has there been prior treatment with stereotactic radiosurgery (including Gamma-Knife, Cyberknife, or other variants) or brachytherapy?

28. If the patient is a woman of childbearing potential, has a negative B-HCG pregnancy test been documented within ≤ 3 days prior to registration?

29. Are women of childbearing potential and men who are sexually active willing/able to use medically acceptable forms of contraception?

30. If the patient is a mother with an infant, has she stopped breastfeeding or is she willing to stop during treatment with dasatinib?

(continued on next page)
31. Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol.

32. Has the patient consented to central pathology review?

33. Has the patient consented to molecular analysis of pre-dasatinib tumor tissue?

34. Patients accrued to Stage 1B only: Does the pre-dasatinib tumor tissue overexpress at least 2 known dasatinib targets?

The following questions will be asked at Study Registration:

1. Name of institutional person registering this case?

2. Has the Eligibility Checklist (above) been completed?

3. Is the patient eligible for this study?

4. Date the study-specific Consent Form was signed? (must be prior to study entry)

5. Patient’s Initials (First Middle Last) [If no middle initial, use hyphen]

6. Verifying Physician

7. Patient’s ID Number

8. Date of Birth

9. Race

10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)

11. Gender

12. Patient’s Country of Residence

13. Zip Code (U.S. Residents)

14. Patient’s Insurance Status

15. Will any component of the patient’s care be given at a military or VA facility?

16. Calendar Base Date

17. Registration/randomization date: This date will be populated automatically.

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18. Medical oncologist’s name.

19. Tissue kept for cancer research?

20. Tissue kept for medical research?

21. Allow contact for future research?

22. If patient was enrolled on RTOG 0525, what was the case #?

23. Is the patient enrolling onto protocol Stage 1B?

If yes, did the molecular profile analysis reveal at least 2 known dasatinib?

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient’s study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by ___________________________   Date ___________________________
1.0 INTRODUCTION
Glioblastoma (GBM) is the most common primary brain tumor in adults, with a uniformly dismal prognosis. Dasatinib is a multi-tyrosine kinase inhibitor that targets several molecular abnormalities driving glioma growth. We will conduct a phase II study of dasatinib for recurrent/progressive GBM and correlate clinical outcome with molecular features of pre-treatment tissue.

1.1 Study Disease
GBMs are diffusely infiltrating tumors that spread microscopically throughout the brain. Therefore, all local therapies, such as surgery and radiation, are inherently palliative. Long term disease control requires therapies targeting tumor cells throughout the brain such as chemotherapy and small molecule pathway inhibitors.

The present standard of care for newly diagnosed GBM involves maximal surgical resection followed by concurrent radiotherapy with temozolomide, an orally available DNA alkylating agent followed by at least 6 months of adjuvant temozolomide. The effectiveness of temozolomide in the management of GBM at diagnosis was recently demonstrated by a large multinational study. A modest survival benefit of 2.5 months was observed for patients treated with radiotherapy and temozolomide relative to radiotherapy alone (14.6 vs. 12.1 months median survival). The benefit of temozolomide was maintained 2 years after diagnosis; however, only 11% of patients were progression free and only 27% of patients were alive at that point. Therefore, long-term disease control remains elusive.

Several clinical trials for recurrent GBMs tested the efficacy of the EGFR inhibitors gefitinib and erlotinib, the PDGFR/KIT inhibitor imatinib, the PDGFR and VEGFR inhibitor PTK787/ZK222584, and the mTOR inhibitor CCI-779 (temsirolimus). Despite initial enthusiasm, treatment of recurrent GBMs with these single pathway inhibitors has generally been disappointing without response or survival rates superior to traditional chemotherapies.

In fact, an as yet unpublished analysis of a data set from the North American Brain Tumor Consortium pooled data from multiple phase II clinical trials for recurrent/progressive GBM, all of which were considered negative. This study demonstrated an overall 6-month progression-free survival rate of 7% for patients with recurrent/progressive GBMs treated with small molecule inhibitors as single agents, and represents an update to the study published in 1999.

The existence of multiple molecular abnormalities driving glioma growth is one reason for failure of therapies that target only one abnormal signaling pathway. The use of single agents that target multiple molecular abnormalities driving glioma growth may improve outcome. Dasatinib is such an agent (see figure).
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Figure: RTK (receptor tyrosine kinases) important in glioma biology and inhibited by dasatinib include PDGFR, EPH2A, and c-KIT. Dasatinib also inhibits the downstream mediator SRC. By contrast, other small molecule inhibitors typically target only a single molecular abnormality. For example, gefitinib and erlotinib inhibit EGFR but not other RTKs, and temsirolimus and related drugs inhibit only the downstream effector mTOR. We hypothesize that overexpression of more dasatinib targets will correlate with tumor sensitivity to dasatinib and that tumors overexpressing no dasatinib targets will be resistant to dasatinib. Multiple arrows indicate that intermediate steps exist but are not shown; arrows without targets indicate the presence of additional activities not shown.

1.2 Dasatinib (4/14/09)
Dasatinib (BMS-354825), an aminotriazole analog, is an orally administered protein tyrosine kinase (PTK) inhibitor with specificity for five kinases/kinase families that have been strongly linked to multiple forms of human malignancies.\[^{13-15}\] These targets include: BCR-ABL, c-SRC, c-KIT, PDGFβ receptor, and EPHA2. In vivo and in vitro studies have established that dasatinib demonstrates potent antiproliferative activity in a wide spectrum of cancer cell lines/types, and early clinical results also suggest anticancer activity of dasatinib in chronic myelogenous leukemia (CML) and solid tumor patients.\[^{16-19}\]

Dasatinib potently and selectively inhibits the five oncogenic PTKs/kinase families by competing with ATP for the ATP-binding sites in the kinases: SRC family kinases (IC\(_{50}\): SRC = 0.55 nM, LCK = 1.1 nM, YES = 0.41 nM, FYN = 0.2 nM); BCR-ABL (<3 nM); c-KIT (13 nM); EPHA2 (17 nM) and PDGFβ receptor (28 nM).\[^{14}\] The agent was found to be less potent against unrelated PTKs and several serine/threonine kinases. Dasatinib also demonstrates potent inhibition of VEGF- and bFGF-driven proliferation of human umbilical vein endothelial cells (HUVECs), with IC\(_{50}\) values of 43 and 248 nM, respectively.
BCR-ABL, a constitutively active cytoplasmic tyrosine kinase, is present in >90% of all patients with CML and in 15-30% of adult patients with acute lymphoblastic leukemia (ALL). The inhibition of BCR-ABL by imatinib, another PTK inhibitor, is effective in the management of CML thus providing proof-of-concept for targeting PTKs. However, resistance to imatinib therapy associated with BCR-ABL gene mutation/over-expression and activation of selected SRC kinases has been increasingly encountered. Dasatinib has activity in a number of imatinib-resistant tumors in addition to being 500-fold more potent than imatinib in inhibiting BCR-ABL.

1.2.1 Nonclinical Studies

Efficacy
Dasatinib inhibits growth of multiple BCR-ABL-dependent leukemic cell lines and also shows activity against 14 of 15 imatinib-resistant BCR-ABL kinase mutants. Inhibition of CML cell lines established from patients who were resistant to imatinib therapy has also been reported. Dasatinib potently inhibits wild-type (IC₅₀: 1-10 nM) and mutant (IC₅₀: 10-100 nM) KIT kinases in M07E cells and human mast cell leukemia cell lines, respectively. Also of note, dasatinib selectively killed primary neoplastic bone marrow mast cells from patients with systemic mastocytosis while sparing other hematopoietic cells.

Dasatinib demonstrated antiproliferative activity in a wide-spectrum of solid tumor types, including mastocytoma, prostate, colon, breast, and rhabdomyosarcoma cell lines with IC₅₀ values ranging from 5.4-845 nM. The agent also inhibited stem cell factor-driven proliferation of three small cell lung cancer (SCLC) cell lines with IC₅₀ values in the range of 114-220 nM and showed activity in head and neck squamous cell carcinoma and non-small cell lung cancer cell lines.

When dasatinib was administered twice daily (BID) on a 5-days-on/2-days-off schedule for a total of 14 to 25 days at doses of 10-50 mg/kg/dose, in vivo antitumor activity of dasatinib was seen in prostate, colon, SCLC, and rhabdomyosarcoma xenograft models. Similarly, dasatinib was effective against K562 and imatinib-resistant K562-R human CML xenografts in SCID mice at doses as low as 2.5-5 mg/kg/day. In combination with paclitaxel, dasatinib produced antitumor effects against PC3 human prostate carcinoma xenografts that were significantly better than the effects of either single agent alone (P = 0.05).

Dasatinib at 20 or 50 mg/kg inhibited the T-cell proliferation response in mice following the transfer of lymphocytes from allogeneic donor mice. In addition, treatment of mice with dasatinib 25 mg/kg BID inhibited the graft-versus-host response in a non-vascularized model of murine heart transplant. The 5-days-on/2-days-off regimen almost completely eliminated immunosuppressive activity in this model.

SRC kinase is known to play a major role in osteoclast function. In short-term studies, dasatinib acted as a potent inhibitor of bone resorption as measured by its ability to reduce the release of calcium into the culture medium by fetal rat long bones in vitro (IC₅₀ = 2 nM). Dasatinib also inhibited parathyroid hormone (PTH)-stimulated release of calcium in a dose-dependent manner with an apparent IC₅₀ of 2 nM. At 5 nM, dasatinib completely blocked PTH-stimulated bone resorption in thyro-parathyroidectomized rats. The therapeutic utility of dasatinib in the treatment of cancer-related hypercalcemic syndromes has not been fully explored, and the long-term effects of dasatinib on bone physiology are also unknown.

Nonclinical Pharmacokinetic and Pharmacodynamic Studies
Nonclinical metabolic and pharmacokinetic (PK) studies were conducted with dasatinib in several species including mouse, rat, dog, and monkeys to assess the absorption, distribution, metabolism, and excretion of the compound in animals. These studies showed that dasatinib has varying degrees of oral bioavailability, ranging from 15% in monkeys to 34% in dogs. The permeability of dasatinib in the Caco-2 cell model is 102 nm/sec at pH 7.4, suggesting that it has the potential for good (>50%) oral absorption in humans. The agent is highly bound to serum proteins (>91%) and has extensive extravascular distribution. Dasatinib is principally eliminated by hepatic metabolism and excreted in feces. The agent is primarily metabolized by the CYP3A4 enzyme to multiple metabolites.
1.2.2 Clinical Experience

Over 2000 subjects have received dasatinib, the majority with CML refractory or intolerant to imatinib. Studies conducted in healthy volunteers include the following: PK; formulation comparisons; the effect of food; drug interactions; and supportive care. Data are pending on 11 phase I and phase II studies in patients with CML, Ph+ ALL, or solid tumors using different dosage regimens and designed to determine PK, pharmacodynamics, safety, and efficacy in these populations. In addition, a phase I study in solid tumor patients on the effect of ketoconazole on dasatinib PK has been initiated.

Pharmacokinetics

Pharmacokinetic studies were conducted using a single 100 mg dose of dasatinib administered to healthy volunteers in four different formulations: 50 mg clinical tablets x 2, 5 mg clinical tablets x 20, 20 mg commercial tablets x 5, and 50 mg commercial tablets x 2. The PK profile of the agent was similar in all four formulations. The PK profile of dasatinib was also assessed in CML and Ph+ ALL patients providing data which showed that the PK parameters in the patient population appear to be similar to that in the healthy volunteers. The agent was absorbed rapidly following oral administration; peak plasma concentrations were achieved in 0.5-3 hours and dose-related increases in plasma concentrations were observed. The mean terminal half-life (t1/2) of dasatinib was 4 hours. Dosing interval exposures and t1/2 values were comparable regardless of whether the agent was administered on a once daily or twice daily (BID) 5-day-on/2-day-off schedule, or BID continuously.

Efficacy

Patients with CML in chronic phase (CP) or advanced disease (accelerated phase/blast crisis) or Ph+ ALL who are intolerant or resistant to imatinib have been treated with dasatinib on a phase I study. Dasatinib was administered once daily at doses ranging from 15 to 180 mg/day or BID at doses ranging from 25 to 50 mg for 5-7 consecutive days each week. Complete hematologic response was documented in 36 of 40 patients in CP and the rate was similar with both schedules (once daily or BID). Thirteen CP patients achieved a complete cytogenetic response and three experienced partial responses. In 42 patients with advanced CML (n=37) and ALL (n=5), 30 major hematologic responses were documented. Cytogenetic responses were documented in 22 patients, including complete responses in 9 patients.

A phase I study being conducted in patients with refractory solid tumors [primarily gastrointestinal stromal tumors (GIST)] is evaluating the safety, tolerability, and the pharmacologic profile of dasatinib. Interim data are available on 33 patients treated in this ongoing study. Patients receive escalating doses (25 to 120 mg) of dasatinib administered BID for 5 consecutive days every week, and patients in alternate dose groups are treated with or without antacids after fasting or a high-fat meal. At the 35 mg BID dose-level, the PK profile in fasting solid tumor patients resembled the experience in fasting patients with hematologic malignancies, but food and GI pH altered PK parameters. That is, while the mean fasting t1/2 was 1.3 hours, the mean t1/2 following food was 4.6 hours. There have been no objective responses on CT scans, but activity has been noted on FDG-PET, and resolution of GIST-associated ascites (one patient) and stable disease for ≥ 3 months (two GIST patients) have
been observed. The investigators noted that the clinical benefits of the agent in a subset of imatinib-resistant GIST patients have been encouraging.

**Safety in CML**

Myelosuppression, probably attributable to suppression of the Ph+ clone, was the most frequent adverse event (AE) in the phase I study in CML or Ph+ ALL, while the most significant AE was grade 3/4 thrombocytopenia (28%).14 Severe myelosuppression was reversible and easily managed with a short dose interruption. In the phase I study in solid tumor patients, no significant myelosuppression other than two instances of grade 3 anemia has been reported. Non-hematologic AEs from the two phase I trials include GI intolerance (primarily diarrhea, nausea, and vomiting), GI hemorrhage, fatigue, dyspnea, anorexia, dehydration, fluid retention, pleural and pericardial effusion, a moderate increase in QTcF (with no QTcF >500 msec), elevated creatinine, depression, and tumor lysis syndrome. In addition to these AEs, dasatinib treatment has the potential to produce skin rashes, other respiratory events, and CNS hemorrhage. There have been eight deaths among the CML or Ph+ ALL patients and six deaths on the solid tumor trial, all of which were considered unrelated to dasatinib therapy. While neither immunosuppression nor osteoclast function abnormalities (e.g., osteoporosis) were observed in these short-term studies, SRC kinase inhibitors have the potential to cause these types of events.

**Safety in GBM**

We accrued 26 eligible patients to stage 1 of this study, at which point accrual was halted to assess efficacy before proceeding to stage 2. Toxicity was minimal despite the relatively high starting dose of 100 mg bid, a dose schedule that is poorly tolerated in other systemic malignancies. For example, there were no grade 4 or 5 treatment-related adverse events and no pleural effusions, events that have been reported in patients with other malignancies treated at this or at lower doses. Potential explanations include unreported or underreported concurrent use of prohibited medications in our patient cohort that could reduce absorption, such as H2 blockers or proton pump inhibitors (See Section 3.2.7.2). These drugs are available over the counter without a prescription. It may also reflect concurrent use of corticosteroids, which is common in patients with GBMs generally; steroid use was reported in 81% (21) of accrued eligible patients. Therefore, specific concurrent medications may account for the toleration of a higher dose of dasatinib in patients with recurrent GBM. Additionally, this raises the possibility that, in this patient population, drug metabolism and clearance may be altered and that otherwise established dosing schedules are subtherapeutic.

### 1.2.3 Potential Drug Interactions

Dasatinib is primarily metabolized by CYP3A4 and therefore, potent inhibitors of this enzyme are contraindicated.14 Dasatinib is also a significant inhibitor of this hepatic enzyme but a weak inhibitor of other cytochrome enzymes, and the agent does not induce CYP3A4. Thus, dasatinib may decrease the clearance of drugs that are significantly metabolized by the CYP3A4 enzyme, and caution should be used with concurrent use of such drugs or substances. In a study in cancer patients, concomitant use of a potent CYP3A4 inhibitor (ketoconazole) produced >5-fold increase in exposure to dasatinib, while healthy subjects treated concurrently with dasatinib and a potent CYP3A4 inducer experienced a 5-fold decrease in dasatinib exposure. When the CYP3A4 substrate simvastatin was studied in combination with dasatinib, increased simvastatin exposure resulted, indicating the necessity of caution when dasatinib is administered with CYP3A4 substrates with a narrow therapeutic margin (e.g., cyclosporine).

This issue is particularly important for patients with GBM and seizures because many antiepileptic drugs induce hepatic enzymes. Therefore, patients taking hepatic enzyme inducing antiepileptic drugs (EIAEDs) are ineligible for this trial unless they are switched to non-hepatic enzyme inducing antiepileptic drugs (non-EIAEDs) ≥ 2 weeks before registration. See Appendix IV for a list of EIAEDs and non-EIAEDs.

### 1.3 Rationale

The majority of GBMs exhibit amplification/overexpression of SRC (~60%), PDGFR (~75%), and ephrin (~90%); approximately half exhibit c-KIT amplification.29-32 Mouse modeling by transgenic and somatic-cell gene transfer methods further confirmed the importance of SRC and PDGFR signaling in gliomagenesis.33
Dasatinib alone inhibits multiple tyrosine kinases with activity against SRC, PDGFR, KIT, and EPHA2. In addition, dasatinib inhibits KIT and PDGFR signaling more potently than imatinib. Therefore, we hypothesize that dasatinib will be more effective for recurrent GBMs than monotherapy with other small molecule inhibitors, such as imatinib, because of the broader spectrum of molecular targets and increased potency against key targets.

1.4 Correlative Studies Background

We will attempt to identify pre-treatment molecular features of tumor tissue that predict response or progression. In this way, subsets of GBMs that may be more or less likely to respond to treatment with dasatinib can be identified. For patients who develop tumor progression while taking dasatinib and undergo re-operation, tissue resected following disease progression will be used to determine molecular correlates of treatment failure.

Expression of dasatinib targets

Among the multiple targets inhibited by dasatinib, there are at least four known targets of major importance in GBM biology: SRC, PDGFRbeta, EPHA2, and KIT. The presence of the targets and activated forms can be evaluated with immunohistochemistry (IHC) of paraffin sections or Western blot (immunoblot) of flash frozen tumor using commercially available antibodies (e.g., anti-PDGFR and anti-phosphoPDGFR). IHC and Western blot of baseline tissue will be performed to identify molecular signatures that predict GBM sensitivity to dasatinib. The presence of the targets and their activated (phosphorylated) forms will be examined and correlated with clinical outcome.

Slides analyzed by IHC will be scored for immunostaining on a 4-point scale (0-3) analogous to that developed by others. Band intensity on Western blot of flash frozen tissue when available will be similarly scored on a 4-point scale. In this scale, 0 indicates no immunostaining/absent Western blot band, and 1-3 indicate mild, moderate, and strong immunostaining/band intensity, respectively. Tumors will be separated into upper and lower halves based on target expression with the lower half with no or mild expression (i.e., score 0-1) and the upper half with strong expression (i.e., score 2-3).

We hypothesize that target expression is necessary for sensitivity to dasatinib. We further hypothesize that dasatinib will be most effective for tumors that overexpress four dasatinib targets, and progressively less effective for tumors overexpressing three targets, two targets, or one target. Therefore, pre-treatment tissue will be analyzed for overexpression of SRC, PDGFRbeta, EPHA2, and KIT. For each target, an IHC staining score of 2-3 will be considered positive.

Pre-screening of tumor tissue:

Single agents targeting one molecular abnormality have been generally ineffective in management of recurrent/progressive GBM (7% 6mPFS rate, NABTC data base). Tumors signaling through only one known dasatinib target are unlikely to respond more effectively to dasatinib than tumors treated with single target pathway modulators. Therefore, tumors of clinically eligible patients will be screened in real time for overexpression/activity of SRC, KIT, PDGFR, and EPHA2. For this trial, the first cohort of 27 patients will consist only of those expressing a molecular signature which is hypothesized will make them more responsive to dasatinib. This signature is overexpression of at least 2 known dasatinib targets (SRC, KIT, PDGFR, and EPHA2). As the population of eligible patients will be enriched in this first cohort, we will double the required 6mPFS/response rate to continue enrolling patients (see Section 13). In this manner, we hypothesize that overexpression of at least 2 known dasatinib targets is necessary but not sufficient for dasatinib effect. If the efficacy in the first cohort is sufficient to continue the study, then we will expand the study to include an additional 56 patients (without regard to pre-screening. Retrospective analysis of tissue from the second stage will allow interrogation of the hypothesis that dasatinib target activity is necessary for dasatinib effect, although it may not be sufficient.

Additional molecular analyses to be performed retrospectively:

In addition, although target expression is likely necessary for sensitivity to dasatinib, it is also likely to be insufficient. For example, the tumor suppressor PTEN is lost or inactivated in approximately 70% of GBMs, leading to unrepressed AKT signaling that is independent of upstream activity of receptor tyrosine kinases. Therefore, normal PTEN expression may also be necessary for tumor sensitivity to dasatinib, and we will analyze PTEN expression in tumor cells by IHC.
Finally, tumor DNA will be extracted from pre-treatment tissue, and the tyrosine kinase domains of SRC, PDGFR, EPHA2, and KIT will be sequenced to identify mutations that increase dasatinib sensitivity. If screening of the tyrosine kinase domains reveals novel mutations, sequencing will be expanded to the entire coding sequence and intron-exon borders. Such sequencing is crucial because it is an emerging paradigm that expression of targets is necessary but not sufficient for tumor sensitivity to small molecule inhibitors and that drug sensitivity is conferred by mutations in the target molecules. For example, expression of EGFRvIII, a constitutively activated mutant form of EGFR that is only expressed in a subset of tumors that also exhibit EGFR amplification, is required for response of GBMs to the EGFR inhibitors erlotinib and gefitinib. Similarly, mutations in exons 18-21 of EGFR have been identified in non-small cell lung cancers that associate with response to erlotinib/gefitinib.

Treatment failure

For patients who develop tumor progression while taking dasatinib and undergo re-operation, such tissue will be analyzed to investigate molecular explanations for treatment failure. As above, we hypothesize that tumors with PTEN loss will be insensitive to upstream tyrosine kinase inhibition by dasatinib. We further hypothesize that dasatinib-insensitive tumors will exhibit uninhibited tyrosine kinase activation as measured by phosphorylated forms of the various dasatinib targets.

2.0 OBJECTIVES

2.1 Primary (4/14/09)

2.1.1 To determine the therapeutic efficacy of dasatinib in all patients (i.e., stages 1B and 2 combined) with recurrent/progressive GBM as measured by 6-month progression-free survival.

2.2 Secondary (4/14/09)

2.2.1 To determine the therapeutic efficacy of dasatinib for stage 1B patients with recurrent/progressive GBM as measured by a hybrid endpoint of 6-month progression-free survival OR objective response of (CR or PR) rate.

2.2.2 To determine patient overall survival.

2.2.3 To determine the toxicity of dasatinib in the treatment of patients with GBM.

2.2.4 To determine radiographic response rate to treatment.

2.2.5 To determine patient progression-free survival.

2.2.6 To explore molecular correlates of clinical outcome.

2.2.7 To explore pharmacokinetic correlates of dosing, toxicity, and efficacy.

3.0 PATIENT SELECTION

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED

3.1 Conditions for Patient Eligibility (4/14/09)

3.1.1 Histologically proven diagnosis of GBM. Since gliosarcoma is a variant of GBM, gliosarcoma is also an eligible diagnosis.

3.1.2 The patient must consent to submission of tissue for central pathology review (See Section 10)

3.1.2.1 Patients who have already undergone central pathology review through their enrollment on another RTOG GBM trial do not need to consent to having their material re-reviewed by the central pathologist for this study.

3.1.3 All patients must consent to molecular analysis of pre-dasatinib tumor tissue.

3.1.3.1 Patients accrued to stage 1 (closed to accrual) or stage 1B (opened to accrual May 5, 2009) must have tumors overexpressing at least 2 known dasatinib targets (SRC, KIT, PDGFR, and EPHA2).

3.1.3.2 Patients accrued to stage 2 (cohort closed; not currently applicable) do not require overexpression of SRC, KIT, PDGFR, and EPHA2.

3.1.4 History and physical examination, including height and weight, within 10 days prior to registration on study

3.1.5 Brain MRI with and without gadolinium within 10 days prior to registration on study

3.1.5.1 Contrast-enhanced CT scans are allowed for patients who cannot undergo MRI scanning

3.1.6 Karnofsky performance status ≥ 60

3.1.7 Age ≥ 18

3.1.8 CBC/differential obtained within 10 days prior to registration on study, with adequate bone marrow function defined as follows:
Conditions for Patient Ineligibility (9/5/07)

3.2.1 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years. (For example, carcinoma in situ of the breast, oral cavity, or cervix are all permissible)

3.2.2 Radiotherapy within 4 weeks or temozolomide within 14 days prior to registration or failure to recover from adverse events of either radiotherapy or temozolomide

3.2.3 Patients may not be receiving any other investigational agents

3.2.4 Severe, active comorbidity, defined as follows:

3.2.4.1 Any clinically significant cardiovascular disease including the following:

3.2.4.1.1 Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months

3.2.4.2 Transmural myocardial infarction or ventricular tachyarrhythmia within the last 6 months

3.2.4.3 Prolonged QTc>480 msec (Fridericia correction)

3.2.4.4 Ejection fraction less than institutional normal

3.2.4.5 Major conduction abnormality (unless a cardiac pacemaker is present)

3.2.4.6 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration

3.2.4.7 Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration

3.2.4.8 Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive and dasatinib may interact with HAART.
3.2.5 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because animal studies with dasatinib have shown embryolethality and fetal skeletal alterations at non-toxic maternal doses. Because there is an unknown but potential risk for adverse events in nursing human infants secondary to treatment of the mother with dasatinib, breastfeeding should be discontinued if the mother is treated with dasatinib.

3.2.6 History of allergic reactions attributed to compounds of similar chemical or biologic composition to dasatinib

3.2.7 Patients who require concurrent treatment with any medications or substances that are potent inhibitors or inducers of CYP3A4 are ineligible. (See Appendix IV for lists of specifically prohibited medications or substances.)

3.2.7.1 Anticonvulsants: Patients must not be taking hepatic enzyme inducing antiepileptic drugs (EIAEDs). If patients were previously on EIAEDs that have been discontinued, patients must have been off EIAEDs for ≥ 2 weeks prior to initiation of dasatinib. It should also be noted whether patients were or were not previously receiving EIAEDs and the last date of administration of EIAEDs.

3.2.7.2 Antacids: This is particularly important for patients with gliomas because such patients are often routinely prescribed H2 blockers, proton pump inhibitors, or locally-active antacids in association with corticosteroids. Because systemic antacids (H2 inhibitors, proton pump inhibitors) decrease dasatinib absorption, patients who require antacids should use short-acting, locally active agents (e.g., Maalox, Mylanta etc.). However, these agents should not be taken within either 2 hours before or 2 hours after the dasatinib dose.

3.2.8 Use of antithrombotic and/or antiplatelet agents (e.g., warfarin, heparin, low molecular weight heparin, aspirin, clopidogrel, ticlopidine, Aggrenox). See also 9.2.3.

3.2.9 Use of ibuprofen and other NSAIDs. See also 9.2.3.1

3.2.10 Patients with any condition (e.g., gastrointestinal tract disease resulting in an inability to take oral medication or a requirement for IV alimentation, prior surgical procedures affecting absorption, or active peptic ulcer disease) that impairs their ability to swallow and retain dasatinib tablets are excluded

3.2.11 Prior treatment with stereotactic radiosurgery (including Gamma-Knife, Cyberknife, or other variants) or brachytherapy.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT
Not applicable to this study.

5.0 REGISTRATION PROCEDURES
There are mandatory pathology requirements for this study. See Section 10 for instructions and details.

5.1 Regulatory Pre-Registration Requirements (4/14/09)
5.1.1 U.S. sites and Canadian sites must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206), along with the completed CTSU-IRB/REB Certification Form, http://www.rtog.org/pdf_file2.html?pdf_document=CTSU-IRBCertifForm.pdf, prior to registration of the institution’s first case:
- IRB/REB approval letter;
- IRB/REB approved consent (English Version)
- IRB/REB assurance number

5.1.2 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS
5.1.2.1 Prior to clinical trial commencement, Canadian institutions must complete and fax to the CTSU Regulatory Office (215-569-0206) Health Canada’s Therapeutic Products Directorates’ Clinical Trial Site Information Form, Qualified Investigator Undertaking Form, and Research Ethics Board Attestation Form.

5.1.2.2 Note: International sites must receive written approval of submitted LOI forms from RTOG Headquarters prior to submitting documents to their local ethics committee for approval. See http://www.rtog.org/pdf_forms.html?members/forms=Intl_LOI_Form.doc

Approved international sites fax copies of the documentation below, along with the completed International REC Certification Form, http://www.rtog.org/pdf_forms.html?members/forms=RTOG%20International%20REC%20C
Online Registration

Patients can be registered only after eligibility criteria are met.

Each individual user must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:

- The investigator and research staff must have completed Human Subjects Training and been issued a certificate (Training is available via http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp).
- A representative from the institution must complete the Password Authorization Form at http://www.rtog.org/members/webreg.html (bottom right corner of the screen), and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

An institution can register the patient by logging onto the RTOG web site (http://www.rtog.org), going to “Data Center Login” and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient’s record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study’s database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

Institutions can contact RTOG web support for assistance with web registration: websupport@phila.acr.org or 800-227-5463 ext. 4189 or 215-574-3189.

In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask for the site’s user name and password. This information is required to assure that mechanisms usually triggered by web registration (e.g., confirmation of registration and patient-specific calendar) will occur.

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6.0 **RADIATION THERAPY**

Not applicable to this trial.

7.0 **DRUG THERAPY**

Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual.

Protocol treatment must begin within 4 days after registration.

7.1 **Dasatinib Administration**

Treatment is intended to be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7.5. Appropriate dose modifications for dasatinib are
described in Section 7.3. No investigational or commercial agents or therapies other than those
described below may be administered with the intent to treat the patient’s malignancy.

7.1.1 **Dose and Schedule (4/14/09)**

Patients will receive dasatinib on an outpatient basis at an initial daily dose of 200 mg, for a total
of four 50-mg tablets, two in the morning and two in the evening, with the potential for
intrapatient dose escalation as outlined in Section 7.3.1. Dasatinib tablets may be taken with or
without food as desired but should be swallowed with at least 8 ounces (240 mL) of water. A
light meal is not required but may improve gastric tolerance for dasatinib. Tablets must be
swallowed whole and may not be broken. If vomiting occurs within 30 minutes of swallowing the
tablet(s), the dose may be replaced if the tablets can be seen and counted. Four weeks (28
days) constitutes one cycle of treatment. Treatment continues until one of the criteria in the
“Duration of Therapy” Section (Section 7.1.3) applies.

7.1.2 **Other Information (1/6/12)**

- Patients should be advised not to consume substantial quantities of grapefruit or grapefruit
  juice during dasatinib treatment.
- Dasatinib tablets should be swallowed whole and cannot be crushed or broken. If tablets
  are accidentally crushed or broken, caregivers should wear disposable chemotherapy
gloves. pregnant women should avoid exposure to crushed and/or broken tablets.
- Patients will be provided with a medication diary for dasatinib (to be included in the forms
  package, available on the NRG Oncology/RTOG website at www.rtog.org), instructed in its
  use, and asked to bring the diary with them to each appointment. A new copy of the
  medication diary will be given to patients whose dose is reduced due to adverse events.
- Patients should be evaluated for signs and symptoms of underlying cardiopulmonary
disease during dasatinib treatment.
  - Symptoms of pulmonary arterial hypertension (PAH) include dyspnea, fatigue,
    hypoxia, and edema. Since other medical conditions may also cause these
    symptoms, non-invasive procedures (including echocardiogram) should be done
    first to rule out more the common etiologies of these symptoms, such as pleural
    effusion, pulmonary edema, anemia, and lung infiltration.
  - Right heart catheterization can confirm the diagnosis of PAH. Hypertension is “pre-
capillary” and not a consequence of left heart failure or chronic lung disease if there
  is normal pulmonary capillary wedge pressure (<15 mm Hg) but elevated pulmonary
  artery pressure (mean pulmonary artery pressure >25 mm Hg). Since PAH may be
  reversible upon discontinuation of dasatinib, a diagnostic approach of interruption of
  dasatinib treatment may be considered at the discretion of the treating physician;
  however, if PAH is confirmed, dasatinib should be permanently discontinued.

7.1.3 **Duration of Therapy**

Treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- General or specific changes in the patient’s condition render the patient unacceptable for
  further treatment in the judgment of the investigator
- Agent-related adverse event(s) unacceptable to the patient (at the discretion of the treating
  physician) — Reasons for removal must be clearly documented on the appropriate case
  report form/flowsheet, and NRG Oncology/RTOG Headquarters data management must be
  notified
- A delay in protocol treatment > 2 weeks because of dasatinib-related adverse events
- The patient may withdraw from the study at any time for any reason. The institution must
  notify NRG Oncology/RTOG Headquarters Data Management about this in writing and follow
  the guidelines set forth in the NRG Oncology/RTOG procedure manual
- Discretion of the treating physician

Patients discontinuing treatment should continue to be followed for study endpoints

7.1.4 **Duration of Follow-Up**

Patients will be followed until death. Patients removed from study for unacceptable adverse
events will be followed until resolution or stabilization of the adverse event.

7.2 **Dasatinib Agent Information [BMS-354825 (NSC 732517)] (5/8/08)**

**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®

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.

Molecular Formula: C_{22}H_{26}CIN_7O_{2}S·H_2O

Molecular Weight: BMS-354825 monohydrate: 506.02 daltons

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.

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

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

Inactive ingredients include lactose, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, and polyethylene glycol.

Storage: Store the intact bottles at controlled room temperature (15°C-25°C) and protect from light.

Stability: Stability studies are ongoing.

Route of Administration: Oral.

Method of Administration: Tablets should be swallowed whole and cannot be crushed or broken. BMS-354825 (dasatinib) can be taken with or without food.

Potential Drug Interactions: Potent CYP3A4 inducers and inhibitors are prohibited on BMS-354825 trials. BMS-354825 is primarily metabolized by the human CYP3A4 enzyme. In healthy subjects, concomitant use of a potent CYP3A4 inducer (ketoconazole) caused a five-fold decrease in BMS-354825 exposure. CYP3A4 substrates known to have a narrow therapeutic index should be administered with caution in patients receiving BMS-354825. BMS-354825 may decrease the metabolic clearance of drugs that are significantly metabolized by the CYP3A4 enzyme.

Systemic antacids (both H₂ receptor antagonists and proton pump inhibitors) are prohibited on BMS-354825 trials. In healthy subjects, a H₂ receptor antagonist reduced BMS-354825 exposure by 61%. Locally acting antacids (e.g., Maalox, Mylanta) can be given up to 2 hours prior or 2 hours following BMS-354825 administration.
BMS-354825 may prolong the QT/QTc interval. Use caution when administering BMS-354825 with other potential QTc-prolonging medications.

Due to the possibility of gastrointestinal, cardiac, and cutaneous hemorrhage, medications that inhibit platelet function or anticoagulants with BMS-354825 should only be used with caution if clearly medically indicated (see 9.2.3 and 9.2.3.1).

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

**7.2.1 Accountability and Drug Ordering:**
Drug accountability records must be maintained at all sites according to good clinical practices and NCI guidelines.

The Principal Investigator (or authorized designee listed by the Investigator on the site’s most recent Supplemental Investigator Data Form [IDF] on file with the PMB) at each participating institution may request dasatinib, BMS-354825 (NSC 732517) from NCI’s Pharmaceutical Management Branch (PMB). PMB policy requires that drug 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. Completed Clinical Drug Requests (NIH-986) should be submitted to the PMB by fax (301) 480-4612 or mailed to the Pharmaceutical Management Branch, CTEP, DCTD, NCI, 9000 Rockville Pike, EPN, Room 149, Bethesda, MD 20892. All forms can be accessed on the NCI web site, http://ctep.cancer.gov/forms/index.html The Investigator Brochure (IB), if available, for this drug will be supplied by the PMB/NCI. All requests for IBs should be e-mailed to ibcoordinator@mail.nih.gov or the IB Coordinator may be contacted at 301-496-5725.

**7.3 Dose Delays/Dose Modifications (4/14/09)**
The dose levels and the general approach to dose modification of dasatinib on this trial are shown below. Adverse events (AEs) should be treated with the appropriate maximum supportive care, and dose reductions should be clearly documented in the case report form.

Patients will be withdrawn from the study if they fail to recover to CTCAE version 3.0 grade 0-1 or tolerable grade 2 (or within 1 grade of starting values for pre-existing laboratory abnormalities) from a treatment-related toxicity within 14 days OR they experience agent-related adverse events requiring dose modification despite two previous dose reductions (i.e., would require a third dose reduction) unless the investigator and CTEP senior investigator agree that the patient should remain on the study because of evidence that the patient is/may continue deriving benefit from continued study treatment, for which dose levels -3 and -4 may be applicable.
7.3.1 **Intrapatient Dose Escalation**

If after one cycle of treatment (28 days), there are no dose limiting toxicities (DLT), then the dose will be increased by one dose level (50 mg) each cycle to a maximum of 200 mg bid (table below), although it is anticipated the highest tolerable dose will be lower than 200 mg bid. A DLT is defined as any grade ≥ 3 toxicity that would require a dose reduction below.

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Dasatinib Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>400 mg total (four 50-mg tablets AM, four 50-mg tablets PM)</td>
</tr>
<tr>
<td>3</td>
<td>350 mg total (three 50-mg tablets AM, four 50-mg tablets PM)</td>
</tr>
<tr>
<td>2</td>
<td>300 mg total (three 50-mg tablets AM, three 50-mg tablets PM)</td>
</tr>
<tr>
<td>1</td>
<td>250 mg total (two 50 mg tablets AM, three 50 mg tablets PM)</td>
</tr>
<tr>
<td>0 (Starting Dose)</td>
<td>200 mg total (two 50-mg tablets AM, two 50-mg tablets PM)</td>
</tr>
<tr>
<td>-1</td>
<td>150 mg total (one 50-mg tablet AM, two 50-mg tablets PM)</td>
</tr>
<tr>
<td>-2</td>
<td>100 mg total (one 50-mg tablet AM, one 50-mg tablet PM)</td>
</tr>
<tr>
<td>-3</td>
<td>100 mg total (two 50-mg tablets simultaneously AM)</td>
</tr>
<tr>
<td>-4</td>
<td>70 mg total (one 50-mg tablet and one 20-mg tablet simultaneously AM)</td>
</tr>
</tbody>
</table>
## Selected Hematologic and Non-Hematologic Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>AE Grade or Observation</th>
<th>Dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>Grade 1 or 2</td>
<td>Maintain dose</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4 (^1)</td>
<td>Hold dasatinib until &lt; grade 2, then <strong>reduce 1 dose level and resume treatment.</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Investigators may reduce the dose by 2 levels for retreatment of patients who have had a grade 4 toxicity, even if it is the first event.</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Grade 1 or 2</td>
<td>Maintain dose</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4 (^1)</td>
<td>Hold dasatinib until &lt; grade 2, then <strong>reduce 1 dose level and resume treatment.</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Investigators may reduce the dose by 2 levels for retreatment of patients who have had a grade 4 toxicity, even if it is the first event.</td>
</tr>
<tr>
<td>Hemorrhage/Bleeding/Coagulopathy (without thrombocytopenia)</td>
<td>Grade 1</td>
<td>No interruption in treatment; maintain current dose. Monitor as clinically indicated</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>Hold dasatinib until AE resolved to &lt; grade 1; reduce dose to next lower dose level, and continue treatment.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If grade 2 or greater hemorrhage/bleeding recurs following dose reduction, stop dasatinib and remove patient from study.</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4</td>
<td>Discontinue treatment and withdraw subject from study. Follow up per protocol (see Section 5.4).</td>
</tr>
<tr>
<td>QTc Prolongation</td>
<td>&gt;480 but &lt; 550 msec</td>
<td>Review patient’s concomitant medications for QT interval-prolonging agents. Correct any electrolyte abnormalities. Continue dasatinib at current dose level and repeat ECG.</td>
</tr>
<tr>
<td></td>
<td>≥ 550 msec</td>
<td>Stop dasatinib and any other QT interval-prolonging agents immediately. Correct any electrolyte abnormalities, then</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. <strong>If there is a plausible explanation for AE other than dasatinib treatment, resume dasatinib at current dose level.</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. <strong>If dasatinib may have contributed</strong> to the AE:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Reduce 2 dose levels and restart dasatinib.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• If QTc remains &lt;480 msec after 14 days at reduced dose, increase one dose level and continue dasatinib.</td>
</tr>
</tbody>
</table>

\(^1\) Recurrent grade 3 events require dose reduction; recurrent grade 4 events require study removal.
General Management Guidelines for Agent-Related Non-Hematologic Toxicity

<table>
<thead>
<tr>
<th>Severity</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st event: Institute supportive therapy. May hold dasatinib, or continue without dose reduction, or reduce by one dose level</td>
</tr>
<tr>
<td>Grade 2</td>
<td>2nd event: Hold dasatinib until ≤ grade 1 and maximize supportive therapy. Decrease dose by one dose level if restarted.</td>
</tr>
<tr>
<td></td>
<td>3rd event: Hold dasatinib until ≤ grade 1. Decrease dose by one dose level if restarted. May discontinue if AE poorly controlled.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1st event: Hold dasatinib until ≤ grade 2. Institute supportive therapy. Restart dasatinib at the same dose or with reduction by one dose level allowed at discretion of the investigator.</td>
</tr>
<tr>
<td></td>
<td>2nd event: Hold dasatinib until ≤ grade 2. Maximize supportive therapy. Dasatinib may be restarted with reduction by one dose level or discontinued if dose already reduced at discretion of the investigator.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>1st event: Hold dasatinib until ≤ grade 2. Maximize supportive therapy. Dasatinib may be restarted with dose reduction by one dose level or discontinued at the discretion of the investigator. Investigators may reduce the dose by 2 levels for retreatment of patients who have had a grade 4 toxicity, even if it is the first event.</td>
</tr>
</tbody>
</table>

During stage 1B (accrual of 12 patients with intrapatient dose escalation to ensure 10 eligible patients):

- Patients who discontinue treatment during cycle 1 or 2, or undergo dose reduction, or do not undergo dose escalation because of disease progression will be replaced in order to be able to accurately estimate toxicity and the percent of patients eligible to undergo dose escalation. (Note that patients replaced because of progression during cycle 1 or 2 will count toward the accrual of 27 patients for efficacy analysis on stage 1B; see Section 13). Patients who discontinue treatment after completing cycle 2 because of disease progression will NOT be replaced, as they will have completed at least one cycle during which the dose was escalated above the starting dose.
- Patients who discontinue treatment during cycle 1 or 2 because of agent-related toxicity will not be replaced.
- Patients who discontinue treatment because of toxicities deemed unrelated or unlikely related to treatment will be reviewed by the study chairs to determine whether they will be replaced.

Note that hypophosphatemia may occur in approximately 10% of patients and does not require a dose delay or reduction if adequate supplementation can be provided.

7.3.2 Pharmacokinetic Analysis: See Appendix V.

7.4 Modality Review

The Medical Oncology Co-Chairs, Andrew B. Lassman, M.D. or Mark R. Gilbert, M.D., will perform a Chemotherapy Assurance Review of all patients who receive or are to receive chemotherapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1. The scoring mechanism is: Per Protocol/Acceptable Variation, Not Per Protocol, and Not Evaluable. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

The Medical Oncology Co-Chairs, Andrew B. Lassman, M.D. or Mark R. Gilbert, M.D., will perform a Quality Assurance Review after complete data for the first 20 cases enrolled has been received at NRG Oncology. Dr. Lassman will perform the next review after complete data for the next 20 cases enrolled has been received at NRG Oncology. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at NRG Oncology, whichever occurs first.
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, Spryel).

**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.

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### Adverse Events with Possible Relationship to Dasatinib (BMS-354825, Spryel) (CTCAE 4.0 Term) [n= 2937]

<table>
<thead>
<tr>
<th>Likely (&gt;20%)</th>
<th>Less Likely (&lt;=20%)</th>
<th>Rare but Serious (&lt;3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLOOD AND LYMPHATIC SYSTEM DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td>Anemia (Gr 3)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CARDIAC DISORDERS</strong></td>
<td>Heart failure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left ventricular systolic dysfunction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Myocardial infarction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pericardial effusion</td>
<td></td>
</tr>
<tr>
<td><strong>GASTROINTESTINAL DISORDERS</strong></td>
<td>Abdominal distension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anal mucositis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>Abdominal pain (Gr 2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>Diarrhea (Gr 3)</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal hemorrhage*</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>Mucositis oral</td>
<td>Nausea (Gr 3)</td>
</tr>
<tr>
<td></td>
<td>Rectal mucositis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Small intestinal mucositis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>Vomiting (Gr 3)</td>
</tr>
<tr>
<td><strong>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</strong></td>
<td>Edema limbs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>Fatigue (Gr 3)</td>
</tr>
<tr>
<td></td>
<td>Fever</td>
<td>Fever (Gr 2)</td>
</tr>
<tr>
<td></td>
<td>General disorders and administration site conditions - Other (generalized edema)</td>
<td>General disorders and administration site conditions - Other (superficial edema)</td>
</tr>
<tr>
<td></td>
<td>General disorders and administration site conditions - Other (superficial edema) (Gr 2)</td>
<td></td>
</tr>
<tr>
<td>Likely (&gt;20%)</td>
<td>Less Likely (&lt;=20%)</td>
<td>Rare but Serious (&lt;3%)</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Non-cardiac chest pain</td>
<td>Pain</td>
<td>Infection&lt;sup&gt;2&lt;/sup&gt; (Gr 3)</td>
</tr>
<tr>
<td>INFECTIONS AND INFESTATIONS</td>
<td>Infection&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Neutrophil count decreased (Gr 3)</td>
</tr>
<tr>
<td>INVESTIGATIONS</td>
<td>Alanine aminotransferase increased</td>
<td>Platelet count decreased (Gr 4)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>Weight gain</td>
<td>Neutrophil count decreased (Gr 3)</td>
</tr>
<tr>
<td>Electrocadiogram QT corrected interval prolonged</td>
<td>Weight loss</td>
<td>Platelet count decreased (Gr 4)</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>White blood cell decreased</td>
<td>White blood cell decreased (Gr 3)</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INVESTIGATIONS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>METABOLISM AND NUTRITION DISORDERS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td></td>
<td>Anorexia (Gr 3)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td></td>
<td>Hypophosphatemia (Gr 3)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>Tumor lysis syndrome</td>
<td></td>
</tr>
<tr>
<td>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td></td>
<td>Myalgia (Gr 2)</td>
</tr>
<tr>
<td>Myalgia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NERVOUS SYSTEM DISORDERS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td>Headache (Gr 3)</td>
</tr>
<tr>
<td>Headache</td>
<td>Intracranial hemorrhage</td>
<td>Leukoencephalopathy</td>
</tr>
<tr>
<td></td>
<td>Reversible posterior leukoencephalopathy syndrome</td>
<td></td>
</tr>
<tr>
<td>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td></td>
<td>Dyspnea (Gr 3)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Laryngeal mucositis</td>
<td>Pleural effusion (Gr 3)</td>
</tr>
<tr>
<td></td>
<td>Pharyngeal mucositis</td>
<td></td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>Pneumonitis</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td></td>
<td>Tracheal mucositis</td>
<td></td>
</tr>
<tr>
<td>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
<td>Erythema multiforme</td>
</tr>
<tr>
<td>Rash maculo-papular</td>
<td>Stevens-Johnson syndrome</td>
<td>Rash maculo-papular (Gr 2)</td>
</tr>
<tr>
<td></td>
<td>Rash acniform</td>
<td>Toxic epidermal necrolysis</td>
</tr>
<tr>
<td>VASCULAR DISORDERS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flushing</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1This 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.

2Gastrointestinal 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.

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

4Gastrointestinal 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:

<table>
<thead>
<tr>
<th>CARDIAC DISORDERS</th>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td>GASTROINTESTINAL DISORDERS</td>
<td>Ascites; Colitis; Dry mouth; Dysphagia; Enterocolitis; Esophageal flatulence; Gastritis; Gastrointestinal disorders - Other (ana fissure); Gastrointestinal disorders - Other (hematemeses); Gastrointestinal disorders - Other (mouth ulceration); Gastrointestinal disorders - Other (oral soft tissue disorder); Gastrointestinal disorders - Other (opharyngeal pain); Gastrointestinal disorders - Other (tongue erosion); Gastrointestinal ulcer - ileus; Oral pain; Pancreatitis; Periodontal disease; Stomach pain</td>
</tr>
<tr>
<td>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</td>
<td>Chills; Edema face; Edema trunk; Flu like symptoms; Gait disturbance; General disorders and administration site conditions - Other (temperature intolerance); Localized edema; Malaise</td>
</tr>
<tr>
<td>HEPATOBILIARY DISORDERS</td>
<td>Cholecystitis; Hepatobiliary disorders - Other (cholelithiasis)</td>
</tr>
<tr>
<td>IMMUNE SYSTEM DISORDERS</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>INFECTIONS AND INFESTATIONS</td>
<td>Infections and infestations - Other (herpes virus infection)</td>
</tr>
<tr>
<td>INJURY, POISONING AND PROCEDURAL COMPLICATIONS</td>
<td>Bruising</td>
</tr>
<tr>
<td>INVESTIGATIONS</td>
<td>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 (temperature abnormal); Lymphocyte count decreased; Lymphocyte count increased</td>
</tr>
<tr>
<td>METABOLISM AND NUTRITION DISORDERS</td>
<td>Dehydration; Hyperkalemia; Hyperuricemia; Hypoalbuminemia; Hypomagnesemia; Hyponatremia</td>
</tr>
<tr>
<td>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</td>
<td>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</td>
</tr>
<tr>
<td>NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (hemangiomatosis)</td>
</tr>
<tr>
<td>NERVOUS SYSTEM DISORDERS</td>
<td>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</td>
</tr>
<tr>
<td>PSYCHIATRIC DISORDERS</td>
<td>Anxiety; Confusion; Depression; Insomnia; Libido decreased; Suicidal ideation</td>
</tr>
<tr>
<td>RENAL AND URINARY DISORDERS</td>
<td>Acute kidney injury; Proteinuria; Urinary frequency</td>
</tr>
<tr>
<td>REPRODUCTIVE SYSTEM AND BREAST DISORDERS</td>
<td>Gynecomastia; Irregular menstruation</td>
</tr>
</tbody>
</table>
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.

7.6 Clinical Trials Agreement
The agent supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as “Collaborators”) 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/industry) 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
   Executive Plaza North, Suite 7111
   Bethesda, Maryland 20892
   FAX 301-402-1584
   Email: anshers@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.

7.7 Adverse Events Guidelines (1/12/16)

Beginning October 1, 2010, this study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for grading of all adverse events. A copy of the CTCAE v4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). The CTEP home page also can be accessed from the RTOG web page at http://www.rtog.org/regulatory/regs.html. All appropriate treatment areas should have access to a copy of the CTCAE v4.0.

All adverse events (AEs) as defined in the tables below will be reported via CTEP-AERS (CTEP Adverse Event Reporting System) application accessed via the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

Serious adverse events (SAEs) as defined in the tables below will be reported via CTEP-AERS. In order to ensure consistent data capture, serious adverse events reported on CTEP-AERS reports also must be reported on an RTOG case report form (CRF). In addition, sites must submit CRFs in a timely manner after CTEP-AERS submissions.

7.7.1 Adverse Events

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.]

The following guidelines for reporting adverse events (AEs) apply to all NCI/RTOG research protocols. AEs, as defined above, experienced by patients accrued to this protocol should be reported on the AE section of the appropriate case report form (see Section 12.1). Note: AEs indicated in the CTEP-AERS Expedited Reporting Requirements in text and/or table in Section 7.8 also must be reported via CTEP-AERS.
NOTE: If the event is a Serious Adverse Event (SAE) [see next section], further reporting will be required. Reporting AEs only fulfills Data Management reporting requirements.

7.7.2 Serious Adverse Events (SAEs) (5/6/09)
All SAEs that fit any one of the criteria in the SAE definition below must be reported via CTEP-AERS. Contact the CTEP-AERS Help Desk if assistance is required.

Certain SAEs as outlined below will require the use of the 24 Hour CTEP-AERS Notification:
- **Phase II & III Studies**: All unexpected potentially related SAEs
- **Phase I Studies**: All unexpected hospitalizations and all grade 4 and 5 SAEs regardless of relationship

**Definition of an SAE**: Any adverse experience occurring during any part of protocol treatment and for 30 days after that results in any of the following outcomes:
- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE drug experience, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.] Any pregnancy occurring on study must be reported via CTEP-AERS as a medically significant event.

Pharmaceutically sponsored studies will require additional reporting over and above that which is required by CTEP.

SAEs (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable, or definite) should be reported via CTEP-AERS.

All supporting source documentation indicated as being provided in the Additional Information Section of the CTEP-AERS Report must be properly labeled with the study/case numbers, the CTEP-AERS ticket number, and the date of the event and must be faxed to both the NCI at 301-230-0159 and the RTOG dedicated SAE FAX, 215-717-0990, before the five or ten-calendar-day deadline to allow RTOG to comply with the reporting requirements of the pharmaceutical company/companies supporting the RTOG trial. The RTOG Case Number without any leading zeros should be used as the Patient ID when reporting via CTEP-AERS. Non-RTOG intergroup study and case numbers must also be included, when applicable. Submitted CTEP-AERS Reports are forwarded to RTOG electronically via the CTEP-AERS system. Use the patient’s case number as the patient ID when reporting via CTEP-AERS.

SAE reporting is safety related and separate and in addition to the Data Management reporting requirements as outlined in the previous AE reporting section. Any event that meets the above outlined criteria for an SAE but is assessed by the CTEP-AERS System as “expedited reporting NOT required” must still be reported for safety reasons and to fulfill the obligations of RTOG to the pharmaceutical company/companies supporting the RTOG trial. Sites must bypass the “NOT Required” assessment and complete and submit the report. CTEP-AERS allows submission of all reports regardless of the results of the assessment. Note: Sites must select the option in CTEP-AERS to send a copy of the report to the FDA or print the CTEP-AERS report and fax it to the FDA, FAX 1-800-332-0178.

7.7.3 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)
AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the **NCI/CTEP Secondary AML/MDS Report Form** available at [http://ctep.cancer.gov/forms/index.html](http://ctep.cancer.gov/forms/index.html). The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification (RTOG study/case numbers). This form will take the place of a report via CTEP-AERS and must be faxed to the Investigational Drug Branch,
7.8 CTEP-AERS Expedited Reporting Requirements (5/1/14)

CTEP defines expedited AE reporting requirements for phase 2 and 3 trials as described in the table below. **Important:** All AEs reported via CTEP-AERS also must be reported on the AE section of the appropriate case report form (see Section 12.1).

7.8.1 Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND: CTEP-AERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days of the Last Dose of the Investigational Agent [Dasatinib] in this Study

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 3</th>
<th>Grades 4 &amp; 5</th>
<th>Grades 4 &amp; 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexpected and Expected</td>
<td>Unexpected</td>
<td>Expected</td>
<td>Unexpected without Hospitalization</td>
<td>Expected without Hospitalization</td>
<td>Unexpected</td>
<td>Expected</td>
</tr>
<tr>
<td>Unrelated</td>
<td>Not Required</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
</tr>
<tr>
<td>Unlikely</td>
<td>Not Required</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
</tr>
</tbody>
</table>

Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:

**CTEP-AERS 24-hour notification followed by complete report within 5 calendar days for:**
- Grade 4 and Grade 5 unexpected events
- CTEP-AERS 10 calendar day report:
  - Grade 3 unexpected events with hospitalization or prolongation of hospitalization
  - Grade 5 expected events

Although an CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Please see exceptions below under section entitled “Additional Instructions or Exceptions.”

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. “On study” is defined as during or within 30 days of completing protocol treatment.

- 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.
- 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 assigned during trial registration on all reports.
8.0 SURGERY
Not applicable to this trial.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy

There is a potential for interaction of dasatinib with other concomitantly administered drugs. Therefore, all prescription and over-the-counter medications as well as herbal treatments or alternative medicines must be fully documented in the case report forms (including indication and dates of administration). All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site’s source documents as concomitant medication.

9.1.1 Anticonvulsants: Anti-seizure medications should be used as indicated. However, only patients taking non-hepatic enzyme inducing antiepileptic drugs (non-EIAEDs) or no antiepileptic drugs are eligible to enroll on this trial. Patients must not be taking EIAEDs for at least 2 weeks prior to registration. See Appendix IV for a list of EIAEDs and non-EIAEDs.

During therapy, patients who were previously on a non-EIAED and need to change anticonvulsants should be started on another non-EIAED if at all possible. No delays in treatment would be required.

Patients who were previously on no anticonvulsants should be treated with non-EIAEDs if at all possible.

If a patient is started on an EIAED while on the study, he/she should immediately be started on another non-EIAED and the EIAED should be tapered and discontinued as quickly as possible. The patient may continue the current dasatinib dose while a non-EIAED is re-started because an EIAED will likely increase metabolism of dasatinib, reducing rather than increasing any potential anti-tumor effect, and therefore any efficacy bias introduced would be negative rather than positive. The dates that the patient took an EIAED should be noted.

Patients who were previously on a non-EIAED and need to permanently change anticonvulsant, but who cannot change to another non-EIAED, will be taken off study.

9.1.2 Analgesics: As needed.

9.1.3 Hematopoietic growth factors: Permitted at the investigator’s discretion and should follow American Society of Clinical Oncology guidelines for their use.

9.1.4 Nutritional supplementation: Permitted.

9.1.5 Antacids: Systemic antacids (H₂ receptor antagonists and proton pump inhibitors) are prohibited. Patients who require antacids should use short-acting, locally-active agents (e.g., Maalox, Mylanta, etc.). However, these agents should not be taken within either 2 hours before or 2 hours after the dasatinib dose.

This is particularly of note for patients with gliomas who are often routinely prescribed H₂ blockers, proton pump inhibitors, or locally-active antacids in association with corticosteroids.

9.1.6 Bisphosphonates: Bisphosphonate therapy should be withheld for the first 8 weeks of treatment in patients receiving such treatment pending assessment of the need for calcium supplementation (see below). If patient’s serum calcium levels remain above the lower limit of normal, patients on prior bisphosphonate therapy may be restarted with caution at the investigator’s discretion.

9.1.7 Calcium supplements: Calcium supplements (e.g., calcium carbonate, 500 mg PO three times daily) may be required to maintain serum calcium levels above the lower limit of normal during dasatinib treatment. Vitamin D supplements (e.g., ergocalciferol, 400 IU PO daily) may be appropriate for persistent hypocalcemia. Bisphosphonate therapy should be deferred in the presence of hypocalcemia.

9.1.8 Antiemetics/antidiarrheals: The nausea, vomiting, and diarrhea that may occur with dasatinib administration can generally be managed through the use of appropriate supportive measures (antiemetics - e.g., 5-HT₃ antagonists, benzodiazepines, prochlorperazine, and anti diarrheal medications - e.g., loperamide). Granisetron, an antiemetic that does not prolong QTc intervals, should be considered early in treatment.
9.1.9 Supportive care for fluid retention: Fluid retention, including pleural effusions, should be controlled by early institution of diuresis (e.g., furosemide, 20-40 mg PO daily and/or spironolactone, 25-50 mg PO, titrated to symptoms). Pleural effusions that remain or become symptomatic despite diuresis should be managed with thoracentesis. Steroid treatment may also be effective for pleural effusion. Chest discomfort may be related to a pericardial effusion; and an echocardiogram should be performed to investigate this possibility in such cases.

9.1.10 Supportive care for inflammation: Inflammation (e.g., pneumonitis, colitis, skin rash) may be appropriately managed with dasatinib interruption and short-term steroid treatment (e.g., 5-7 days methylprednisolone with rapid taper). Concurrent antibiotics are appropriate if there is clinical suspicion of infection.

9.2 Non-permitted Supportive Therapy (9/5/07)

9.2.1 CYP3A4 inhibitors: Agents or substances that strongly induce or inhibit CYP3A4 are prohibited during dasatinib treatment because the patient’s exposure to dasatinib is significantly affected by such materials. For CYP3A4 inhibitors, a washout period of ≥7 days is required prior to starting dasatinib. The washout period should be based on the half life of the particular CYP 3A4 inhibitor which can be substantially longer than 7 days in some cases. The Study Chair should be alerted if the patient is taking any agent known to affect or with the potential to affect selected P450 isoenzymes. See Appendix IV for a list of specifically prohibited CYP3A4 inhibitors and inducers.

Other inhibitors, inducers, and substrates of CYP3A4 may affect dasatinib metabolism, and restriction of their use is recommended. Additional information can be found at http://medicine.iupui.edu/flockhart/.

9.2.2 Agents with proarrhythmic potential: Use of agents with proarrhythmic potential is not permitted during the study, and a washout period of ≥7 days is required prior to starting dasatinib. The washout period should be based on the half life of the particular proarrhythmic agent which can be substantially longer than 7 days in some cases (e.g., amiodarone). See Appendix IV for a list of proarrhythmic agents that are specifically prohibited during dasatinib treatment. A comprehensive list of agents with the potential to cause QTc prolongation can be found at http://torsades.org.

9.2.3 Anticoagulants/medications that inhibit platelet function: Thrombocytopenia and hemorrhagic events can occur with dasatinib treatment. For this reason, patients may not be taking anticoagulants or medications that inhibit platelet function at study entry, including but not limited to warfarin, heparin, aspirin, clopidogrel, ticlopidine, and Aggrenox. All such medications must have been stopped ≥7 days prior to starting dasatinib to allow an appropriate washout period. If the patient requires any surgical (including dental) procedure while on study, dasatinib should be stopped 1 day before the procedure and not reinstituted until 1 to 2 days afterward or until adequate hemostasis is achieved. However, if patients develop a medical problem during treatment that would otherwise require use of such agents (including but not limited to ischemic stroke, transient ischemic attack, deep venous thrombosis, pulmonary embolus, myocardial infarction or ischemia/angina) that is felt by the treating physician to be unrelated or unlikely to be related to dasatinib, then anticoagulants and/or antiplatelet agents may be used but only with caution if clearly medically indicated. Patients should also be instructed that concurrent treatment with anticoagulants/antiplatelet drugs and dasatinib may increase a risk of hemorrhage.

9.2.3.1 Ibuprofen and other NSAIDs: As ibuprofen and other NSAIDs can also inhibit platelet function, patients may not be taking ibuprofen or other NSAIDs at study entry, and such agents must also have been stopped ≥7 days prior to starting dasatinib to allow an appropriate washout period. If a patient develops pain during treatment that is felt by the treating physician to require the use of ibuprofen or another NSAID, then such agents may be used but only with caution if clearly medically indicated. Patients should also be instructed that concurrent treatment with ibuprofen/NSAIDs and dasatinib may increase a risk of hemorrhage.

9.2.4 Herbal products: Discouraged.

10.0 TISSUE/SPECIMEN SUBMISSION

10.1 General Information (10/22/14)

The NRG Oncology Biospecimen Bank at the University of California San Francisco acquires and maintains high quality specimens from NRG Oncology trials. Tissue from each block is preserved through careful block storage and processing. The NRG Oncology Biospecimen Bank provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic
questions. The Biospecimen Bank also collects tissue for central review of pathology. Central review of tissue can be for eligibility and/or analysis.

In this study, tissue will be submitted for central pathology review (mandatory), pre-dasatinib molecular analysis (mandatory), post-dasatinib molecular analysis (strongly recommended for patients who undergo re-resection), and tissue banking (recommended).

### 10.1.1 Molecular Analysis Related to Dasatinib Treatment

In brief, we will attempt to identify pre-treatment molecular features of tumor tissue that predict response or progression. In this way, subsets of GBMs that may be more or less likely to respond to treatment with dasatinib can be identified. Tissue resected following disease progression will be used to determine molecular correlates of treatment failure. Tissue analyses will be performed in the laboratory of Dr. Ken Aldape. This will include immunohistochemistry of unstained slides and other assays. See Section 1.3 for additional information.

### 10.2 For Patients Accrued to Stage 1 or Stage 1B (cohort RE-OPENED as of May 5, 2009): (4/14/09)

#### Specimen Collection for Central Pathology Review and Pre-Dasatinib Molecular Analysis (mandatory PRE-registration)

10.2.1 For patients **WHO HAVE** undergone central pathology review through enrollment on another RTOG GBM trial:

Contact the NRG Oncology Biospecimen Bank at the address listed below. The Biospecimen Bank will forward any needed material to Dr. Aldape.

**Mailing Address: For Non-frozen Specimens Only**
NRG Oncology Biospecimen Bank
University of California San Francisco
Campus Box 1800
1657 Scott Street, Room 223
San Francisco, CA 94143-1800

**Courier Address (FedEx, DHL, etc.): For Frozen Specimens**
NRG Oncology Biospecimen Bank
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

Questions: 415-476-7864/FAX 415-476-5271; RTOG@ucsf.edu

10.2.2 For patients **WHO HAVE NOT** undergone central pathology review through enrollment on another RTOG GBM trial:

Submit the following materials directly to Dr. Aldape (see Section 10.6 for contact information):

- At least one and preferably all H & E stained slides containing tumor
- A paraffin-embedded tissue block labeled with the surgical pathology number. If the block is unavailable, 15 unstained slides may be submitted. Blocks or slides must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.
- A Pathology Report documenting that the submitted tissue contains tumor
- A Specimen Transmittal Form (ST)
- A Central Pathology Review Form (P4) completed by the local pathologist

Once all analyses are complete, Dr. Aldape will email the P6 form to the institution. If the patient over-expresses at least 2 dasatinib targets, the patient can be registered to the trial per Section 5.0. Dr. Aldape will then send remaining material to the NRG Oncology Biospecimen Bank for consenting patients (See Section 10.5). He will return remaining material to the submitting institution for non-consenting patients. **Please note that anticipated turnaround time from receipt of tissue to determination of molecular profile for eligibility will be approximately**
one week. Patients cannot be registered until this is complete and Dr. Aldape has approved the P6 form. This may necessitate repeating of some examinations.

10.3 For Patients Accrued to Stage 2 Through Study Closure (cohort CLOSED/NOT CURRENTLY APPLICABLE): (4/14/09)

NOTE: Tissue submission is required for this cohort, but molecular profiling will not be performed before registration and is not an eligibility criteria.

Specimen Collection for Central Pathology Review and Pre-Dasatinib Molecular Analysis (mandatory POST-registration)

10.3.1 For patients WHO HAVE undergone central pathology review through enrollment on another RTOG GBM trial:

Contact the RTOG Biospecimen Resource at the address listed below. The Biospecimen Resource will forward any needed material to Dr. Aldape.

Mailing Address: For Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
1657 Scott Street, Room 223
San Francisco, CA 94143-1800

Courier Address (FedEx, DHL, etc.): For Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

Questions: 415-476-RTOG (7864)/FAX 415-476-5271; RTOG@ucsf.edu

10.3.2 For patients WHO HAVE NOT undergone central pathology review through enrollment on another RTOG GBM trial:

Submit the following materials directly to Dr. Aldape:

- At least one and preferably all H & E stained slides containing tumor
- A paraffin-embedded tissue block labeled with the surgical pathology number. If the block is unavailable, 15 unstained slides may be submitted. Blocks or slides must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.
- A Pathology Report documenting that the submitted tissue contains tumor. The report must include the RTOG protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.
- A Specimen Transmittal Form clearly stating that tissue is being submitted to Dr. Aldape. The form must also include the RTOG protocol number and patient’s case number.
- A Central Pathology Review Form (P4) completed by the local pathologist

Submit all materials to Dr. Aldape per Section 10.6.

Once all analyses are complete, Dr. Aldape will send remaining material to the RTOG Biospecimen Resource for consenting patients (See Section 10.5). He will return remaining material to the submitting institution for non-consenting patients.

10.4 Specimen Collection for Post-Dasatinib Molecular Analysis (strongly recommended for patients who undergo re-resection)

Submit the following materials directly to Dr. Aldape:

- A paraffin-embedded tissue block labeled with the surgical pathology number. If the block is unavailable, 15 unstained slides may be submitted. Block or slides must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.
- A Pathology Report documenting that the submitted tissue contains tumor. The report must include the RTOG protocol number and patient’s case number. The patient’s name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.
- A Specimen Transmittal Form clearly stating that tissue is being submitted to Dr. Aldape. The form must also include the RTOG protocol number and patient’s case number.

10.5 Specimen Collection for Tissue Banking (recommended but not required) (4/14/09)
Tissue sent per Sections 10.2 and 10.3 will be stored at the NRG Oncology Biospecimen Bank for patients consenting to the banking of their tissue for future research outside of this study.

10.6 Specimen Submission Mailing Information
Submit all materials to:

Ken Aldape, MD
Toronto General Hospital
200 Elizabeth Street, 11th Floor
Toronto, Ontario M5G 2C4 Canada

ken.aldape@uhn.ca

10.7 Reimbursement
Please note that with the start of the new NCI National Clinical Trials Network (NCTN) Program, NCI funds for reimbursement for protocol-specified biospecimen materials will be distributed per the requirements/methods specified by the new NCTN Program. This information will be made available with the other registration materials in the Oncology Patient Enrollment Network (OPEN) portal system. OPEN will serve as the registration system for all patient enrollments onto NCI-sponsored NCTN trials, including this study, which will be transitioned into the new Program from the NCI-sponsored Cooperative Group Clinical Trials Program.

10.8 Confidentiality/Storage (10/22/14)
(See the Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/biospecimen/tissuefaq.html for further details.)

10.8.1 Upon receipt, the specimen is labeled with the NRG Oncology/RTOG protocol number and the patient’s case number only. The NRG Oncology Biospecimen Bank database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.8.2 Specimens for tissue banking will be stored for an indefinite period of time. Specimens for central review will be retained until the study is terminated. Specimens for the molecular analysis component of this protocol will be retained until the study is terminated, unless the patient has consented to storage for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters: See Appendix II.

11.2 Measurement of Effect

11.2.1 Antitumor Effect – Solid Tumors
The primary endpoint of this study is 6-month progression free-survival. Therefore, measurable disease is not required for study entry. However, radiographic responses will be measured.

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. The same technique (CT or MRI) must be used for intrapatient comparisons throughout the study.

11.2.1.1 Definitions
Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with dasatinib.
Evaluable for 6-month progression-free survival: All patients will be evaluable for 6mPFS except those that are removed from the study before the end of cycle 1 for reasons other than clinical progression (such as toxicity). Patients who suffer clinical progression without radiographic confirmation of progression will be considered to have progressive disease in determination of 6mPFS.

Evaluable for radiographic response (CR or PR) rate: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated radiographically will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. Patients with measurable disease at study entry who suffer clinical progression without radiographic confirmation of progression will be considered to have progressive disease in determination of radiographic response rate. Clinical progression requires the absence of other causes of decline, such as anticonvulsant toxicity or overly rapid corticosteroid taper, and that steroids be increased to a prior level before scoring as progression.

### 11.2.1.2 Disease Parameters and Response Criteria

Response and progression will be evaluated in this study using standard criteria for patients with malignant gliomas. A major difference from RECIST and other criteria for measuring response in solid tumors is the requirement that patients be on a stable or decreasing dose of corticosteroids when evaluating for response because of the potentially confounding impact of corticosteroids on contrast enhancement during brain tumor imaging. The tumor size will be measured in millimeters and is the largest cross-sectional area using perpendicular measurements of contrast enhancing abnormality.

**Complete Response (CR):** Complete disappearance of all enhancing tumor on consecutive CT or MRI scans at least 1 month apart, off corticosteroids, and neurologically stable or improved.

**Partial Response (PR):** ≥ 50% decrease in size of enhancing tumor on consecutive CT or MRI scans at least 1 month apart, corticosteroids stable or reduced, and neurologically stable or improved.

**Stable Disease (SD):** Does not qualify for CR, PR, or PD.

**Progression:** ≥ 25% increase in the size of enhancing tumor or any new tumor; or neurologically worse, and steroids stable or increased.

**Best Radiographic Response:** The best response will be defined as the best radiographic response (CR, PR, SD, or PD) for patients evaluable for radiographic response.

### 11.2.1.3 Duration of Response

**Duration of overall response:** The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

**Duration of stable disease:** Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

### 11.2.1.4 Progression-Free Survival

Progression-free survival is defined as the duration of time from start of treatment to time of progression or death.
12.0 DATA COLLECTION (1/12/16)
Data should be submitted to:

NRG Oncology*  
1818 Market Street, Suite 1720  
Philadelphia, PA 19103

*If a data form is available for web entry, it must be submitted electronically.

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 Summary of Data Submission

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Analysis Form (P6)</td>
<td>A copy of the form must be mailed to NRG Oncology with the following identifiers: case # and institution #</td>
</tr>
<tr>
<td>(emailed by Dr. Aldape to your institution)</td>
<td></td>
</tr>
<tr>
<td>Demographic Form (A5)</td>
<td>For Stage 1B Patients: Prior to registration (see Section 10.2.2)</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td>For All Other Patients: Within 4 weeks after registration (see Section 10.3.2.)</td>
</tr>
<tr>
<td>Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>Slides/Blocks (P2)</td>
<td></td>
</tr>
<tr>
<td>Specimen Transmittal Form (ST)</td>
<td></td>
</tr>
<tr>
<td>For patients without prior RTOG tissue banking</td>
<td></td>
</tr>
<tr>
<td>Specimen Transmittal Form (SP)</td>
<td></td>
</tr>
<tr>
<td>For patients with prior RTOG tissue banking</td>
<td></td>
</tr>
<tr>
<td>Central Pathology Review Form (P4)</td>
<td></td>
</tr>
<tr>
<td>Follow-up Form (F1)</td>
<td>Every 4 weeks while the patient is receiving dasatinib; every 8 weeks after dasatinib treatment has been discontinued.</td>
</tr>
</tbody>
</table>
13.0  **STATISTICAL CONSIDERATIONS**

13.1  **Study endpoints (4/14/09)**

13.1.1  **Primary Endpoint**

13.1.1.1  To estimate the 6-month progression-free survival rate (6mPFS)

13.1.2  **Secondary Endpoints**

13.1.2.1  To estimate the rate of patients achieving objective response (PR or CR) OR 6mPFS

13.1.2.2  To estimate the overall survival distribution

13.1.2.3  To estimate rates of treatment adverse events

13.1.2.4  To estimate treatment objective response rates (complete response, partial response, stable disease, progression)

13.1.2.5  To estimate the progression-free survival distribution

13.1.2.6  To explore molecular correlates of clinical outcome

13.1.2.7  To explore pharmacokinetic correlates of dosing, toxicity, and efficacy

13.2  **Sample Size (4/14/09)**

13.2.1  **Sample Size Derivation**

This study is designed using the method described by Fleming. 

An as yet unpublished analysis of a data set from the North American Brain Tumor Consortium pooled data from multiple phase II clinical trials for recurrent/progressive GBM, all of which were considered negative. This study demonstrated an overall 6mPFS rate of 7% for patients with recurrent/progressive GBMs treated with small molecule inhibitors as single agents, and represents an update to the study published in 1999. 

However, this 6mPFS rate (7%) was derived from trials that accrued patients without regard to molecular pre-screening. Among pre-screened patients representing a population enriched for tumors likely to be dasatinib sensitive, we would require a higher level of efficacy to reject the hypothesis that the drug is ineffective in recurrent/progressive GBM. We are also accepting radiographic responses that are not sustained for at least 6 months as evidence of efficacy in order to reduce the time required to complete step one of the trial. Accepting non-sustained responses further raises our efficacy goals to declare the drug possibly active. Therefore, we are requiring that at least 3 patients in the first step demonstrate 6 months of progression-free survival or objective radiographic responses (regardless of duration) in order to proceed to step two. If fewer than 3 patients in the first step demonstrate 6 months of progression-free survival or objective radiographic responses, accrual to the trial will be terminated at the time that this determination is made.

With our primary endpoint being a hybrid of objective response and 6mPFS, we will set \( p_0 \) to 11% as the estimate of 6mPFS assuming dasatinib to be ineffective. This is based on the molecular heterogeneity in the entire cohort of patients in both steps one and two, with \( p_0 \) between 7% in unselected patients and at least twice that (14%) in the patients with tumors overexpressing at least 2 known dasatinib targets. We will set \( p_1 \) to 25% (looking for an improvement of 14%). Error rates will be set at 5% for the false positive rate (alpha) and 5% for the false negative rate (beta). Based on the above design parameters, a sample size of 77 patients will be required. Twenty-seven analyzable patients (which, as described in the background will consist only of patients having what is suspected to be a molecular profile making them sensitive to dasatinib) will be accrued in the first step, with an additional 50 analyzable patients to be accrued based on the results of the first group of patients without regard to molecular profiling.

13.2.2  **Revised Study Design**

Among the first 29 patients entered into stage 1 for the original design, 26 patients were analyzable. One patient achieved 6 months of progression-free survival; one patient achieved a partial radiographic response confirmed on a follow up brain MRI; one patient statistically achieved 6 months of progression-free survival with the MRI performed after 7 months demonstrating disease progression. However, it is also possible this patient had a progression-free survival of less than 6 months even though he remained stable 5 months after registration. Therefore, based on the analysis of these 26 analyzable patients, the evidence of efficacy to support opening stage 2 as originally planned if at least 3 patients demonstrated efficacy (which for the purposes of proceeding to stage 2 was defined as either 6mPFS or radiographic response of any duration) is ambiguous. The toxicity analysis based on the 26 analyzable patients shows that toxicity was relatively mild, and the conjecture is that a higher dose may
have produced greater efficacy without undue toxicity; therefore, this study was amended to allow intrapatient dose-escalation. Stage 1B is used to address the possibility of dose escalation following 1 cycle of therapy absent a DLT (defined in section 7.3.1). If dose escalation to level 1 (250 mg total per day, see Section 7.3) for cycle 2 is possible without a resulting DLT, that dose escalation will be considered tolerable. Patients entered on stage 1B will be used to address the possibility of dose escalation improving the efficacy. The tolerability of intrapatient dose escalation will initially be evaluated in the first 10 patients who complete at least 2 cycles or whose treatment was discontinued either in the first or second cycle because of toxicity. Patients who discontinue therapy because of progressive disease before completing the second cycle will not be included in this analysis but will be included in the efficacy analyses.

The study will utilize a two-stage phase II design [stage 1 (1B) and stage 2]. We will keep the original study hypothesis: p0 to 11% (null hypothesis); p1 to 25% with a 14% increase (alternative hypothesis). Error rates will be set at 10% for the false-positive rate (alpha) and 10% for the false-negative rate (beta). Simon's minmax two-stage designs is use to calculate the required sample size.64 Stage 1 (stage 1B) consists of 27 analyzable patients. Guarding against up to a 10% ineligibility rate and possible patient drop-out, accrual for stage 1B will be 29 cases in order to ensure 27 analyzable patients. If 2 or fewer patients experience 6-month PFS or objective radiographic responses (regardless of duration), accrual to the trial will be terminated to reject the experimental arm (regardless of the analysis of intrapatient dose escalation feasibility). Otherwise accrual will continue to a total of 50 analyzable patients. However, for the final efficacy analysis after stage 2, the primary endpoint will be only 6mPFS. If stage 2 continues, the following rules will be used to judge the efficacy of the experimental arm: if 8 or fewer patients experience 6mPFS, we will reject the alternative hypothesis that the 6mPFS rate of the experimental arm is 25%; if 9 or more patients experience 6mPFS, we will reject the null hypothesis that the 6-month PFS of the experimental arm is 11%. Guarding against up to a 10% ineligibility rate and possible patient drop out, accrual for stage IB and 2 will be 55 cases in order to ensure 50 analyzable patients. With 29 patients having already finished the initial stage 1 assessment, the total target sample size of the revised study design becomes 84.

13.3 Patient Accrual (5/6/09)
Based on the accrual experience in the first 29 patients in the original stage 1, the monthly accrual rate is expected to be at least 4 cases 4 months after re-opening. Therefore, it is anticipated that the 29 patients for stage 1B will be accrued in approximately 11 months. As all patients may need to be followed for a minimum of 6 months in order to demonstrate 6mPFS, it may be a minimum of 9 months between the time that the first stage of accrual is met, all relevant case report forms are received and processed at RTOG Headquarters, and the decision is made as to whether there is sufficient evidence to proceed to the second stage of accrual. This interval may be shorter since radiographic response (PR or CR) of any duration is also considered a success. Should the determination be made that the study be reopened for the second stage of patient accrual, it is anticipated that it will take no longer than 6 months to accrue the required 26 patients (23 analyzable patients). Patients will be accrued in the second stage without regard to molecular profiling of pre-dasatinib tissue.

13.4 Analysis Plan (5/6/09)
13.4.1 Special Interim Analysis of Intrapatient Dose-Escalation
The analysis will occur when there are 10 patients who complete at least 2 cycles or whose treatment was discontinued either in the first or second cycles because of toxicity. Patients with progressive disease during the first or second cycle will not be included in this analysis. Patients who complete the second cycle and have progressive disease before cycle 3 will be included. If intrapatient dose escalation to ≥ dose level 1 occurs in at least 6 of these 10 patients (a majority) and no DLT is subsequently observed with the escalated dose level 1, then intrapatient dose-escalation will be judged tolerable and safe. If there are less then 6 patients, then intrapatient dose escalation will be judged as NOT tolerable and should not be used. In that event, accrual will be terminated and stage 2 will not be conducted. Patients remaining on study at that time may continue to take dasatinib at the discretion of the treating physician.

13.4.2 Primary Efficacy Endpoint for Stage 1B
If 2 or fewer of the 27 analyzable patients are alive and progression free at 6 months OR achieved a CR or PR objective response, we will accept the null hypothesis that the true 6mPFS rate with
dasatinib is no better than 11% and will not accrue any more patients to the study. Otherwise, we will accrue an additional 23 analyzable patients for stage 2 without regard to molecular profiling.

13.4.3 Primary Efficacy Endpoint Following Stage 2
The analysis will be performed after all stage 2 patients have been enrolled and potentially followed for 6 months. The decision as to the effectiveness of dasatinib will be based upon the combined stage 1B and stage 2 patients and is as follows:

13.4.3.1 If 9 or more of the cases (≥18%) are progression free and alive at 6 months, we will reject the null hypothesis that the true rate is no better than 11%.

13.4.3.2 If 8 or fewer of the cases (≤16%) are progression free and alive at 6 months, we will reject the alternative hypothesis that the true rate is at least 25%.

13.4.4 Secondary Endpoints

13.4.4.1 The crude incidence rates of treatment responses (PR + CR) and toxicity will be calculated for the combined analyzable stage 1B and stage 2 patients on the study. With 50 analyzable patients, the maximum width of any exact 95% confidence interval is less than 0.277.

13.4.4.2 The Kaplan-Meier method will be used to estimate the progression-free and overall survival distributions.

13.4.4.3 As patients in the second stage will be accrued without regard to molecular profiling, the entire cohort will contain patients with tumors that do and do not overexpress at least 2 known dasatinib targets. Pre-dasatinib tumor tissue from patients enrolled in step two will be molecularly profiled retrospectively. We will use results to explore whether dasatinib target expression influences response.

13.4.4.4 Pharmacokinetic (PK) Analyses

NOTE: PK analyses are mandatory for the first 10 eligible patients in stage 1B assessable for tolerability of intrapatient dose escalation (Section 13.4.1). PK analyses are optional for all patients thereafter.

Concentrations of dasatinib will be quantitated with a modification of an LC-MS/MS assay that was developed and validated by Bristol-Myers Squibb (BMS documents CEDRA DCN: 11-996-V1 and CEDRA DCN 11-996-V1 ad2). Authentic standards for dasatinib and stable-labeled internal standard have been provided by Bristol-Myers Squibb. Plasma is mixed with internal standard, after which dasatinib and internal standard are processed with solid phase extraction devices. Samples are analyzed on an LC-MS/MS system consisting of an Agilent 1100 refrigerated autosampler, solvent degasser and delivery system that is fitted with a Phenomenex phenyl-hexyl Luna analytical column (2x50 mm, 3 μm). Dasatinib and internal standard are eluted with an isocratic mobile phase that is pumped at 0.3 mL/min and consists of distilled water:methanol:ammonium acetate, pH 3.0. Column eluate is monitored with a Waters Quattro-Micro tandem mass spectrometer operating in positive ion electrospray mode. The ion transition monitored for dasatinib is m/z 488>401. The ion transition monitored for internal standard is m/z 494>407.

Dasatinib trough concentration, C_{max} and T_{max} will be determined visually from the plasma dasatinib concentration versus time curves. The area under the curve of dasatinib plasma concentrations versus time and the plasma half-life of dasatinib will be estimated non-compartmentally using PK Solutions 2.0 (Summit Research Services, Montrose, CO, USA; www.summitPK.com). In addition, a one-compartment model with zero-order absorption after a lag may also be fit to the dasatinib concentration versus time data. This will be done with the ADAPT 5 software for pharmacokinetic/pharmacodynamic systems analysis [D’Argenio DZ, Schumitzky A; ADAPT II user’s guide: pharmacokinetic/pharmacodynamic systems analysis software. University of Southern California, Los Angeles, 1997]. The maximum likelihood equation in ADAPT 5 will be used for all estimations.

13.4.5 Interim Analysis to Monitor the Study Progress

Interim reports will be prepared twice per year until the initial paper reporting the treatment results has been submitted. In general, the interim reports will contain information about the patient accrual rate with a projected completion date for the accrual phase; rates of patient exclusion due to ineligibility; compliance rate of treatment delivery with the distributions of important prognostic baseline variables; and the frequencies and severity of treatment-related adverse events. The interim reports will not contain the results from of the efficacy endpoints (progression-free survival or objective PR and CR rates).

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

13.5 Inclusion of Minorities (4/14/09)
In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we address this issue here, as we will also analyze treatment differences by gender, race, and ethnicity. The following table lists the projected accrual for each racial and ethnic group based upon previous RTOG GBM trials.

### Projected Distribution of Gender and Minorities

<table>
<thead>
<tr>
<th>Gender</th>
<th>Ethnic Category</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hispanic or Latino</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Not Hispanic or Latino</td>
<td>31</td>
<td>49</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Ethnic Category: Total of all subjects</td>
<td>31</td>
<td>52</td>
<td>83</td>
</tr>
<tr>
<td>Gender</td>
<td>Racial Category</td>
<td>Females</td>
<td>Males</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td>American Indian or Alaskan Native</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Black or African American</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Native Hawaiian or other Pacific Islander</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>White</td>
<td>29</td>
<td>50</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>Racial Category: Total of all subjects</td>
<td>31</td>
<td>52</td>
<td>83</td>
</tr>
</tbody>
</table>

Based upon the 29 patients entered into the original study, gender, race, and ethnicity projections have been modified for the revised study design as follows:

<table>
<thead>
<tr>
<th>Gender</th>
<th>Ethnic Category</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hispanic or Latino</td>
<td>12</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Not Hispanic or Latino</td>
<td>32</td>
<td>37</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>Ethnic Category: Total of all subjects</td>
<td>44</td>
<td>40</td>
<td>84</td>
</tr>
<tr>
<td>Gender</td>
<td>Racial Category</td>
<td>Females</td>
<td>Males</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td>American Indian or Alaskan Native</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Black or African American</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Native Hawaiian or other Pacific Islander</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>White</td>
<td>42</td>
<td>39</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>Racial Category: Total of all subjects</td>
<td>44</td>
<td>40</td>
<td>84</td>
</tr>
</tbody>
</table>
REFERENCES (4/14/09)

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have a glioblastoma, a type of brain tumor that has grown following treatment with radiation and the drug temozolomide.

Why is this study being done?

The purpose of this study is to find out what effects, good and/or bad, dasatinib has on you and your brain tumor. Dasatinib inhibits growth messages in tumor cells. Dasatinib is an investigational agent for the treatment of glioblastoma, although it has been approved by the Food and Drug Administration for another cancer type.

How many people will take part in the study? (5/6/09)
About 84 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the study … (5/18/07)
You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.
- Blood tests to check your blood counts, liver and kidney function
- MRI or CT scan of your brain
- EKG
- If you are a woman of childbearing potential, you will have a serum pregnancy test
In addition, your study doctor will need to send some of the tissue obtained at the time of your brain tumor surgery to a central pathology site. There, a pathologist will confirm that your tumor is a glioblastoma. The pathologist will also look at your tumor tissue to identify some of its molecular features; this will help the study doctors determine whether dasatinib works better with certain tumor features. This tissue submission to confirm that your tumor is a glioblastoma and to identify its molecular features is mandatory for study participation. **NOTE:** If you have already participated in a Radiation Therapy Oncology Group glioblastoma study that required submission of central pathology review, your study doctor may not need to send additional tissue, since your tissue is already in the tissue repository.

If you are one of the first group of patients to be considered for enrollment in this trial, you will have to wait until your tumor tissue is analyzed, which could take a week. If the results of this analysis reveal that your tumor is suspected of being affected by dasatinib, then you may be eligible to participate in this study. If the results of this analysis reveal that your tumor is suspected not to be affected by dasatinib, then you will not be eligible to participate in this study. If patients in the first group demonstrate response from dasatinib, an additional group of patients will be enrolled. If you are in this group of patients, you will not need to wait for the results to come back before you can enroll. Your tumor will still be analyzed for central review and molecular features. However, it will be analyzed at a later date.

**During the study … (4/14/09)**

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

- Routine blood tests every week
- Neurologic and physical exam every other week
- MRI or CT of your brain every 8 weeks
- EKG every 4 weeks

If you are among the first 10 analyzable patients to enroll in this study after **May 5, 2009**, you will also receive blood tests to determine the amount of dasatinib in your blood. Your blood will be tested for this purpose as follows:

- **At the beginning of cycle 1 (week 1) of your dasatinib treatment:**
  5 samples: just before you receive your morning dasatinib dose and 1, 2, 4, 6-8 hours afterwards

- **At the beginning of cycle 3 (week 9) of your dasatinib treatment:**
  5 samples: just before you receive your morning dasatinib dose and 1, 2, 4, 6-8 hours afterwards

- **At the beginning of cycle 5 (week 17) of your dasatinib treatment:**
  5 samples: just before you receive your morning dasatinib dose and 1, 2, 4, 6-8 hours afterwards

- **At the beginning of cycle 7 (week 25) of your dasatinib treatment:**
  5 samples: just before you receive your morning dasatinib dose and 1, 2, 4, 6-8 hours afterwards
[NOTE: If you enter the study after the first 10 analyzable patients have enrolled following May 5, 2009 then these blood tests will be optional.]

You will receive dasatinib orally (in tablet form) twice a day. You can take the dasatinib with or without food, but you should swallow it with at least 8 ounces of water. You can take the dasatinib indefinitely, as long as your tumor doesn’t grow and you don’t have side effects or other problems that prevent you from continuing the treatment. If you don’t have bad side effects, then your dose will be increased every 4 weeks.

You will also be asked to complete a medication diary while you are receiving dasatinib; this will help document when you take your medication and any side effects you experience.

WHEN I AM FINISHED TAKING DASATINIB …

The frequency of visits and scans after you have finished taking dasatinib will be determined by your study doctor as part of his or her standard way of monitoring your disease.

How long will I be in the study?

You will be asked to take dasatinib continuously unless your tumor grows. After you are finished taking dasatinib, we would like to keep track of your medical condition for the rest of your life.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the dasatinib can be evaluated by him/her. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the study? (1/12/16)

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, researchers don’t know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the dasatinib. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.
Risks and side effects related to dasatinib include those that are:

### Risk Profile for Dasatinib (CAEPR Version 2.6, September 1, 2015)

<table>
<thead>
<tr>
<th>COMMON, SOME MAY BE SERIOUS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In 100 people receiving dasatinib, more than 20 and up to 100 may have:</strong></td>
</tr>
<tr>
<td>- Anemia which may require blood transfusion</td>
</tr>
<tr>
<td>- Diarrhea, nausea</td>
</tr>
<tr>
<td>- Tiredness</td>
</tr>
<tr>
<td>- Bruising, bleeding</td>
</tr>
<tr>
<td>- Pain</td>
</tr>
<tr>
<td>- Headache</td>
</tr>
<tr>
<td>- Shortness of breath</td>
</tr>
<tr>
<td>- Fluid in the body</td>
</tr>
<tr>
<td>- Rash</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OCCASIONAL, SOME MAY BE SERIOUS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In 100 people receiving dasatinib, from 4 to 20 may have:</strong></td>
</tr>
<tr>
<td>- Infection, especially when white blood cell count is low</td>
</tr>
<tr>
<td>- Bloating, constipation, heartburn, vomiting</td>
</tr>
<tr>
<td>- Bleeding from multiple sites</td>
</tr>
<tr>
<td>- Internal bleeding which may cause black tarry stool or blood in vomit</td>
</tr>
<tr>
<td>- Sores in mouth which may cause difficulty swallowing</td>
</tr>
<tr>
<td>- Swelling of the body which may cause shortness of breath</td>
</tr>
<tr>
<td>- Fever</td>
</tr>
<tr>
<td>- Weight gain</td>
</tr>
<tr>
<td>- Weight loss, loss of appetite</td>
</tr>
<tr>
<td>- Dizziness</td>
</tr>
<tr>
<td>- Cough, sore throat</td>
</tr>
<tr>
<td>- Hair loss, itching, acne</td>
</tr>
<tr>
<td>- Flushing</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RARE, AND SERIOUS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In 100 people receiving dasatinib, 3 or fewer may have:</strong></td>
</tr>
<tr>
<td>- Heart failure or heart attack which may cause shortness of breath, swelling of ankles, and tiredness</td>
</tr>
<tr>
<td>- Change in the heart rhythm</td>
</tr>
<tr>
<td>- Kidney damage which may require dialysis</td>
</tr>
<tr>
<td>- Bleeding in the brain which may cause confusion</td>
</tr>
<tr>
<td>- Damage to organs which may cause changes in thinking</td>
</tr>
<tr>
<td>- Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome)</td>
</tr>
<tr>
<td>- Severe skin rash with blisters and peeling which can involve mouth and other parts of the body</td>
</tr>
</tbody>
</table>

You should not drink grapefruit juice while you are receiving dasatinib because it may interact with the way your body processes the drug. In addition, some over-the-counter and herbal
remedies may affect how your body handles dasatinib. If you participate in this study, you should talk to your study doctor before taking any of these products.

**Reproductive risks:** You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. If you are a woman of childbearing potential, you may have a pregnancy test before enrolling in this study.

For more information about risks and side effects, ask your study doctor.

**Are there benefits to taking part in the study?**

Taking part in this study may or may not make your health better. While researchers hope that dasatinib will be useful against your tumor, there is no proof of this yet. We do know that the information from this study will help researchers learn more about dasatinib as a treatment for cancer. This information could help future cancer patients.

**What other choices do I have if I do not take part in this study?**

Your other choices may include:

- Getting treatment or care for your tumor without being in a study
- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your study doctor about your choices before you decide if you will take part in this study.

**Will my medical information be kept private?**

Data are housed at NRG Oncology Statistics and Data Management Center in a password-protected database. We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations/individuals who may look at and/or copy your medical records for research, quality assurance, and data analysis include but are not limited to:

- NRG Oncology
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
 Qualified representatives of the sponsoring pharmaceutical company, Bristol-Myers Squibb

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

What are the costs of taking part in this study?

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

The study agent, dasatinib, will be provided free of charge while you are participating in this study. However, if you should need to take the study agent much longer than is usual, it is possible that the supply of free study agent that has been supplied to the NCI could run out. If this happens, your study doctor will discuss with you how to obtain additional drug from the manufacturer and you may be asked to pay for it.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute’s Web site at http://www.cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the “Clinical Trials and Insurance Coverage” information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, __________________ [investigator’s name(s)], if you feel that you have been injured because of taking part in this study. You can tell the study doctor in person or call him/her at ________________ [telephone number].

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of
your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

**Who can answer my questions about the study?**

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor __________________ [name(s)] at __________________ [telephone number].

For questions about your rights while taking part in this study, call the __________________ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at __________________ (telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). [*Only applies to sites using the CIRB.*]

Please note: This section of the informed consent form is about additional research that is being done with people who are taking part in the main study. You may take part in this additional research if you want to. You can still be a part of the main study even if you say ‘no’ to taking part in this additional research.

You can say “yes” or “no” to the following study. Below, please mark your choice.

**Use of Tissue for Research**

[The following example of tissue consent has been taken from the NCI Cancer Diagnosis Program’s model tissue consent form found at the following URL 

**Consent Form for Use of Tissue for Research**

**About Using Tissue for Research**

You have already had surgery to see what type of brain tumor you have. Your doctor removed some of your tumor to do some tests. The results of these tests were given to you by your doctor and were used to plan your care.

We would like to keep some of the tissue that is left over for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other
diseases. Please read the information sheet called “How is Tissue Used for Research” to learn more about tissue research. This information sheet is available to all at the following web site: http://www.cancerdiagnosis.nci.nih.gov/specimens/patient.pdf

If your tumor progresses while you are receiving dasatinib, your study doctor may suggest that you have more surgery on your tumor. If you do have surgery again, we would also like to keep some of the tissue that is left over. This will help us to see if your tumor progressed during dasatinib treatment due to certain molecular features of your tumor.

The research that may be done with your tissue is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your tissue will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

**Things to Think About**

The choice to let us keep the left over tissue for future research is up to you. No matter what you decide to do, it will not affect your care or your participation in the main part of the study.

If you decide now that your tissue can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue. Then any tissue that remains will no longer be used for research and will be returned to the institution that submitted it.

In the future, people who do research may need to know more about your health. While NRG Oncology may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue is used for genetic research (about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records. Your tissue will be used only for research and will not be sold. The research done with your tissue may help to develop new products in the future.

**Benefits**

The benefits of research using tissue include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

**Risks**

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

**Making Your Choice**
Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. My tissue may be kept for use in research to learn about, prevent, or treat cancer.
   Yes No

2. My tissue may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
   Yes No

3. Someone may contact me in the future to ask me to take part in more research.
   Yes No

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at: http://www.cancer.gov/

• For NCI’s clinical trials information, go to: http://cancer.gov/clinicaltrials/
• For NCI’s general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all ______ [insert total of number of pages] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant ________________________________

Date ________________________________
APPENDIX II (1/6/12)

STUDY PARAMETER TABLE
Baseline evaluations, including imaging studies, are to be conducted within 10 days of study registration and within 14 days of the administration of protocol therapy. In the event that the patient’s condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-Study</th>
<th>Wk 1</th>
<th>Wk 2</th>
<th>Wk 3</th>
<th>Wk 4</th>
<th>Wk 5</th>
<th>Wk 6</th>
<th>Wk 7</th>
<th>Wk 8</th>
<th>Wk 9</th>
<th>Wk 10</th>
<th>Wk 11</th>
<th>Wk 12</th>
<th>Wk 13 and on(^a)</th>
<th>Off Study(^b)</th>
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</thead>
<tbody>
<tr>
<td>Medical history</td>
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<td></td>
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<tr>
<td>Concurrent meds</td>
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<td>X</td>
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<tr>
<td>Physical exam</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>Vital signs</td>
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<td>Weight</td>
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<tr>
<td>Performance status</td>
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<td>X</td>
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<tr>
<td>Pharmacokinetic blood(^d)</td>
<td>X</td>
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<tr>
<td>CBC w/ diff, pltts</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>Serum chemistry(^d)</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>EKG (as indicated)(^g)</td>
<td>X</td>
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<td>X</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>Adverse event evaluation</td>
<td>X</td>
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<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Radiologic evaluation</td>
<td>X</td>
<td>Radiologic measurements should be performed every 8 weeks.</td>
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<tr>
<td>B-HCG</td>
<td>X(^e)</td>
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</tr>
<tr>
<td>Tissue Submission</td>
<td>Pre-Registration</td>
<td>Post-Registration/Pre-Treatment</td>
<td>Post-Treatment</td>
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</tr>
<tr>
<td>For central histology review’ &amp; pre-dasatinib molecular analysis</td>
<td>Mandatory for all patients in stages 1 and 1B</td>
<td>Mandatory for all patients in stage 2</td>
<td>Strongly recommended for patients who undergo re-resection</td>
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<tr>
<td>For post-dasatinib analysis</td>
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</tr>
</tbody>
</table>

a. Other tests at the discretion of the treating physician. History and physical and blood work should be done a minimum of every 2nd cycle. MRI scans required every 2nd cycle.
b. Off-study evaluation.
c. Mandatory for the first 10 eligible patients assessable for intrapatient dose escalation in stage 1B. Optional for all other patients. See Appendix V. [NOTE: NRG Oncology will broadcast notification when blood sampling for PK analysis becomes optional.]
d. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT[AST], SGPT[ALT], sodium.
e. Serum pregnancy test (women of childbearing potential) within ≤ 3 days prior to registration.
f. Mandatory for patients not previously enrolled in an RTOG GBM trial mandating central review.
g. Patients with signs or symptoms of pulmonary arterial hypertension (PAH), such as dyspnea, fatigue, hypoxia, and edema, should undergo non-invasive procedures (including echocardiogram) to rule out more the common etiologies of these symptoms, such as pleural effusion, pulmonary edema, anemia, and lung infiltration. As clinically indicated, right heart catheterization should be performed to confirm the diagnosis of PAH. Since PAH may be reversible upon discontinuation of dasatinib, a diagnostic approach of interruption of dasatinib treatment may be considered at the discretion of the treating physician; however, if PAH is confirmed, dasatinib should be permanently discontinued.
# KARNOFSKY PERFORMANCE SCALE

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Normal; no complaints; no evidence of disease</td>
</tr>
<tr>
<td>90</td>
<td>Able to carry on normal activity; minor signs or symptoms of disease</td>
</tr>
<tr>
<td>80</td>
<td>Normal activity with effort; some sign or symptoms of disease</td>
</tr>
<tr>
<td>70</td>
<td>Cares for self; unable to carry on normal activity or do active work</td>
</tr>
<tr>
<td>60</td>
<td>Requires occasional assistance, but is able to care for most personal needs</td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance and frequent medical care</td>
</tr>
<tr>
<td>40</td>
<td>Disabled; requires special care and assistance</td>
</tr>
<tr>
<td>30</td>
<td>Severely disabled; hospitalization is indicated, although death not imminent</td>
</tr>
<tr>
<td>20</td>
<td>Very sick; hospitalization necessary; active support treatment is necessary</td>
</tr>
<tr>
<td>10</td>
<td>Moribund; fatal processes progressing rapidly</td>
</tr>
<tr>
<td>0</td>
<td>Dead</td>
</tr>
</tbody>
</table>
APPENDIX IV

SUBSTANCES PROHIBITED DURING DASATINIB TREATMENT

CYP3A4 Inhibitors:
- itraconazole, ketoconazole, miconazole, voriconazole
- amprenavir, atazanavir, fosamprenavir, indinavir, nelfinavir, ritonavir
- ciprofloxacin, clarithromycin, diclofenac, doxycycline, enoxacin, imatinib, isoniazid, ketamine nefazodone, nicardipine, propofol, quinidine, telithromycin

CYP3A4 Inducers:
- aminogluthethimide, primidone, rifabutin, rifampin, St. John’s wort
- nevirapine, rifapentine
- Some anticonvulsants:

The following agents are potential hepatic enzyme inducing antiepileptic drugs (EIAEDs) and should not be used:
- Carbamazepine (Tegretol, Tegretol XR, Carbatrol)
- Oxcarbazepine (Trileptal)
- Phenytoin (Dilantin, Phenytek)
- Fosphenytoin (Cerebyx)
- Phenobarbital
- Pentobarbital
- Primidone (Mysoline)

The following agents are not known to affect dasatinib metabolism and are acceptable (non-EIAEDs):
- Valproic acid (Depakote, Depakene, Depacon)
- Gabapentin (Neurontin)
- Lamotrigine (Lamictal)
- Topiramate (Topamax)
- Tiagabine (Gabitril)
- Zonisamide (Zonegran)
- Levetriacetam (Keppra)
- Clonazepam (Klonopin)
- Clonozam (Frisium)

Agents With Proarrhythmic Potential
- quinidine, procainamide, disopyramide, amiodarone, sotalol, ibutilide, dofetilide
- erythromycins, clarithromycin
- chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide
- cisapride, bepridil, droperidol, methadone, arsenic, chloroquine, domperidone, halofantrine, levomethadyl, pentamidine, sparfloxicin, lidoflazine
1.0 OBJECTIVE OF MANUAL
All dasatinib pharmacokinetic analyses will be performed by the Clinical Pharmacology Analytical Lab at the University of Pittsburgh Cancer Institute led by Merrill Egorin, M.D., FACP.

The objective of this procedure manual is to provide the study site with clear, detailed procedures for handling dasatinib PK samples. This site manual contains instructions and forms for collecting, handling, storing, and shipping of all pharmacokinetic samples taken during the conduct of the trial. Study site personnel will be responsible for collecting the samples according to the protocol-specific times and processing them properly for shipping and handling. Therefore, it is important that the study personnel fully understand what will be involved in handling and tracking the samples.

2.0 CONTACTS
Questions concerning study-related issues should be directed to:

Andrew B. Lassman, MD
Memorial Sloan-Kettering Cancer Center
Neurology
1275 York Avenue
New York, NY 10021
212-639-6037/FAX 212-717-3519
lassmana@mskcc.org

Questions concerning PK sample collection and handling should be directed to:

Merrill J. Egorin, M.D., FACP
Professor of Medicine and Pharmacology
University of Pittsburgh Cancer Institute
Room G27E, Hillman Research Pavilion
5117 Centre Ave
Pittsburgh, PA 15213-1863
412-623-1213 (office)
412-623-3248 (laboratory)
FAX 412-623-1212
egorinmj@upmc.edu

3.0 COLLECTION SCHEDULE - PLASMA PK SAMPLES

Dasatinib PK Samples
All processes/procedures for sample collection, handling, labeling, and shipping should conform to universal precautions for the handling of bodily secretions. Pharmacokinetic sample collection times are listed in the table below. The PK blood samples will be mandatory for the first 10 eligible patients assessable for intrapatient dose escalation in stage 1B during cycles 1, 3, and 5. PK analyses are optional for all other patients.

<table>
<thead>
<tr>
<th>Sample Collection Time (hour)</th>
<th>0 (immediately pre-AM dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At the start of: cycle 1 (week 1), cycle 3 (week 9), cycle 5 (week 17), and cycle 7 (week 25)</td>
<td>1</td>
</tr>
</tbody>
</table>
a. Hour is relative to dosing time (t = 0) on Day 1.
b. The first sample is to be drawn immediately prior to the morning dasatinib dose administration for day 1 of cycles 1, 3, 5, and 7 before escalating the dose. For cycle 1 this first sample is to be drawn before the first dose of dasatinib.

4.0 COLLECTION AND PROCESSING SUPPLIES
The following supplies should be obtained by the site:

Pharmacokinetic Supplies and Equipment for Sample Processing

- Centrifuge, refrigerated
- PK labels for both collection and storage tubes
- All collection tubes (3 mL K$_3$EDTA, lavender-top tube)
- Transfer pipettes
- 5-mL polypropylene transport cryovials with screw-cap (Sarstedt catalog# 60.558) for plasma storage.
- PK case report forms and/or harvest logs
- 23-gauge or larger needles
- Crushed ice or ice bath
- −20 ± 10 °C freezer
- Dry ice shipping mailers
- Zip-lock Bags
- Dry ice
- Shipping containers

5.0 PLASMA COLLECTION AND PROCESSING FOR DASATINIB
Blood samples are to be collected from an indwelling catheter or by direct venipuncture. If a catheter is used for blood collection, then approximately 1.0 mL of blood should be withdrawn initially and discarded.

- At each collection time point, 3.0 mL of blood will be collected into a pre-labeled K$_3$EDTA lavender top tube.
- Immediately after collection, each blood sample will be gently inverted 8-10 times for complete mixing with the anticoagulant.
- Place the EDTA 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.

*Note: Room temperature centrifugation is permitted if the blood is pre-chilled for at least 10 min.*

- Transfer plasma into a labeled, screw-cap, polypropylene plasma drug tube, or equivalent.
- Plasma samples should be stored at, or below, -20°C.

*Note: There are no stability data to support the storage of dasatinib PK samples at temperatures lower than -20°C.*

6.0 PHARMACOKINETIC SAMPLE LABELS

- Labels should be provided by the site and include 1 for the collection tube, 1 for the plasma transfer tube, and a label for the PK Study Form (optional).

- It is essential that the label contain:
  - RTOG 0627,
  - patient study number,
  - date of collection,
  - cycle #,
  - day #,
  - time of dasatinib administration
  - planned collection hour (i.e. 1 hour, etc.),
  - actual sampling time (i.e., 1 hour 12 minutes),
  - matrix (For example: Plasma),
  - dasatinib dose in mg

RTOG 0627
**Dasatinib Dose Level**

- Labels should be placed lengthwise (from top of the tube to the bottom). **All information should be visible.**

- For each plasma sample obtained, affix the corresponding label (with the date and precise time of each sample) onto the designated area of the PK Study Form.

- In addition to the Notification of Shipment Form, a photocopy of the appropriate PK Acquisition Form/ PK Study Form must be included with the sample shipment.

**Fax a copy of the Notification of Shipment Form 24-hours prior to the shipment of samples to Dr. Egorin's Clinical Pharmacology Analytical Labs at 412 623-1212**

**7.0 PACKAGING AND SHIPPING FROZEN PHARMACOKINETIC SAMPLES**

*Note: Please store samples at –20 °C and ship all accumulated samples at the end of each month.*

The shipment of human blood samples must comply with appropriate regulations as specified by the carrier. At a minimum, all samples must be packaged within two containers with absorbent material between containers to control any spill or leakage. The outer container must be puncture resistant (e.g. cardboard mail tube, corrugated cardboard box). A biohazard sticker must be affixed to both the inner and outer containers.

**It is essential that all samples are thoroughly frozen prior to packing for shipment and that all tubes are securely capped.** All samples should be shipped by overnight express courier via insulated containers with enough dry ice to maintain the samples in a frozen state. They should not come into direct contact with dry ice, which might lead to cracking of the tubes. Samples should be accompanied by the appropriate sample acquisition form/ PK Study Form and Shipping Form/Notification of Intent to Ship that indicates the material, the name of the individual shipping the samples, and a phone number, fax number, and e-mail contact for confirmation of sample receipt in Pittsburgh. Samples should be shipped to Pittsburgh by overnight express mail and should only be shipped on Monday, Tuesday, or Wednesday to insure that samples do not arrive on Saturday or Sunday.

All shipments must be accompanied by the following documentation inside the shipper:

- a) A photocopy of the completed air bill (the original of which will be affixed to the outside of the shipping container)
- b) A photocopy of the appropriate PK Acquisition Form/ PK Study Form

To avoid the possibility of a shipment being refused by an airline, special attention to packing and labeling should be exercised with every shipment.

Follow your local courier’s specific shipping instructions. The following tips may be considered when packaging biological samples for shipment:

- Sort and group the samples by patient and time point order within each box. Pack the samples in a cardboard box.
- Place the zip-lock bags containing the frozen samples in the insulated shipping container.
- Pack the samples with at least 10 pounds of dry ice and replace the foam lid.
- Put a copy of all applicable Sample Collection Records in a separate large zip-lock bag and place bag on top.
- Seal the shipping box securely.
- Complete the appropriate Airbill and place the provided IATA required shipping labels and Dry Ice labels on the box. Fill in the amount of dry ice in kg (10 lbs = 4.5 kg).

Ship samples to the attention of:
FED EX account # is 1393-1706-8.

Telephone your overnight courier service to arrange for pickup.

When the agent arrives, sign the Airbill and keep the sender’s copy. Your copy of the Airbill is part of the audit trail that documents the shipping process.

*Note: Nationally observed holidays may cause shipment delivery delays. Contact your overnight courier and Dr. Egorin’s Office for holiday pick-up and delivery schedules.*

**Labeling**

Your local courier should provide the appropriate labels and instructions for shipment of frozen diagnostic specimens.

- The following labels must be adhered to the outside of the box
  - Complete Shipper and Consignee details
  - Standard OSHA approved Biological Hazard labels (2) - fluorescent, orange-red labels
  - Misc #9. Dry Ice Label
  - Amount of Dry Ice (in kg) written on the Label
  - Two orientation (arrows up) Labels (on opposite sides of the box)

---

*Sample of a box completely labeled for the transport of: Diagnostic Specimens packed on Dry Ice.*
NOTIFICATION OF INTENT:
SHIPMENT OF PK BIOLOGICAL SAMPLES FORM
DASATINIB - INVESTIGATOR SPONSORED TRIAL

RTOG 0627

24 hours prior to shipment
Fax this completed form to the attention of the analytical lab (noted below). The original of this form should be kept in the Study File.

SENDING INFORMATION

Investigator Name: __________________________ Total # of Samples: ______________________
Site Number: ___________________________ Site Fax Number: __________________________

Plasma Samples for (PK) analysis of DASATINIB (BMS-354825)

<table>
<thead>
<tr>
<th>Patient #</th>
<th># samples shipped</th>
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<tbody>
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</tbody>
</table>

Fax Form and Ship Samples To:
Merrill J. Egorin, M.D., FACP
University of Pittsburgh Cancer Institute
Room G27E, Hillman Research Pavilion
5117 Centre Ave
Pittsburgh, PA 15213-1863
Office: 412-623-1213
Laboratory: 412-623-3248
Fax: 412-623-1212
E-mail: egorinmj@upmc.edu

All PK Samples are to be shipped frozen on Dry Ice

See Section 7.0 of this appendix for account information

Originator's printed name and signature: ____________________________________________
Receiver's printed name and signature: ____________________________________________
Overnight Courier shipment tracking number: _______________________________________
Page will be faxed back to study site when the samples are received at the University of Pittsburgh.
PHARMACOKINETIC STUDY FORM FOR PLASMA SAMPLES
RTOG 0627

Blood samples drawn for dasatinib

Site # ___________________ Patient # ___________________

Cycle __, Day __ Date: |__/__|__/__/__/| Dose Level: ___

Body Surface Area: |___|°|___| m² Total Dose: |___| |___| |___| mg per day

Blood samples (3 ml) will be collected in K₃EDTA tubes. The exact time that the sample is drawn, and the exact time that the drug is administered must be recorded below:

**Time Dose Administered:** ____________

<table>
<thead>
<tr>
<th>Blood Sample No.</th>
<th>Scheduled Time</th>
<th>Actual Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Before the morning dose of dasatinib</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1 hour after dose</td>
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</tr>
<tr>
<td>3</td>
<td>2 hours after dose</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4 hours after dose</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>6-8 hours after dose</td>
<td></td>
</tr>
</tbody>
</table>

Method of Centrifugation Used (☐ refrigerated or ☐ room temperature): ____________

Data are to be recorded on this Pharmacokinetic Study Form, which must accompany the sample.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: ____________________________ Date: ____________