For **Protocol** and **Consent** Amendment # 12 to: RTOG 0627, Phase II Trial of Dasatinib in Patients With Recurrent Glioblastoma Multiforme

NCI/Local Protocol #: RTOG 0627

NCI Protocol Version Date: January 12, 2016  (Broadcast January 27, 2016)

<table>
<thead>
<tr>
<th>Section</th>
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<tbody>
<tr>
<td>Cover Pages</td>
<td>Contact information was updated for Mark Gilbert, MD. Suite 1600 was updated to 1720 for Peixin Zhang, MD. The document history table was updated to include this amendment.</td>
</tr>
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</table>
| 7.5 | In response to a CTEP Request for Rapid Amendment (RAA), the CAEPR for dasatinib (Version 2.6, September 1, 2015) was revised as follows:  
- **Added New Risk:**  
  - Rare but Serious: Erythema multiforme; Stevens-Johnson syndrome; Toxic epidermal necrolysis  
Although there is modified risk information for dasatinib, the added risks are very similar to risks that were already included in the previous version of the CAEPR and would have been communicated to patients in the informed consent document (ICD). In this case, (1) Erythema multiforme, Stevens-Johnson syndrome, and Toxic epidermal necrolysis are all severe forms of rash maculopapular, which is a previously identified risk on the ICD.  
CTEP believes that this new and/or modified risk information does not significantly alter the risk-benefit profile for patients in studies that involve dasatinib since dasatinib is already known to cause serious adverse events, and this new information does not change the overall weight given to risks versus benefits for patients in these studies.  
Patients who received dasatinib on this study should be informed of the risk profile changes outlined in the Action Letter in accordance with local IRB policies. |
| 7.7.3 | RTOG Headquarters was updated to NRG Oncology, and Suite 1600 was updated to 1720. |
| 12.0 | Suite 1600 was updated to Suite 1720. |
| Appendix 1 –Informed Consent Template for Cancer Treatment Trials | The risk profile for dasatinib was updated to be consistent with the revised CAEPR as follows:  
- **Added New Risk:**  
  - Severe skin rash with blisters and peeling which can involve mouth and other parts of the body  
- **Provided Further Clarification:**  
  - Bleeding from multiple sites including the brain which may cause confusion (under Occasional) is now reported as Bleeding from multiple sites (under Occasional) and Bleeding in the brain which may cause confusion (under Rare and Serious).  
PLEASE NOTE: The potential risks listed in the CAEPR whose relationship to dasatinib is still undetermined are not required by CTEP to be described in the ICD; however, they may be communicated to patients according to local IRB requirements. |
For Protocol Amendment 11 to: RTOG 0627, Phase II Trial of Dasatinib in Patients with Recurrent Glioblastoma Multiforme

NCI/Local Protocol #: RTOG-0627

NCI Protocol Version Date: October 22, 2014 (Broadcast: November 10, 2014)

<table>
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| Global                       | • Due to the transition to the National Clinical Trials Network (NCTN), “Radiation Therapy Oncology Group”, “RTOG Headquarters”, and “RTOG” were replaced with “NRG Oncology” or deleted, as appropriate, throughout the protocol.  
• References to the “RTOG Biospecimen Resource” were replaced with “NRG Oncology Biospecimen Bank”. |
| Title pages                  | The Neuropathy and Correlative Biology co-chair’s institutional affiliation and contact information was updated.                         |
| 10.7                         | This section was updated per current NRG Oncology standard text.                                                                           |
| Appendix 1 –Informed Consent Template for Cancer Treatment Trials | Under “Will my medical information be kept private?” and in the “Things to Think About” section of the Consent Form for Use of Tissue for Research supplement, references to RTOG were updated the NRG Oncology. |
For **Protocol** Update to: RTOG 0627, Phase II Trial of Dasatinib in Patients With Recurrent Glioblastoma Multiforme

NCI/Local Protocol #: RTOG 0627

NCI Protocol Version Date: January 12, 2012
Update Date: May 1, 2014 (Broadcast May 1, 2014)

<table>
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<td>Cover pages</td>
<td>This update was added to the document history table. Peixin Zhang has replaced Minhee Won as the Statistician.</td>
</tr>
<tr>
<td>Global</td>
<td>As required by CTEP, references to the &quot;Adverse Event Reporting System (AdEERS)&quot; have been changed to &quot;CTEP Adverse Event Reporting System (CTEP-AERS)&quot; throughout the protocol.</td>
</tr>
<tr>
<td>Informed Consent</td>
<td>No changes</td>
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SUMMARY OF CHANGES
Amendment #10, Version Date: January 12, 2012
(Broadcast: January 13, 2012)

RTOG 0627, Phase II Trial of Dasatinib in Patients With Recurrent Glioblastoma Multiforme

Study Chair: Andrew B. Lassman, MD; 212-639-6037; lassmana@mskcc.org

Title Page
- The version date was updated to include Amendment 10, Version Date January 12, 2012.
- Contact information was updated for Dr. Lassman.
- A document history table was added per current RTOG standard.
SUMMARY OF CHANGES
Amendment #9, Version Date: January 6, 2012
(Broadcast: January 13, 2012)

RTOG 0627, Phase II Trial of Dasatinib in Patients With Recurrent Glioblastoma Multiforme

Study Chair: Andrew B. Lassman, MD; 212-639-6037; lassmana@mskcc.org

In response to a CTEP Request for Rapid Amendment (RRA) for protocols using dasatinib (NSC 732517) RTOG 0627 was amended due to the following:

Background
On October 11, 2011, the FDA issued a Drug Safety Communication warning the public that dasatinib may increase the risk of pulmonary arterial hypertension (PAH), a rare but serious condition. Updated US prescribing information can be found at www.sprycel.com. Therefore, additional safety monitoring and new monitoring guidelines are required.

Risk Mitigation Plan
Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating dasatinib and during treatment. Symptoms of PAH (including dyspnea, fatigue, hypoxia, and edema) are also symptoms of other adverse events; therefore, non-invasive procedures (including echocardiogram) should be done to rule out PAH before initiating invasive procedures.

Related protocol changes were made as outlined below:

Title Page: The version date was updated to include Amendment 9, Version Date January 6, 2012.

Section 7.1.2: The last main bullet and 2 sub-bullets were added to address the Risk Mitigation Plan noted above.

Section 7.5: CAEPR Version 2.2 (February 17, 2010) was replaced by CAEPR Version 2.4 (October 31, 2011). Specific changes are as follows:
- The Agent Specific Adverse Event List (ASAEL) is now termed the Specific Protocol Exceptions to Expedited Reporting (SPEER) and includes grades for adverse events found on the SPEER that are used to determine if expedited reporting is required.
- Increase in Risk Attribution:
  - Changed to Rare but Serious from Reported But Undetermined: Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Pulmonary hypertension

Appendix I/Sample Consent, Risks associated with dasatinib: The risk profile was updated to reflect the revised CAEPR. Specific changes are as follows:
- Increase in Risk Attribution:
  - Changed to Rare but Serious from Reported But Undetermined: Heart failure: inability of the heart to adequately pump blood to supply oxygen to the body; Decrease in heart's ability to pump blood during the "active" phase of the heartbeat (systole); Heart attack caused by a blockage or decreased blood supply to the heart; High blood pressure of the blood vessels in the lungs.

Appendix II/Study Parameter Table: Footnote g was added to the EKG row to address the Risk Mitigation Plan noted above.
SUMMARY OF CHANGES
Update: July 22, 2010
(Broadcast: July 22, 2010)

RTOG 0627, Phase II Trial of Dasatinib in Patients With Recurrent Glioblastoma Multiforme

Study Chair: Andrew B. Lassman, MD; 212-639-6037; lassmana@mskcc.org

RTOG 0627 was updated as follows:

Appendix V: The Fed Ex account number was updated.
RTOG 0627, Phase II Trial of Dasatinib in Patients With Recurrent Glioblastoma Multiforme

**Study Chair:** Andrew B. Lassman, MD; 212-639-6037; lassmana@mskcc.org

**RTOG 0627** was amended as follows:

As mandated by CTEP, CTCAE version 3.0 reporting requirements were converted to CTCAE version 4.0. Changes were made to **Section 7.7**.
In response to a request for an amendment (RA) from CTEP, the protocol was amended to reflect the migration of the Comprehensive Adverse Events and Potential Risks List (CAEPR) for dasatinib from Common Terminology Criteria for Adverse Events (CTCAE) 3.0 language to CTCAE 4.0 language.

Please Note: Although the revised CAEPR reflects the CTCAE migration, there is no new or modified risk information for dasatinib.

Changes were made to the following sections:

Section 7.5: CAEPR Version 2.0 (December 17, 2008) was replaced by CAEPR Version 2.2 (February 17, 2010).

Appendix I/Sample Consent, Risks associated with dasatinib: The risk profile was updated to reflect the revised CAEPR.
RTOG 0627, Phase II Trial of Dasatinib in Patients With Recurrent Glioblastoma Multiforme

Study Chair: Andrew B. Lassman, MD; 212-639-6037; lassmana@mskcc.org

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RTOG 0627 has been amended as follows:

Cover Page: Sample size corrected

Eligibility Checklist, Page 4, Question 18: "oncologists' " corrected to "oncologist's"

Section 7.7.2
- Heading and 1st paragraph: Paragraph breaks adjusted for clarity
- 3rd paragraph, 1st sentence: "drug" deleted before "experience" because it was included in error; "so days" corrected to "30 days"
- 5th paragraph, 1st sentence: "the AdEERS ticket number" added for clarity and accuracy

Section 13.2.2
- Heading: Numbering altered for increased clarity
- 2nd paragraph, 8th sentence: Number of analyzable patients corrected
- 2nd paragraph, 2nd-to-last sentence: Protocol accrual stages corrected
- 2nd paragraph, last sentence: Assessment for protocol accrual stages corrected

Section 13.3: 2nd-to-last sentence: Number of accrued and analyzable patients corrected

Section 13.4.4.1: 2nd sentence: Number of analyzable patients and maximum width of confidence interval corrected

Appendix I/Informed Consent/
"How many people will take part in this study?"
Sample size corrected
RTOG 0627, Phase II Trial of Dasatinib in Patients With Recurrent Glioblastoma Multiforme

Study Chair: Andrew B. Lassman, MD; 212-639-6037; lassmana@mskcc.org

Study Design Modifications

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.

There were 26 grade 3 events in 14 patients at least possibly attributable to dasatinib (see table below). We did observe metabolic abnormalities (n=6), leukopenia (2), lymphopenia (5), fatigue (3), diarrhea (3), nausea (1), hemorrhage (3: 1 rectal, 2 subdural), myocardial ischemia (1) causing angina (1), and muscle weakness (1).

<table>
<thead>
<tr>
<th>Category</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood/bone marrow</td>
<td>1</td>
</tr>
<tr>
<td>Cardiac general</td>
<td>2</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>3</td>
</tr>
<tr>
<td>Dermatology/skin</td>
<td>4</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>5</td>
</tr>
<tr>
<td>Hemorrhage/bleeding</td>
<td>6</td>
</tr>
<tr>
<td>Infection</td>
<td>7</td>
</tr>
<tr>
<td>Lymphatics</td>
<td>8</td>
</tr>
<tr>
<td>Metabolic/laboratory</td>
<td>9</td>
</tr>
<tr>
<td>Musculoskeletal/soft tissue</td>
<td>10</td>
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</tbody>
</table>
In the original protocol for stage 1, patients received dasatinib on an outpatient basis at a starting dose of 100 mg BID. If efficacy could be demonstrated (6mPFS, CR, or PR) in at least 3 patients, then stage 2 would open to accrual of 50 additional patients. There were 2 patients with clear evidence of efficacy and one with more controversial outcome. The first patient achieved 6 months of progression-free survival. However, during therapy the patient experienced leukopenia, myocardial ischemia causing angina, fatigue, diarrhea, AST elevation, and a subdural hematoma (traumatic), all grade 3, requiring multiple dose reductions. The second patient achieved a partial radiographic response confirmed on a follow up brain MRI 1 month later but also experienced grade 3 hypophosphatemia. The third patient technically achieved 6 months of progression-free survival. However, after approximately 4 months of protocol treatment, during which he experienced unlikely related but otherwise unexplained diarrhea that was persistent and substantially reduced quality of life, he subsequently developed a spontaneous subdural hematoma (atraumatic) for which he came off study. Following successful surgical drainage, the treating physician chose to continue dasatinib off protocol because his tumor had remained stable 5 months after registration. The diarrhea improved following a dose reduction. No 6-month scan was performed to assess 6mPFS because, with the patient off study-based treatment, it was no longer required. However, an MRI performed after 7 months demonstrated disease progression. In addition to the chronic grade 2 diarrhea and the grade 3 subdural hematoma, this patient also experienced grade 3 lymphopenia and hypophosphatemia. This patient would technically qualify as a third case demonstrating efficacy defined as either 6mPFS, PR, or CR. However, it is also possible this patient had a PFS of less than 6 months. Therefore, the evidence of efficacy to support opening stage 2 as originally planned if at least 3 patients had efficacy appears weak.

A higher dasatinib dose may, however, have produced greater efficacy without undue toxicity for several reasons. First, toxicity was relatively mild despite the "high" starting dose, especially when compared to other trials in melanoma that demonstrated intolerable toxicity at this dose. Second, the MTD of various cytotoxic chemotherapies and small molecular inhibitors is often substantially higher in glioma patients than in other patient populations. Third, all 3 patients with at least some evidence of clinical benefit in stage 1 experienced toxicity at least possibly related to the agent, suggesting that efficacy can only be achieved by a dose also high enough to produce at least mild toxicity. Along these lines, when the dose was reduced in one patient with stable disease, the tumor then progressed on the next MRI.

Unfortunately, much of this is conjecture because we did not perform a phase I
component to determine if the MTD in patients with glioma is higher than 100 mg BID and because pharmacokinetic analyses (PK) were not performed in stage 1 of the original design. The toxicity analysis based on the 26 analyzable patients did show 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. PK analysis was added to provide further data on plasma concentration of drug. All other eligibility criteria, including molecular tissue analysis, remain unchanged. Stage 1B will be used to address the possibility of dose escalation following 1 cycle of therapy absent a DLT. If dose escalation to level 1 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 eligible patients. Patients who discontinue treatment during cycle 1 or 2 because of disease progression will be replaced in order to ensure ability to estimate toxicity and the percent of patients eligible to undergo dose escalation. Patients who discontinue treatment during cycle 1 or 2 for 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. 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 and patient enrollment will continue until a total of 27 patients are enrolled on stage 1B. (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). If there are less than 6 patients, then intrapatient dose escalation will not be judged tolerable and should not be used. In that event, accrual will be terminated for stage 1B and the study will not proceed to stage 2.

In the efficacy analysis for stage 1B, radiographic partial and complete responses that are not sustained for at least 6 months will also be considered as evidence of efficacy in addition to 6mPFS. This was done in order to reduce the time required to complete stage 1B of the trial. However, for the final efficacy analysis after stage 2, the primary endpoint will be only 6mPFS.

As a result of this modified study design, changes were made to the following sections:

**Schema page**

- Reference to dose escalation schedule in Section 7.3.1 added.
- Overexpression requirements per protocol stage added under Patient Population
- Sample size adjusted

**Section 1.2.2:** 2nd-to-last paragraph: CML added in heading; last paragraph: added

**Section 2.1.1:** Estimating 6mPFS was moved from a secondary objective to the primary objective for the entire study.
Section 2.2.1: Estimating the rate of patients achieving objective response (PR or CR) OR 6mPFS was moved from the primary objective to a secondary objective to be used only for stage 1B analysis.

Section 2.2.7: Added

Section 3.1.3.1 and 3.1.3.2: Overexpression requirements per protocol stage added. Corresponding change made to Eligibility Checklist Question 34/page 3 and Question 23/page 4.

Section 7.1.1: 1st sentence rewritten

Section 7.3: All tables moved to Section 7.3.1

Section 7.3.1:

- Added
- Dose Level table (moved from Section 7.3 as described above): 1st 4 lines added from original Section 7.3.
- General Management Guidelines for Agent-Related Non-Hematologic Toxicity table (moved from Section 7.3 as described above): Management instructions expanded for clarity.

Section 7.3.2: Added

Section 10.2: Heading cohort description modified to reflect requirements per protocol stage

Section 10.3: Heading cohort description modified to reflect requirements per protocol stage

Section 12.1: P6 form added

Section 13.1.1.1: Estimating 6mPFS was moved from a secondary endpoint to the primary endpoint for the entire study.

Section 13.1.2.1: Estimating the rate of patients achieving objective response (PR or CR) OR 6mPFS was moved from the primary endpoint to a secondary endpoint to be used only for stage 1B analysis.

Section 13.1.2.7: Added

Section 13.2.1: Last 2 paragraphs added

Section 13.2.1.1: Added.
Sections 13.3: Rewritten.

Section 13.4-13.4.5: Rewritten and all affected sections appropriately renumbered

Section 13.5: Revised table for "Projected Distribution of Gender and Minorities" added

References: References 46-47 adjusted per 13.2.1.1 addition

Appendix I/Informed Consent

- How many people will take part in this study?" Sample size adjusted
- During the study:" 2nd through 3rd paragraphs added ("If you are among the first 10 analyzable patients…" through "…then these blood tests will be optional." Last sentence of 4th paragraph added

Appendix II/Study Parameter Table

- Pharmacokinetic testing added
- Tissue submission section modified to reflect requirements per protocol stage. Footnotes incorporated into table text for added clarity.

Appendix V: Added

Other Modifications

Cover page: Contact information was added for the study statistician. Contact information for RTOG Headquarters was updated.

Eligibility Checklist, page 3: "Is the patient taking systemic H2 blockers or proton pump inhibitors?," added as question 23 for consistency with Section 3.2.7.2. All subsequent questions were appropriately renumbered.

Section 5.1: Regulatory Pre-Registration Requirements were added per current RTOG standard. Subsequent sections were appropriately renumbered.

Section 7.3.1

- Information concerning hypophosphatemia management added as the last sentence.
- General Management Guidelines for Agent-Related Non-Hematologic Toxicity table (moved from Section 7.3): Management instructions expanded for clarity.

AE reporting descriptions were revised per current RTOG standard in the following places:
Section 7.7: last 2 paragraphs
Section 7.7.1: last 2 paragraphs
Section 7.7.2: entire section
Section 7.8: 1st sentence added

Section 10: The RTOG Tissue Bank has been renamed the RTOG Biospecimen Resource and has moved from LDS Hospital to the University of California San Francisco. This section was updated accordingly throughout.

Section 10.2.2: Description of P6 form added to 2nd-to-last sentence for clarity.

Section 10.3.2: The reference to Section 10.X was corrected to 10.5.

Section 10.8: The link to the RTOG Patient Tissue Consent Frequently Asked Questions was updated.

Section 12.1: For the A5 due date, "within 4 weeks of study entry" was changed to "within 4 weeks after study entry" for clarity

Appendix II

- 2nd-to-last column (Week 13 and on), plus corresponding footnote, added for clarity and accuracy
- Footnotes re-lettered so that they appear in alphabetical order in order of occurrence in the table:
  - New a: Added (per description immediately above)
  - New b: Former c
  - New c: Added (per description in study design modifications above)
  - New d: Former a
  - New e: Former b
  - New f: Former d
- Under Tissue Submission, "histology" added before "review" and "molecular" added before "analysis" for clarity

Appendix III: The Zubrod performance scale was deleted per current RTOG standard. Assessments for this study are based on the Karnofsky scale.
SUMMARY OF CHANGES
Amendment #4, Version Date: February 17, 2009
(Broadcast: June 2, 2009)

RTOG 0627, Phase II Trial of Dasatinib in Patients With Recurrent Glioblastoma Multiforme

Study Chair: Andrew B. Lassman, MD; 212-639-6037; lassmana@mskcc.org

In response to a request for a rapid protocol amendment from CTEP, the protocol was amended to reflect changes to the Comprehensive Adverse Events and Potential Risks List (CAEPR) for dasatinib. Changes were made to the following sections:

Section 7.5:
CAEPR Version 2.0 (March 29, 2006) was replaced by CAEPR Version 2.1 (December 17, 2008). Specific changes are as follows:

- Added New Risk:
  - Less Likely: Left ventricular systolic dysfunction (congestive heart failure); Infection with unknown ANC - Select; Lymphatics - Other (generalized edema); Calcium, serum-low (hypocalcemia); Phosphate, serum-low (hypophosphatemia); Pain - Chest/thorax NOS; Pain - Joint; Pain - Pain NOS; Cough
  - Rare but Serious: Hemorrhage, CNS; Neurology - Other: (Reversible posterior leukoencephalopathy syndrome [RPLS])
  - Reported but Undetermined: Palpitations; Hypotension; Pulmonary hypertension; Sweating (hyperhidrosis); Alopecia; Contusion; Dry skin; Ascites; Colitis; Taste alteration (dysgeusia); Infectious colitis; Hyperkalemia; Hypoalbuminemia; Proteinuria; Muscle weakness; Myositis (muscle inflammation); Conjunctivitis; Dry eye; Hypoxia; Pneumonitis/pulmonary infiltrates; Hemangiomatosis
- Increase in Risk Attribution:
  - Changed to Likely from Less Likely: Hemoglobin; Neutrophils/granulocytes (ANC/AGC); Fatigue (asthenia, lethargy, malaise); Rash/desquamation; Nausea; Pain - Head/headache; Pleural effusion (non-malignant)
  - Changed to Likely from Reported but Undetermined: Dyspnea (shortness of breath)
  - Changed to Less Likely from Reported but Undetermined: Rigors/chills; Weight gain; Weight loss; Constipation; Mucositis/stomatitis (functional/symptomatic) - Select; Ulcer, GI - Select; Dizziness; Pain - Muscle
  - Changed to Rare but Serious from Reported but Undetermined: Prolonged QTc interval
- Decrease in Risk Attribution:
• Changed to Less Likely from Likely: Pericardial effusion (non-malignant)
• Changed to Reported but Undetermined from Less Likely: Leukopenia; Flushing; Dehydration; Flatulence; Limb edema; Creatinine

• Modified Agent Specific Adverse Events List (ASAEL) reporting requirements:
  o Added: Hemoglobin; Neutrophils/granulocytes (ANC/AGC); Platelets; Fatigue (asthenia, lethargy, malaise); Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1 x 10^9/L); rash/desquamation; Diarrhea; Nausea; Vomiting; Lymphatics - Other (superficial edema); Pain - Head/headache; Dyspnea (shortness of breath); pleural effusion (non-malignant)

Appendix I/Sample Consent, Risks associated with dasatinib
The risk profile was updated to reflect the revised CAEPR. Specific changes are as follows:

• Added New Risk:
  o Less Likely: Decrease in the heart's ability to pump blood; Infection; Generalized swelling; Superficial swelling; Decreased blood calcium level; Decreased blood phosphate level; Chest pain; Joint pain; Pain; Cough; Nerve damage causing numbness, tingling, burning
  o Rare but Serious: Neurology - Bleeding into the brain or spinal cord

• Increase in Risk Attribution:
  o Changed to Likely from Less Likely: Decrease in a red blood cell protein that carries oxygen in the body (lay language re-written to meet current CTEP standard); Decreased number of a type of white blood cell; Fatigue or tiredness; Rash/flaking or shedding of outer layer of skin; Nausea; Headache or Head pain; Excess fluid that accumulates in the pleural cavity, the fluid-filled space that surrounds the lungs
  o Changed to Likely from Reported but Undetermined: Shortness of breath
  o Changed to Less Likely from Reported but Undetermined: Chills; Weight gain; Weight loss; Constipation; Irritation or sores in the lining of the digestive tract; Ulcer of the digestive tract; Dizziness; Muscle pain
  o Changed to Rare but Serious from Reported but Undetermined: Abnormal electrical conduction within the heart

• Decrease in Risk Attribution:
  o Changed to Less Likely from Likely: Fluid in the sac around the heart
SUMMARY OF CHANGES
Amendment #3, Version Date: May 8, 2008
(Broadcast May 16, 2008)

RTOG 0627, Phase II Trial of Dasatinib in Patients With Recurrent Glioblastoma Multiforme

Study Chair: Andrew B. Lassman, MD; 212-639-6037; lassmana@mskcc.org

To allow patients experiencing toxicity at Dose Level -2 to continue to receive protocol treatment, RTOG 0627 has been amended to include the following additional dose levels:

- Dose level -3: two 50-mg dasatinib tablets daily simultaneously (a regimen associated with less toxicity than twice-daily dosing); and
- Dose level -4: one 50-mg dasatinib tablet and one 20-mg tablet daily simultaneously.

Specific changes were made to the following sections:

- **Section 7.2:** Under "How Supplied,"
  - The first bullet was added to provide information concerning the 20-mg tablet.
  - The second bullet was updated to include "(or 'BMS' on one side and '528' on the other side)."

- **Section 7.3:**
  - 2nd paragraph, last sentence: Reference was added to dose levels -3 and -4.
  - Table: Dose levels -3 and -4 were added.
SUMMARY OF CHANGES
Amendment #2, Version Date: September 5, 2007

RTOG 0627, Phase II Trial of Dasatinib in Patients With Recurrent Glioblastoma Multiforme

Study Chair: Andrew B. Lassman, MD; 212-639-6037; lassmana@mskcc.org

To allow patients to receive antithrombotic, antiplatelet, and/or anti-inflammatory agents in a restricted fashion if they develop a problem during the study (e.g., deep vein thrombosis, angina, myocardial infarction, etc.) that is felt to be unrelated or unlikely to be related to protocol treatment, RTOG 0627 has been amended as follows:

Sections 3.2.8: This criterion was rewritten to be consistent with the changes made to Section 9.2.3 (see below). The criterion now reads, "Use of antithrombotic and/or antiplatelet agents (e.g., warfarin, heparin, low molecular weight heparin, aspirin, clopidogrel, ticlopidine, Aggrenox). See also 9.2.3."

Section 3.2.9: This criterion was rewritten to be consistent with the changes made to Section 9.2.3.1 (see below). The criterion now reads, "Use of ibuprofen and other NSAIDs. See also 9.2.3.1." The corresponding change to Eligibility Checklist page 3, question 24 was also made.

Section 7.2: Under "Potential Drug Interactions", the last sentence was rewritten to be consistent with the changes made to Section 9.2.3-9.2.3.1 (see below). The criterion now reads, "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)."

Section 9.2.3:

- The second sentence was rewritten to indicate that patients may not be taking anticoagulants and medications that inhibit antiplatelet function at the time of study entry, and the list of possible agents in this category was expanded. The sentence now reads, "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.
- The last two sentences were added to allow patients to receive anticoagulants and medications that inhibit platelet function if used with caution if medically indicated due to a problem that is felt to be unrelated or unlikely to be related to dasatinib.
Section 9.2.3.1: This section was added in light of the changes described above to more specifically detail that patients are permitted to receive ibuprofen and other NSAIDs if used with caution and if medically indicated as described above.
SUMMARY OF CHANGES
Update Date: May 31, 2007

RTOG 0627, Phase II Trial of Dasatinib in Patients With Recurrent Glioblastoma Multiforme

Study Chair: Andrew B. Lassman, MD; 212-639-6037; lassmana@mskcc.org

RTOG 0627 has been updated as follows:

Eligibility Checklist page 3, question 32: The numbering was corrected from #33 to #32.

NOTE: These are editorial/administrative changes to the protocol. NCI now requires that these changes be documented on the protocol title page with the date of the update noted as "Update Date," not as an amendment.

An updated protocol is available on the RTOG website: www.rtog.org
SUMMARY OF CHANGES
Amendment #1, Version Date: May 18, 2007

RTOG 0627, Phase II Trial of Dasatinib in Patients With Recurrent Glioblastoma Multiforme

Study Chair: Andrew B. Lassman, MD; 212-639-6037; lassmana@mskcc.org

RTOG 0627 has been amended as follows:

Cover Page: The phone number for Dr. Gilbert and the fax number for Dr. Aldape have been updated. In addition, the activation date has been added per RTOG standard.

Eligibility Checklist page 1, question 1: Gliosarcoma was added as a possible diagnosis per Section 3.1.1.

Eligibility Checklist page 1, question 10: The sub-question was added to clarify that patients are ineligible if they have received prior therapy other than radiotherapy and temozolomide.

Eligibility Checklist page 3, question 26: "including Gamma-Knife, Cyberknife, or other variants" was added parenthetically to qualify stereotactic radiosurgery for increased clarity.

Section 3.1.1: The second sentence was added to clarify that patients with gliosarcoma are eligible.

Section 3.1.11:"including Gamma-Knife, Cyberknife, or other variants" was added parenthetically to qualify stereotactic radiosurgery for increased clarity.

Section 10: The entire section was rewritten to more clearly describe tissue submission logistics for the first 27 eligible patients and for patients 28 through study closure.

Appendix I, "Before you begin the study," last paragraph

- In the third sentence, "to not be affected" was corrected to "not to be affected."
- The last two sentences were re-written for increased clarity.
RTOG 0627, Phase II Trial of Dasatinib in Patients With Recurrent Glioblastoma Multiforme

Study Chair: Andrew B. Lassman, MD; 212-639-6037; lassmana@mskcc.org

RTOG 0627 has been updated as follows:

Cover page: New phone number for Dr. Aldape

Section 10.3.6.1:
• First sentence: P3 form corrected to P6
• Second sentence: Re-written for increased clarity

Section 13: Formatting corrected

Section 13.4.2: Numbering of sub-sections corrected

In addition, the following text was updated to reflect Bristol-Myers Squibb's most recent dasatinib-related information:

• Section 7.1.2: Second bullet
• Section 7.2: Method of Administration, first sentence; Special Handling, entire section
• Appendix I/Sample Consent: During the Study, second paragraph, second sentence: Added for consistency with the protocol

NOTE: These are editorial/administrative changes to the protocol. NCI now requires that these changes be documented on the protocol title page with the date of the update noted as "Update Date," not as an amendment.

An updated protocol is available on the RTOG website: www.rtog.org