A Phase II Trial of Dasatinib in KIT-Positive Patients with Unresectable Locally Advanced or Stage IV Mucosal, Acral and Vulvovaginal Melanomas

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ALLIANCE / Alliance for Clinical Trials in Oncology

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### CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

<table>
<thead>
<tr>
<th>To submit site registration documents:</th>
<th>For patient enrollments:</th>
<th>Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:</th>
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<tbody>
<tr>
<td>CTSU Regulatory Office</td>
<td>Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at <a href="https://www.ctsu.org/OPEN_SYSTEM/">https://www.ctsu.org/OPEN_SYSTEM/</a> or <a href="https://OPEN.ctsu.org">https://OPEN.ctsu.org</a>.</td>
<td>ECOG-ACRIN Operations Office - Boston, FSTRF, 900 Commonwealth Avenue Boston, MA 02215 (ATTN: DATA). Phone # 617-632-3610 Fax # 617-632-2990</td>
</tr>
<tr>
<td>1818 Market Street, Suite 1100</td>
<td>Contact the CTSU Help Desk with any OPEN-related questions at <a href="mailto:ctsucontact@westat.com">ctsucontact@westat.com</a>.</td>
<td>Data should be sent via postal mail. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.</td>
</tr>
<tr>
<td>Philadelphia, PA 19103</td>
<td></td>
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<tr>
<td>Phone – 1-866-651-CTSU</td>
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<tr>
<td>Fax – 215-569-0206</td>
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<td>CTSU Regulatory Office</td>
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<tr>
<td>Email: <a href="mailto:CTSURegulatory@ctsu.coccg.org">CTSURegulatory@ctsu.coccg.org</a></td>
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The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at [https://www.ctsu.org](https://www.ctsu.org). Access to the CTSU members’ website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.

**For clinical questions (i.e. patient eligibility or treatment-related)**, contact the Study PI of the Coordinating Group.

**For questions unrelated to patient eligibility, treatment, or data submission** contact the CTSU Help Desk by phone or e-mail:

CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

**For detailed information on the regulatory and monitoring procedures for CTSU sites** please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members’ website [https://www.ctsu.org](https://www.ctsu.org) > education and resources tab > CTSU Operations Information >CTSU Regulatory and Monitoring Policy.

The CTSU Web site is located at [https://www.ctsu.org](https://www.ctsu.org)
Acral melanomas are defined as melanomas occurring on the palms, soles, or subungual sites.

1. Patients are to have a tumor assessment every 6 weeks.
2. Local c-KIT report must indicate c-KIT positive mutation status with at least one mutation in exon 9, 11, 13, 17 or 18 of the c-KIT gene. Patient may proceed directly to registration to treatment.
3. Submit tissue and supporting documentation within 5 working days following pre-registration (see Section 10). Patient can not be registered to treatment (Step 1) until site receives verification of positive c-KIT mutation status from the central laboratory performing the assessments.

**Schema**

1 cycle = 21 days

<table>
<thead>
<tr>
<th>Rev. 1/12</th>
<th>Stage 1 Accrual: 57 patients</th>
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<td>Rev. 11/11</td>
<td>Stage 2 Accrual Goal: 30 KIT-positive patients in Step 1</td>
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</table>

*Acral melanomas are defined as melanomas occurring on the palms, soles, or subungual sites

1. Patients are to have a tumor assessment every 6 weeks.
2. Local cKIT report must indicate cKIT positive mutation status with at least one mutation in exon 9, 11, 13, 17 or 18 of the c-KIT gene. Patient may proceed directly to registration to treatment.
3. Submit tissue and supporting documentation within 5 working days following pre-registration (see Section 10). Patient can not be registered to treatment (Step 1) until site receives verification of positive c-KIT mutation status from the central laboratory performing the assessments.
1. Introduction

In the United States, it is estimated that approximately 62,000 people will be diagnosed with melanoma per year, and more than 8000 people are expected to die of this disease. Effective therapy for advanced melanoma remains elusive. Response rates to cytotoxic agents are generally low, and responses that do occur are typically transient. High dose Interleukin-2 is associated with durable responses in a small minority of highly selected patients, but, as yet, no treatment has been demonstrated to prolong median survival. Recently, mutations and amplifications in the receptor tyrosine kinase c-kit have been reported in acral melanomas, mucosal melanomas, and cutaneous melanomas which arise in the setting of chronic sun damage.

While cutaneous melanomas typically arise in sun-exposed areas, other melanomas can occur in sun-protected areas, such as the palms, soles, or subungual sites (acral melanomas) and on mucosal membranes. Melanomas that occur at these unusual sites generally carry a worse prognosis than those arising in the more common sites. When metastatic they are highly refractory to treatment.

Cutaneous melanomas are known to have mutations in the RAS/RAF/MAP-Kinase signaling pathway, with BRAF most commonly affected by somatic mutations with a mutation rate of 60-80% in some subtypes of melanoma (2). However, melanomas arising in a background of chronic sun-induced skin damage rarely have B-RAF mutations (about 10%). Melanomas of the mucosal and acral subtypes also show infrequent mutations in BRAF. The finding that mutations in BRAF are restricted to melanomas arising in intermittently sun-exposed skin led to the investigation of oncogenes other than BRAF that are activated in these three categories of melanomas (3).

Emerging data suggests a critical role of amplification and mutations in KIT in the pathogenesis of mucosal, acral, and cutaneous melanomas arising in the setting of chronic, sun-induced skin damage (3). In a cohort of 102 primary melanomas from mucosa (n=38), acral skin (n=28), and skin with (n=18) and without (n=18) chronic sun-induced damage, seven tumors were found to have overlapping amplifications on chromosome 4q12, which includes KIT, by comparative genomic hybridization. Eleven more tumors were noted to have increased copy numbers affecting this region. None of these 18 tumors were cutaneous melanomas without chronic sun damage.

After identifying the seven tumors which showed amplification on chromosome 4q12, the remaining 95 tumors were examined. 15/38 (39%) of mucosal melanomas, 10/28 (36%) of acral melanomas, 5/18 (28%) of skin with chronic sun-induced damage, were noted to have KIT abnormalities, as defined by mutations or copy number increases. 0/18 of melanomas on skin without sun-induced damage displayed KIT genetic alterations.

By immunohistochemistry, 11/14 (79%) of melanomas with KIT mutations and 8/15 (53%) of those with increased KIT copy number expressed KIT protein in the vertical growth phase. When a higher antibody concentration was used, all but 1 of the originally IHC-negative tumors expressed the protein. However, 6/19 (31%) of samples without detectable KIT mutation or copy number also showed increased expression of the KIT protein in the vertical growth phase under standard antibody concentrations. It is possible that these tumors may display KIT abnormalities that were not discovered in this study.
This study implicates KIT as an oncogene important in the progression of melanomas of the mucosa, and cutaneous melanomas arising in acral sites or in sun-damaged skin. Although these melanoma categories account for only about a quarter of all melanomas in Western countries, acral and mucosal melanomas are the most prevalent melanoma types in the rest of the world, and thus are likely to represent a major share of the global melanoma burden, and a considerable therapeutic opportunity.

1.1 Clinical Trials of KIT Inhibitors in Melanoma

Because of early data suggesting the expression of KIT in melanoma, phase II trials were initiated to examine the role of inhibition of KIT/PDGFR in metastatic melanoma. One phase II trial enrolled 26 patients with metastatic melanoma who were treated with 800mg daily of imatinib. Patients with metastatic disease were eligible for enrollment, regardless of whether their tumor displayed expression of KIT/PDGFR. During analysis, 3 patients had moderate (2+) staining for KIT on IHC and 5 patients had weak (1+) staining. Weak (1+) staining of PDGFR was present on a total of seven patients. In addition to significant toxicities associated with this dose, no patients were free of disease progression six months after treatment started (4). In another phase II trial, 21 patients, who had been previously screened by IHC for > 25% of KIT, PDGFR, c-abl, or ARG, were treated with imatinib. 20/21 patients experienced disease progression by 12 weeks; however, the one patient with the strongest expression of KIT in over 75% of tumor cells achieved a near complete response (5). Intriguingly, this was the only patient with acral melanoma in this cohort. Also, with further study, the patient was demonstrated to have a deletion affecting a splice site resulting in an aberrant transcript of KIT, suggesting that a select group of patients having abnormal KIT may derive significant benefit from imatinib or other inhibitors of KIT.

1.2 Dasatinib and Its Use in Melanoma

The spectrum of genetic alterations of KIT in melanoma, which includes mutations of the juxtamembrane and kinase domains as well as copy number increases of the wild type gene, makes dasatinib a promising drug to treat melanomas with activation of the KIT pathway. It has been reported that dasatinib potently inhibits wild type KIT, juxtamembrane domain mutant KIT autophosphorylation, and KIT-dependent activation of downstream pathways (6). The fact that dasatinib also has demonstrated activity against PDGFR may broaden its clinical applicability for melanoma, as PDGFRA is widely expressed in melanoma in general and is co-amplified with KIT in the categories of melanoma described above (7). Dasatinib is also a potent inhibitor of Src Family Kinases (SFK's). In vitro studies suggest that activation of SFK's, particularly Yes and Fyn, is a common event in melanoma, and correlates with metastatic potential (8).

Dasatinib has been evaluated in a phase II trial in patients with advanced melanoma. Twelve of the thirty subjects had acral, mucosal, or CSD melanoma, but an alteration in c-KIT was not required for eligibility. Three patients had partial responses, including one with an exon 13 c-KIT mutation. Although the mutational status of all subjects has not been reported, it appears that the activity of dasatinib is modest in unselected patients with melanoma (19).
1.3 Previous Hypothesis

The preclinical and clinical data support the hypothesis that KIT inhibition is a rational therapeutic consideration in patients with melanomas harboring somatic alterations in c-kit. These mutations are found primarily in acral melanoma, mucosal melanoma, or cutaneous melanoma with evidence of chronic sun damage (hereafter referred to as “solar melanomas”). We plan to test the efficacy of dasatinib monotherapy in this population.

1.4 Current Hypothesis and Preliminary Data

In Addendum #3, the study was changed to enroll Kit-positive acral /mucosal melanoma and vulvovaginal melanoma patients. The rationale for this change is based largely on the report by Kluger, et al., of a phase II trial of Dasatinib in patients with advanced melanoma. Twelve of the thirty subjects had acral, mucosal, or CSD melanoma, but an alteration in c-kit was not required for eligibility. Three patients had partial responses, including one with an exon 13 c-kit mutation. Although the mutational status of all subjects has not been reported, it appears that the activity of dasatinib is modest in unselected patients with melanoma (19). We do not feel that dasatinib is worthy of further exploration in c-kit wild-type melanoma (or melanoma in which the c-kit mutational status is unknown). Furthermore, E2607 preliminary data suggest that the rate of c-kit mutations in acral, mucosal and CSD melanomas is lower than previously reported and that an interim comparison of response rates in the c-kit mutant and wild-type populations may not yield interpretable results.

The updated hypothesis is that KIT inhibition is a rational therapeutic consideration in patients with Kit-positive acral/mucosal melanoma or vulvovaginal melanoma.

Per Amendment 3, melanomas with CSD will no longer be screened as part of this protocol. In the largest study to date reporting the frequency of KIT mutations in CSD melanoma, Handolias, et al. analyzed 254 non-acral cutaneous melanomas for mutations in exons 11, 13 and 17. Three melanomas were found to harbor KIT mutations. Two of the three were associated with solar elastosis. In the remaining cohort, 43% had chronically sun damaged skin. The authors concluded that KIT mutations are uncommon in CSD melanoma (20).

1.5 Gender and Ethnicities

This study is open to both men and women and to all racial/ethnic groups. The patient enrollment pattern is expected to be similar to that of typical ECOG melanoma studies. According to the most recent ECOG experience, there is no evidence for outcome to be affected by either race or gender. The study will not have separate accrual targets for different subgroups.
2. Objectives

2.1 Primary Objective

To estimate the objective tumor response rate for dasatinib monotherapy in treatment-naïve or previously treated KIT-positive patients with advanced or metastatic acral or mucosal melanoma. Measurement of effect will be performed by RECIST criteria.

2.2 Secondary Objectives

2.2.1 To estimate the response duration for dasatinib monotherapy in this patient population

2.2.2 To estimate the progression free survival for dasatinib monotherapy

2.2.3 To evaluate the safety profile of this treatment

2.2.4 To evaluate the PDGFR expression, and activation of Src Family Kinases in tumor samples and correlate these parameters with response to treatment.
3. **Selection of Patients**

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient’s eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient’s chart.

**In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.**

ECOG-ACRIN Patient No. __________________________

Patient’s Initials (L, F, M) __________________________

**NOTE:** All questions regarding eligibility should be directed to the ECOG-ACRIN Study Chair at (617) 643-3614.

**NOTE:** Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration by the treating physician.

### 3.1 Pre-Registration (Step 0)

- **3.1.1** Age ≥ 18 years.
- **3.1.2** ECOG performance status of 0 or 1.
- **3.1.3** Histological or cytological confirmed melanoma that is metastatic or unresectable.

Patients must have measurable disease (at least one measurable lesion) as defined by RECIST criteria in Section 6.1.

**NOTE:** All sites of disease must be evaluated **within 4 weeks prior to registration to treatment** (Step 1).

Patients must have a history of melanoma of one of the following subtypes:

- **Acral** (as defined as occurring on the palms, soles, or subungual sites),
- Melanoma arising from the vagina and/or vulva
- Melanoma arising on other mucosal surface (not vagina or vulva)

**3.1.4** c-KIT mutation status determination, local versus central assessments. At least one must apply:

- **3.1.4.1** Performed locally by Polymerase Chain Reaction (PCR) and sequencing prior to pre-registration: The melanoma harbors at least one mutation in exon 9, 11, 13, 17 or 18 of the c-KIT gene.

**NOTE:** Registration to Step 1 may occur upon confirmation of pre-registration
Or

3.1.4.2 Performed locally by Polymerase Chain Reaction (PCR) and sequencing prior to pre-registration: If the melanoma harbors at least one mutation in the c-KIT gene but is not in an exon listed in 3.1.4.1 or is uncertain whether it is in one of these exons then eligibility to register to step 1 requires approval of a designated central reviewer. Submit the cKIT report within 24 hours after pre-registration as indicated in Appendix VI.

Or

3.1.4.3 If local assessment is not possible, metastatic (preferred) or primary tumor tissue should be on hand PRIOR to pre-registration and will be submitted to Massachusetts General Hospital – Pathology (MGH) within 5 working days following pre-registration as outlined in Section 10. If submission of tissue will be submitted more than 5 working days after pre-registration, immediately notify MGH (Massachusetts General Hospital) (617-726-0503, ecog.e2607_tissue@jimmy.harvard.edu) to discuss the potential submission timeline.

IMPORTANT: If the c-KIT status will be determined by MGH, strict attention is to be paid to the timeframes dictated in Section 3.2. Specifically, clinical assessments which must fall within 4 weeks of registration to treatment (Step 1) may be performed or repeated during pre-registration to fall within the required timeframe.

3.1.5 Both naïve and previous systemically treated patients are included.

a) Prior chemotherapy or immunotherapy is permitted.

b) Prior investigational agents are permitted, however, no prior treatment with targeted therapies directed to c-KIT/PDGFR allowed (e.g., imatinib or sunitinib).

c) Limb perfusion allowed.

d) If radiation has been administered to a lesion, there must be radiographic evidence of progression of that lesion in order for that lesion to constitute measurable disease or to be included in the measured target lesions.

3.1.6 Patients must not have ocular melanoma.

3.1.7 Patients must not have any evidence of bleeding diathesis.

3.1.8 Patients must not have other current malignancies, other than basal cell skin cancer, squamous cell skin cancer, in situ cervical cancer, ductal or lobular carcinoma in situ of the breast. Patients with other
malignancies are eligible if they have been continuously disease-free for ≥ 5 years prior to the time of randomization.

History of malignancies other than basal cell skin cancer, squamous cell skin cancer, in situ cervical cancer, ductal or lobular carcinoma in situ of the breast.

Yes _____ No _______

If yes, continuously disease free for ≥ 5 years?

Yes _____ No _______

Any other history of invasive melanoma?

Yes _____ No _______

3.1.9 Patients must not have clinically significant psychiatric illness/social situations that would limit compliance with study requirements.

3.1.10 Patients must not have any clinically significant cardiovascular disease including the following: myocardial infarction or ventricular tachyarrhythmia within 6 months, prolonged QTc >480 msec (Fridericia correction), ejection fraction less than institutional normal, major conduction abnormality (unless a cardiac pacemaker is present). Patients with any cardiopulmonary symptoms of unknown cause (e.g. shortness of breath, chest pain, etc.) are to be evaluated by a baseline echocardiogram with or without stress test as needed in addition to electrocardiogram (EKG) to rule out QTc prolongation. The patient may be referred to a cardiologist at the discretion of the principal investigator. Patients with underlying cardiopulmonary dysfunction are excluded from the study.

__________________________________________
Physician Signature

__________________________________________
Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.
3.2 Registration (Step 1)

3.2.1 The patient must be the eligibility criteria outlined in Section 3.1.

3.2.2 The melanoma must harbor a c-KIT mutation determined by PCR and sequencing as defined in Section 3.1.4 either by:

Local Assessment:
Date of assessment: ______________
Mutation in exon 9,11,13,17 or 18 (Yes or No/Uncertain) ________
If “No/Uncertain”, date of central reviewer approval ______________

OR
cKIT positive mutation status determined by MGH (Yes or No) _______
If “Yes”, Date of assessment: _________________________

3.2.3 Patients must have measurable disease (at least one measurable lesion) as defined by RECIST criteria in Section 6.1. All sites of disease must be evaluated within 4 weeks prior to registration to treatment (Step 1).

3.2.4 If patient has received previous systemic treatment, at least 4 weeks must have elapsed since the last chemotherapy, radiotherapy or immunotherapy and the beginning of protocol therapy and the patient must have recovered from toxicity due to the previous therapy (i.e., toxicity has resolved to baseline or is deemed irreversible).

Prior chemo/immunotherapy (yes or no) _____    Date of last treatment _________
Prior radiation therapy (yes or no)  _____    Date of last treatment __________

3.2.5 Patients with a history or clinical evidence of brain metastasis must have completed radiation therapy or surgical treatment of brain lesions and have no evidence of CNS progression for at least eight weeks at the time of registration. Patients must not require corticosteroids for treatment of cerebral edema from brain metastases. Patients must be evaluated with a head MRI within 4 weeks prior to registration.

History of brain metastases (yes or no)_______
If yes, date of surgery or completion of radiotherapy, whichever is more recent ______________
If yes, date of head MRI: _________________________
If yes, corticosteroids required? (yes or no) ____________

3.2.6 Women of childbearing potential must not be pregnant or breastfeeding. The effects of dasatinib treatments on an unborn fetus are unknown.
All females of childbearing potential must have a blood test or urine study within 2 weeks prior to registration to rule out pregnancy. A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Female? ______ (Yes/No)
Date of blood test or urine study: ______________________

_____ 3.2.7 Women of childbearing potential and sexually active males must be strongly advised to use an accepted method of contraception

_____ 3.2.8 Patients must have the following within 4 weeks prior to registration:

CT Chest with IV and oral agent
Yes ____ No _____ Date of test _____

CT Pelvis/Abdomen with IV and oral agent
Yes ____ No _____ Date of test _____

MRI Brain with gadolinium
Yes ____ No _____ Date of test _____

For patients with known bone metastases, elevated alkaline phosphatase or symptoms raising suspicion of bone metastases, a baseline bone scan is required.

Bone Scan
Yes _____ No _____ Date of test _____

_____ 3.2.9 Baseline laboratory values (evaluated within 4 weeks prior to registration):

_____ White Blood Count ≥ 3,000/mm³  WBC _____  Date of test _____

_____ Absolute Granulocyte Count ≥ 1,500/mm³  AGC _____  Date of test _____

_____ Platelet Count ≥ 100,000/mm³  Platelet _____  Date of test _____

_____ Serum creatinine ≤ 2.0 x upper limit of normal (ULN) or serum creatinine clearance (CrCl) ≥ 40 ml/min (drug is not cleared by the kidney)
Creatinine _____  Date of test _____  ULN ______
(CrCl = WT (kg) x (140-age)*/72 x Cr. Level, * female x 0.85)

_____ Total Bilirubin ≤ 1.5 x ULN (< 3.0 x ULN in the presence of Gilbert’s disease)
Bilirubin _____  Date of test _____  ULN ______
AST and ALT ≤ 2.5 x ULN (≤ 5.0 ULN in the presence of liver metastases)

AST _____ Date of Test _____ ULN _____
ALT _____ Date of Test _____ ULN _____

Serum potassium and magnesium levels within institutional normal limits. Patients with low potassium and magnesium levels may be repleted to allow for protocol entry.

Potassium _____ Date of test _____ ULN _____ LLN _____
Magnesium ____ Date of test _____ ULN _____ LLN _____

Total serum calcium or ionized calcium level ≥ institutional lower limit of normal.

Total or ionized Calcium _____
Date of test _____ ULN _____ LLN _____

INR ≤ 1.5 and PTT within normal limits (Patients who are on therapeutic anticoagulation with warfarin should have documentation of INR ≤ 1.5 or PTT within normal limits prior to initiating that therapy).

INR _____ PTT _____ PTT ULN _____
LDH Date of test _______

3.2.10 Patients must not be taking cytochrome P450 enzyme-inducing antiepileptic drugs (phenytoin, carbamazepine, or Phenobarbital), rifampin, or St. John’s Wort

3.2.11 Patients must not have uncontrolled hypertension as defined by systolic blood pressure ≥ 150 mm Hg or diastolic blood pressure ≥ 90 mm Hg. Patient may be eligible once hypertension is adequately controlled with medications.

3.2.12 Patients must not have QTc prolongation defined as a QTc interval equal to or greater than 450 msecs.

3.2.13 EKG date: _______

3.2.14 Patients must not have a serious intercurrent illness including, but not limited to, ongoing or active infection requiring parenteral antibiotics.

Physician Signature ___________________________ Date ___________________________

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.
Registration Procedures

CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed Statement of Investigator Form (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed Supplemental Investigator Data Form (IDF)
- a completed Financial Disclosure Form (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the CTEP Investigator Registration Help Desk by email at <pmbregpend@ctep.nci.nih.gov>.

CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members’ website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the CTEP Associate Registration Help Desk by email at <ctepreghelp@ctep.nci.nih.gov>.

CTSU Registration Procedures

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

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members’ website by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.
Downloading Site Registration Documents:
Site registration forms may be downloaded from the E2607 protocol page located on the CTSU members’ website.
- Go to https://www.ctsu.org and log in to the members’ area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the ECOG-ACRIN link to expand, then select trial protocol E2607
- Click on the Site Registration Documents link

Requirements for E2607 site registration:
- CTSU IRB Certification (for sites not participating via the NCI CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)

Submitting Regulatory Documents
Submit completed forms along with a copy of your IRB Approval and Model Informed Consent to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
FAX: (215) 569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

Required Protocol Specific Regulatory Documents
1. CTSU Regulatory Transmittal Form.
   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.
3. A. CTSU IRB Certification Form.
   Or
   B. HHS OMB No. 0990-0263 (Replaces the HHS 310 Form).
   Or
   C. IRB Approval Letter
   NOTE: The above submissions must include the following details:
   - Indicate all sites approved for the protocol under an assurance number.
   - OHRP assurance number of reviewing IRB
   - Full protocol title and number
   - Version Date
• Type of review (full board vs. expedited)
• Date of review.
• Signature of IRB official

Checking Your Site’s Registration Status:
Check the status of your site’s registration packets by querying the RSS site registration status page of the members’ section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

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

Patient Enrollment
Patients must not start protocol treatment prior to registration (step 1).

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at <https://eapps-ctep.nci.nih.gov/iam/index.jsp>) and a ‘Registrar’ role on either the LPO or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members’ side of the website at https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

• All eligibility criteria has been met within the protocol stated timeframes.
• All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

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

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

4.1 Pre-Registration (Step 0)
4.1.1 Protocol Number
4.1.2 Investigator Identification
4.1.2.1 Institution and affiliate name
4.1.2.2 Investigator’s name
4.1.3 Patient Identification
4.1.3.1 Patient’s initials and chart number
4.1.3.2 Patient’s Social Security number
4.1.3.3 Patient demographics
   4.1.3.3.1 Sex
   4.1.3.3.2 Birth date (mm/yyyy)
   4.1.3.3.3 Race
   4.1.3.3.4 Ethnicity
   4.1.3.3.5 Nine-digit ZIP code
   4.1.3.3.6 Method of payment

4.1.4 Eligibility Verification
Patients must meet all of the eligibility requirements listed in Section 3.1. An eligibility checklist has been appended to the protocol. A confirmation of registration will be forwarded by the ECOG-ACRIN Operations Office - Boston.

4.1.5 Classification
c-KIT positive mutation status:
   4.1.5.1 Known: local assessment, known mutation in exon 9, 11, 13, 17 or 18
   4.1.5.2 Known: local assessment, other or uncertain mutation, central review approval required
   4.1.5.3 Unknown: Tissue to be submitted for central assessment

4.1.6 Additional Requirements
   4.1.6.1 Patients must provide a signed and dated, written informed consent form.

   4.1.6.2 Regarding c-KIT mutation status:
   • If unknown: Pathological materials must be submitted for central assessment of c-KIT mutation status as indicated in Section 10 within 5 working days following pre-registration. The results of the assessment will be faxed to the site and to the ECOG-ACRIN Operations Office - Boston within 10 working days of sample receipt by MGH. Patient registration (step 1) may proceed 24 to 72 hours after receipt of a cKIT+ mutation status result by the ECOG-ACRIN Operations Office - Boston.

   The submission of inadequate materials for review will delay the turn around time for reporting results to the institution. Requests for additional materials are to be accommodated as quickly as possible to shorten any delay time.
Please do not call the Massachusetts General Hospital Laboratory for results, as testing data cannot be provided over the telephone. Schedule expected patient treatment to account for the turn around time of the assay and distribution of results as expedited processing and analysis is not available.

- If eligibility based on the locally determined c-KIT mutation status requires designated reviewer approval for patient eligibility, the local cKIT report is to be submitted as outlined in Appendix VI within 24 hours following pre-registration. Notification of patient eligibility will occur within 24 to 72 hours following receipt of the report by the ECOG-ACRIN Operations Office - Boston.

4.2 Registration (Step 1)

Only patients meeting all the eligibility criteria (Sections 3.1 and 3.2) are eligible for registration.

For those patients which cKIT mutation status required determination by MGH or central reviewer approval of local results, it will take 24 to 72 hours (if weekend or holiday) after receipt of the assay or reviewer results for ECOG-ACRIN Operations Office - Boston to enter the results into the ECOG-ACRIN randomization system. Registration cannot proceed until this information is received and entered by the ECOG-ACRIN Operations Office - Boston.

Patients must not start protocol treatment prior to registration.

Treatment should start within ten days after registration.

The following information will be requested:

4.2.1 Protocol Number

4.2.2 Investigator Identification

4.2.2.1 Institution and affiliate name

4.2.2.2 Investigator’s name

4.2.3 Patient Identification

4.2.3.1 Patient’s initials and chart number

4.2.3.2 Patient’s Social Security number

4.2.3.3 Patient demographics

4.2.3.3.1 Sex

4.2.3.3.2 Birth date (mm/yyyy)

4.2.3.3.3 Race

4.2.3.3.4 Ethnicity

4.2.3.3.5 Nine-digit ZIP code

4.2.3.3.6 Method of payment
4.2.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.0. An eligibility checklist has been appended to the protocol. A confirmation of registration will be forwarded by the ECOG-ACRIN Operations Office - Boston.

4.2.6 Classification Factors

4.2.6.1 Subtype

- 4.2.6.1.1 Acral Melanoma
- 4.2.6.1.2 Mucosal Melanoma - Vulvovaginal Melanoma
- 4.2.6.1.3 Mucosal Melanoma - Other

4.2.7 Additional Requirements

4.2.7.1 Tumor specimens are requested from patients consenting to participate in the Laboratory Research Studies or tissue banking. See Section 10.

4.2.8 Investigator’s Drug Brochure and Safety Alerts

A copy of the Investigator’s Drug Brochure (IDB) is available for download from the ECOG webpage. The IDB provides relevant and current scientific information about the investigational product. The IDB should be submitted to your IRB/EC according to GCP regulations. The IDB and any correspondence to the Institutional Review Board (IRB)/Ethics Committee (EC) should be kept in the E2607 regulatory files.

Should any SAE report on this study qualify as a safety alert report requiring expedited reporting, the SAE report will be sent by the sponsors to regulatory authorities globally (including the FDA) and ECOG-ACRIN. If applicable, ECOG-ACRIN will disseminate these safety alert reports to all ECOG-ACRIN investigators in the bimonthly group mailings. These reports should be forwarded to your IRB/EC within 90 days of receipt for review. Reporting instructions are provided with each safety alert. These safety alerts and any correspondence to your IRB/EC should be maintained in your E2607 study file.

4.2.9 IND Status

The use of Dasatinib in this trial is classified as “off-label” or unapproved use of FDA-approved drugs. When a drug or combination of drugs used in an off-label manner as part of a clinical trial, it is, by rule, considered as an investigational treatment regimen. However, while these treatment regimens are not approved by the FDA, their use is exempt from the requirements for an IND to conduct this study as defined under Title 21 CFR 312.2(b) of the codified FDA regulations.
4.2.10 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted according to the instructions in the E2607 Forms Packet. Document the reason for not starting protocol treatment on the Off-Treatment Form. Also report the date and type of the first non-protocol treatment that the patient receives.
5. Treatment Plan

5.1 Administration Schedule

Patients will receive dasatinib 70 mg PO twice daily (two tablets; one 50 mg tablet and one 20 mg tablet) on an open-label, single-arm basis. The medication is to be taken once in the morning and once in the evening with or without food. The cycle length of dasatinib is 21 days; however, the medication should be taken every day. There are no breaks between cycles. Please, note that these are flat doses of the drugs. There is no adjustment of dose for BSA. Patients who are tolerating treatment may continue on therapy until disease progression.

Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating dasatinib and during treatment. Symptoms of pulmonary arterial hypertension (PAH) should be investigated as outlined in Section 5.4. If PAH is confirmed, dasatinib should be permanently discontinued.

5.2 Adverse Event Reporting Requirements

5.2.1 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (please refer to the E2607 Forms Packet for the list of forms with directions for routine adverse event reporting). Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. The following sections provide information about expedited reporting.

5.2.2 Determination of Reporting Requirements

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the grade (severity), the relationship to the study therapy (attribution), and the prior experience (expectedness) of the adverse event; 3) the phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

Steps to determine if an adverse event is to be reported in an expedited manner:

Step 1: Identify the type of event: The description and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized until September 30, 2010 for AE reporting. CTCAE version 4.0 will
be utilized beginning October 1, 2010. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

Step 2: Grade the event using the NCI CTCAE v 4.0.

Step 3: Determine whether the adverse event is related to the protocol therapy (investigational or commercial). Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected for expedited reporting purposes only, when either the type of event or the severity of the event is NOT listed in:

- Arm A – the drug package insert or protocol

Step 5: Review Section 5.2.6 for E2607 and/or ECOG-ACRIN specific requirements for expedited reporting of specific adverse events that require special monitoring.

NOTE: For general questions regarding expedited reporting requirements, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497.

5.2.3 Reporting Methods

This study requires that expedited adverse event reporting use CTEP’s Adverse Event Reporting System (CTEP-AERS). CTEP’s guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted electronically to ECOG-ACRIN and the appropriate regulatory agencies via the CTEP-AERS Web-based application located at http://ctep.cancer.gov.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (617-632-3610) and
- the FDA (800-332-1088)

An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Supporting and follow up data: Any supporting or follow up documentation must be faxed to ECOG-ACRIN (617-632-2990), Attention: AE within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the FDA (800-332-0178) in the same timeframe.

NCI Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncitewith@ctep.nci.nih.gov or by phone at 1-888-283-7457.
5.2.4 When to Report an Event in an Expedited Manner

When an adverse event requires expedited reporting, submit a full CTEP-AERS report within the timeframes outlined in Section 5.2.6.

**NOTE:** Adverse events that meet the reporting requirements in Section 5.2.6 and occur within 30 days of the last dose of protocol treatment must be reported on an expedited adverse event report form (using CTEP-AERS). For any adverse events that occur more than 30 days after the last dose of treatment, only those that have an attribution of possibly, probably, or definitely AND meet the reporting requirements in Section 5.2.6 must be reported on an expedited adverse event report form (using CTEP-AERS).

5.2.5 Other Recipients of Adverse Event Reports

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

A drug supporter representative may call a site for additional information regarding a serious adverse event. Any additional written AE information requested by the drug supporter MUST be submitted to BOTH ECOG-ACRIN and the drug supporter.

5.2.6 Expedited Reporting for Commercial Agents

Commercial reporting requirements are provided below. The IND exempt/commercial agent used in arm A of this study is Dasatinib.

<table>
<thead>
<tr>
<th>Attribution</th>
<th>Grade 4</th>
<th>Grade 5a</th>
<th>ECOG-ACRIN and Protocol-Specific Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unexpected</td>
<td>Expected</td>
<td>Unexpected</td>
</tr>
<tr>
<td>Unrelated or Unlikely</td>
<td></td>
<td></td>
<td>7 calendar days</td>
</tr>
<tr>
<td>Possible, Probable, Definite</td>
<td>7 calendar days</td>
<td></td>
<td>7 calendar days</td>
</tr>
</tbody>
</table>

**7 Calendar Days:** Indicates a full CTEP-AERS report is to be submitted within 7 calendar days of learning of the event.

a This includes all deaths within 30 days of the last dose of treatment regardless of attribution.

**NOTE:** Any death that occurs > 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the treatment must be reported within 7 calendar days of learning of the event.

b Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited reporting for this trial:

**Serious Events:** Any event following treatment that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS within 7 calendar days of learning of the event. For instructions on how to specifically report these events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com 301-897-7497.
5.2.7 Reporting Second Primary Cancers

The following NOTE is specific for E2607. The second primary reporting requirements are different for this protocol, in that all second primaries require both routine and expedited reporting via CTEP-AERS, regardless of relationship to prior therapy. Follow the instructions below to report an occurrence of any second primary.

**E2607 Specific Note:** In addition to all routine AE reporting mechanisms and Cooperative Group-specific second/secondary malignancy reporting requirements, all new malignant tumors must be reported through CTEP-AERS whether or not they are thought to be related to previous or current treatment. All new malignancies should be reported including solid tumors, skin malignancies, hematologic malignancies, AML/MDS, and in situ-tumors. If no other cause is evident, an attribution to new primary tumor may be made.

In CTCAE v4.0, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, 3) Treatment-related secondary malignancy, or 4) Neoplasm-other. These events should be reported for as long as the study participants are followed.

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur in patients on NCI-sponsored trials during or following their chemotherapy for cancer must be reported to ECOG-ACRIN. Report the following information for a diagnosis of a second primary cancer:

1. Submit a completed Second Primary Form within 30 days to ECOG-ACRIN at:
   ECOG-ACRIN Operations Office - Boston
   FSTRF
   900 Commonwealth Avenue
   Boston, MA 02215
   *Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, c.) treatment related secondary malignancy, or d.) Neoplasm - Other*
3. Submit a copy of the pathology report to ECOG-ACRIN and NCI/CTEP confirming the diagnosis.
4. If the patient has been diagnosed with AML/MDS, submit a copy of the cytogenetics report (if available) to ECOG-ACRIN and NCI/CTEP.

**NOTE:** The Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

**NOTE:** If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated
pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

**NOTE:** Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form.
5.3 Comprehensive Adverse Events and Potential Risks list (CAEPR)

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

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. They are developed and continuously monitored by the CTEP Investigational Drug Branch (IDB). The information listed in the CAEPR below, as well as the other resources described in the 'Determination of reporting requirements' part of the Adverse Event Reporting section in this protocol, can be used to determine expectedness of an event when evaluating if the event is reportable via CTEP-AERS. Frequency is provided based on 2937 patients. Below is the CAEPR for dasatinib (BMS-354825).

<table>
<thead>
<tr>
<th>Adverse Events with Possible Relationship to Dasatinib (BMS-354825) (CTCAE 4.0 Term) [n= 2937]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Likely (&gt;20%)</td>
</tr>
<tr>
<td>BLOOD AND LYMPHATIC SYSTEM DISORDERS</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
</tr>
<tr>
<td>CARDIAC DISORDERS</td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>Left ventricular systolic dysfunction</td>
</tr>
<tr>
<td>Pericardial effusion</td>
</tr>
<tr>
<td>GASTROINTESTINAL DISORDERS</td>
</tr>
<tr>
<td>Abdominal distension</td>
</tr>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Anal mucositis</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Dyspepsia</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Small intestinal mucositis</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</td>
</tr>
<tr>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Edema limbs</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>General disorders and administration site</td>
</tr>
<tr>
<td>conditions - Other (generalized edema)</td>
</tr>
<tr>
<td>General disorders and administration site</td>
</tr>
<tr>
<td>conditions - Other (superficial edema)</td>
</tr>
<tr>
<td>Non-cardiac chest pain</td>
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<tr>
<td>Pain</td>
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<table>
<thead>
<tr>
<th>INFECTIONS AND INFESTATIONS</th>
</tr>
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<tbody>
<tr>
<td>Infection</td>
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<table>
<thead>
<tr>
<th>INVESTIGATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine aminotransferase increased</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
</tr>
<tr>
<td>Electrocardiogram QT corrected interval</td>
</tr>
<tr>
<td>prolonged</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
</tr>
<tr>
<td>Weight gain</td>
</tr>
<tr>
<td>Weight loss</td>
</tr>
<tr>
<td>White blood cell decreased</td>
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</table>

<table>
<thead>
<tr>
<th>METABOLISM AND NUTRITION DISORDERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia</td>
</tr>
<tr>
<td>Hypocalcemia</td>
</tr>
<tr>
<td>Hypokalemia</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
</tr>
<tr>
<td>Tumor lysis syndrome</td>
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<table>
<thead>
<tr>
<th>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</th>
</tr>
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<tbody>
<tr>
<td>Arthralgia</td>
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<table>
<thead>
<tr>
<th>NERVOUS SYSTEM DISORDERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
</tr>
<tr>
<td>Leukoencephalopathy</td>
</tr>
<tr>
<td>Reversible posterior leukoencephalopathy syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
</tr>
<tr>
<td>Dyspnea</td>
</tr>
<tr>
<td>Laryngeal mucositis</td>
</tr>
<tr>
<td>Pharyngeal mucositis</td>
</tr>
<tr>
<td>Pleural effusion</td>
</tr>
<tr>
<td>Pneumonitis</td>
</tr>
<tr>
<td>Tracheal mucositis</td>
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<tr>
<td>Pulmonary hypertension</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
</tr>
<tr>
<td>Pruritus</td>
</tr>
<tr>
<td>Rash maculo-papular</td>
</tr>
</tbody>
</table>
VASCULAR DISORDERS

| Flushing |

1. This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

2. Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

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

4. Gastrointestinal ulcer includes Anal ulcer, Colonic ulcer, Duodenal ulcer, Esophageal ulcer, Gastric ulcer, Ileal ulcer, Jejunal ulcer, Rectal ulcer, and Small intestine ulcer under the GASTROINTESTINAL DISORDERS SOC.

Also reported on dasatinib (BMS-354825) trials but with the relationship to dasatinib (BMS-354825) still undetermined:

CARDIAC DISORDERS - Acute coronary syndrome; Atrial fibrillation; Cardiac disorders - Other (cardiomegaly); Cardiac disorders - Other (heart rate increased); Chest pain - cardiac; Myocarditis; Palpitations; Pericarditis; Sinus tachycardia; Ventricular tachycardia

CONGENITAL, FAMILIAL AND GENETIC DISORDERS - Congenital, familial and genetic disorders - Other (Keratosis follicular)

EAR AND LABYRINTH DISORDERS - Ear pain; Middle ear inflammation; Tinnitus; Vertigo

EYE DISORDERS - Blurred vision; Conjunctivitis; Dry eye; Eye disorders - Other (optic nerve neuritis)

GASTROINTESTINAL DISORDERS - Ascites; Colitis; Dry mouth; Dysphagia; Enterocolitis; Esophagitis; Flatulence; Gastritis; Gastrointestinal disorders - Other (anal fissure); Gastrointestinal disorders - Other (hematemesis); Gastrointestinal disorders - Other (mouth ulceration); Gastrointestinal disorders - Other (oral soft tissue disorder); Gastrointestinal disorders - Other (oropharyngeal pain); Gastrointestinal disorders - Other (tongue eruption); Gastrointestinal ulcer; Ileus; Oral pain; Pancreatitis; Periodontal disease; Stomach pain

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Edema trunk; Flu like symptoms; Gait disturbance; General disorders and administration site conditions - Other (temperature intolerance); Localized edema; Malaise

HEPATOBILIARY DISORDERS - Cholecystitis; Hepatobiliary disorders - Other (cholestasis)

IMMUNE SYSTEM DISORDERS - Anaphylaxis

INFECTIONS AND INFESTATIONS - Infections and infestations - Other (herpes virus infection)

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising

INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; Cardiac troponin T increased; CD4 lymphocytes decreased; CPK increased; Creatinine increased; GGT increased; Investigations - Other (bone densitometry); Investigations - Other (EKG T-wave inversion); Investigations - Other (pancytopenia); Investigations - Other (thermometry abnormal); Lymphocyte count decreased; Lymphocyte count increased

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperkalemia; Hyperuricemia; Hypoalbuminemia; Hypomagnesemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Back pain; Bone pain; Chest wall pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (epiphyses delayed fusion); Musculoskeletal and connective tissue disorder - Other (muscle spasm); Musculoskeletal and connective tissue disorder - Other (muscle stiffness); Musculoskeletal and connective tissue disorder - Other (nuchal rigidity); Musculoskeletal and connective tissue disorder - Other (rhabdomyolysis); Musculoskeletal and connective tissue disorder - Other (tendonitis); Myositis; Osteoporosis; Pain in extremity

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (hemangiomatosis)

NERVOUS SYSTEM DISORDERS - Acoustic nerve disorder NOS; Amnesia; Cognitive disturbance; Concentration impairment; Dysarthria; Dysgeusia; Ischemia cerebrovascular; Lethargy; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Somnolence; Syncope; Transient ischemic attacks; Tremor

PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia; Libido decreased; Suicidal ideation

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Gynecomastia; Irregular menstruation

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Bronchospasm; Epistaxis; Hypoxia; Pulmonary edema; Sore throat

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Bullous dermatitis; Dry skin; Hyperhidrosis; Nail loss; Pain of skin; Palmar-plantar erythrodysesthesia syndrome; Periorbital edema; Photosensitivity; Purpura; Skin and subcutaneous tissue disorders - Other (acute febrile neutrophilic dermatosis); Skin and subcutaneous tissue disorders - Other (hair color changes); Skin and subcutaneous tissue disorders - Other (panniculitis); Skin ulceration; Urticaria

VASCULAR DISORDERS - Hematoma; Hot flashes; Hypertension; Hypotension; Phlebitis; Superficial thrombophlebitis; Thromboembolic event; Vasculitis

NOTE: Dasatinib (BMS-354825) 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.
### Dose Reductions for Drug-Related Hematologic and Non-Hematologic Toxicities

All toxicity grades below are described using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of CTCAE version 4.0 can be downloaded from the CTEP website ([http://ctep.cancer.gov](http://ctep.cancer.gov)).

**NOTE:** Up to two dose reductions are allowed. If unacceptable toxicity recurs despite optimal supportive care after two dose reductions, the subject must come off study.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic:</strong> Absolute Neutrophil Count (ANC) (x $10^9$/L) and Platelets (x $10^9$/L)</td>
<td></td>
</tr>
<tr>
<td>ANC &lt; 1,000 OR platelets &lt; 50,000</td>
<td>Stop Dasatinib when ANC ≤ 1,000 OR platelets ≤ 50,000 Resume when ANC &gt; 1,000 AND platelets &gt; 50,000</td>
</tr>
</tbody>
</table>
| ANC < 1,000 for > 7 days OR platelets are < 25,000 | Stop Dasatinib Resume when ANC ≥ 1,000 AND platelets ≥ 50,000.  
2nd event: Resume at reduced dose of 100 mg once daily  
3rd event: Resume at 70 mg daily  
4th event: Discontinue |

**Non-Hematologic**

| Severity: Grade 2 | 1st event: Institute appropriate therapy; may continue without dose reduction. May reduce to 100 mg once daily if poorly controlled.  
2nd event: Interrupt or maximize appropriate therapy; decrease dose to 100 mg once daily once resolved to grade 1 or less.  
3rd event: Interrupt; may discontinue or modify dose to 70 mg daily once resolved to grade 1 or less.  
4th event: Discontinue |
|-------------------|--------------------------------------------------|
| Severity: Grade 3 or 4 | 1st event: Interrupt. Institute appropriate therapy; restart with dose reduction to 100 mg once daily. Toxicity must have returned to Grade ≤ 1 or baseline to resume with this dose reduction.  
2nd event: Interrupt or maximize appropriate therapy; may discontinue if poorly controlled, or restart with dose modification to 70 mg daily. Toxicity must have returned to Grade ≤ 1 or baseline to resume with this dose reduction.  
3rd event: Discontinue |

**Pulmonary Arterial Hypertension (PAH)**

| Symptoms but PAH unconfirmed: Interrupt at physician’s discretion  
PAH confirmed: Discontinue |

* If nonhematologic event lasts for > 2 weeks despite interruption in treatment, discontinue the study medication.

** 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 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.

5.5 Supportive Care

5.5.1 All supportive measures consistent with optimal patient care will be given throughout the study.

5.5.2 Guidance is provided for management of common side effects of dasatinib in order to maximize the opportunity for benefit. Non-hematologic side effects are typically CTCAE Grade 1-2 and responsive to outpatient treatment; interruption and/or dose reduction may be necessary. Myelosuppression, although frequent in subjects with Ph+ leukemias, has been minimal in subjects with solid tumors.

5.5.3 Nausea, diarrhea, pain, fever, and headache are generally responsive to usual supportive care measures.

5.5.4 Fluid retention, commonly including pleural effusion, has been noted during treatment with dasatinib. Early institution of diuresis is appropriate (i.e. furosemide 20-40 mg, PO, daily, and/or spirinolactone 25-50 mg, PO, daily with titration to symptoms). Pleural effusions that remain or become symptomatic despite diuresis should be managed with thoracentesis. Steroid treatment (see 5.4.5) may also be effective for pleural effusion. Chest discomfort may be related to a pericardial effusion; an echocardiogram should be performed to investigate this side effect.

5.5.5 Signs of inflammation, including pneumonitis, colitis, or skin rash, have been observed during dasatinib therapy. During interruption and short-term steroid treatment (i.e. 5-7 days methylprednisolone with rapid taper) may be appropriate. Concurrent antibiotics are appropriate if there is a clinical suspicion for infection.

5.5.6 Use of growth factor support is not expected, but it is permitted if indicated. Based on preclinical data, dasatinib may inhibit platelet aggregation. Rare instances have been observed of increased bleeding risk. Potential occult blood loss should be carefully evaluated.

5.5.7 Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating dasatinib and during treatment. Symptoms of PAH are to be investigated as recommended in Section 5.4

5.6 Duration of Therapy

Patients will receive protocol therapy unless:

5.6.1 Progression of disease during dasatinib treatment: Stop protocol therapy at the time progressive disease is documented.

5.6.2 Extraordinary medical circumstances: If at any time the constraints of this protocol are detrimental to the patient's health (i.e. unacceptable
toxicity), protocol treatment should be discontinued. In this event submit forms according to the instructions in the E2607 Forms Packet.

5.6.3 Patient withdraws consent. In this event, document the reason(s) for withdrawal.

5.6.4 Patient meets criteria for stopping study medication due to toxicity as outlined in Section 5.4.

5.7 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for survival for 5 years from the date of registration. All patients must also be followed through completion of all protocol therapy.
6. Measurement of Effect

6.1 Solid Tumor Response Criteria (RECIST)

6.1.1 Malignant Disease Evaluation

To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. Measurable disease is defined by the presence of at least one measurable lesion.

All measurements should be recorded in metric notation by use of a ruler or calipers. The same method of assessment and the same technique should be used to characterize each identified lesion at baseline and during follow-up. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than four weeks before registration.

The term evaluable in reference to measurability will not be used because it does not provide additional meaning or accuracy.

At baseline, tumor lesions will be characterized as either measurable or non-measurable.

6.1.1.1 Measurable

Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as > 20 mm (2.0 cm) with conventional techniques or as > 10 mm (1.0 cm) with spiral CT scan.

If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

6.1.1.2 Non-Measurable

All other lesions, including small lesions [longest diameter < 20 mm (2.0 cm) with conventional techniques or < 10 mm (1.0 cm) with spiral CT scan] and truly non-measurable lesions.

Lesions considered to be truly non-measurable include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions.

Tumor lesions situated in a previously irradiated area must demonstrate progression after completion of radiation to be considered measurable.
6.1.2 Definitions of Response

6.1.2.1 Target Lesions

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs. Target lesions should be selected on the basis of their size (those with the longest diameters) and their suitability for accurate repeated measurements.

The sum of the longest diameters of all target lesions will be calculated at baseline and reported as the baseline sum longest diameter. The sum longest diameter will be used to characterize the objective tumor response. For lesions measurable in 2 or 3 dimensions, always report the longest diameter at the time of each assessment.

6.1.2.2 Complete Response (CR)

The disappearance of all target lesions. To be assigned a status of complete response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

6.1.2.3 Partial Response (PR)

At least a 30% decrease in the sum of the longest diameters of target lesions, taking as reference the baseline sum longest diameter. To be assigned a status of partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

6.1.2.4 Progressive Disease (PD)

At least a 20% increase in the sum of the longest diameters of target lesions, taking as reference the smallest sum longest diameter recorded since the baseline measurements, or the appearance of one or more new lesion(s).

For subcutaneous lesions, the appearance of a new lesion, measuring at least 1 cm in diameter, visible on the skin surface, and documented by photography with a centimeter-scale ruler.

6.1.2.5 Stable Disease (SD)

Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease. To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of six weeks.
6.1.3 Nontarget Lesions

All other lesions or sites of disease. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

6.1.3.1 Complete Response (CR)

The disappearance of all nontarget lesions and normalization of tumor marker levels, if applicable. To be assigned a status of complete response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

6.1.3.2 Incomplete Response/Stable Disease (SD)

The persistence of one or more nontarget lesion(s) and/or the maintenance of tumor marker levels above the normal limits. To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of six weeks.

6.1.3.3 Progressive Disease (PD)

The appearance of one or more new lesion(s) and/or unequivocal progression of existing nontarget lesions.

6.1.4 Symptomatic Deterioration

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having symptomatic deterioration.

6.2 Evaluation of Patient’s Best Overall Response

The best overall response is the best response recorded from registration until disease progression/recurrence, taking as reference for progressive disease the smallest measurements recorded since registration. The table below provides overall responses for all possible combinations of tumor responses in target and nontarget lesions, with or without new lesions.

To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of six weeks.
## Overall Response for all Possible Combinations of Tumor Response

<table>
<thead>
<tr>
<th>Target Lesions</th>
<th>Nontarget Lesions</th>
<th>New Lesions</th>
<th>Overall Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>CR</td>
<td>Incomplete response/SD</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>PR</td>
<td>Non-PD</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>SD</td>
<td>Non-PD</td>
<td>No</td>
<td>SD</td>
</tr>
<tr>
<td>PD</td>
<td>Any</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>PD</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
</tr>
</tbody>
</table>

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease

### 6.2.1 First Documentation of Response
The time between initiation of therapy and first documentation of PR or CR.

### 6.2.2 Confirmation of Response
To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed **no less than four weeks** after the criteria for response are first met.

### 6.2.3 Duration of Response
Duration of overall response – the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded since treatment started.

#### 6.2.3.1 Duration of Overall Complete Response
The period measured from the time measurement criteria are met for complete response until the first date that recurrent disease is objectively documented.

#### 6.2.3.2 Duration of Stable Disease
A measurement from registration until the criteria for disease progression is met, taking as reference the smallest measurements recorded since registration. To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of six weeks.

### 6.2.4 Survival
Survival will be measured from the date of entry on study.
6.2.5 Time to Progression

This interval will be measured from the date of entry on the study to the appearance of new metastatic lesions or objective tumor progression.

6.2.6 Methods of Measurement

Imaging based evaluation is preferred to evaluation by clinical examination. The same imaging modality must be used throughout the study to measure disease.

6.2.6.1 CT and MRI

CT and magnetic resonance imaging (MRI) are the best currently available and most reproducible methods for measuring target lesions. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed by use of a 5 mm contiguous reconstruction algorithm. This specification applies to tumors of the chest, abdomen, and pelvis, while head and neck tumors, and those of the extremities require specific procedures.

6.2.6.2 Chest X-Ray

Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by an aerated lung. However, CT is preferable.

6.2.6.3 Tumor Markers

Tumor markers alone cannot be used to assess response. If initially above the upper normal limit, a tumor marker must return to normal levels for a patient to be considered in complete clinical response when all tumor lesions have disappeared.

6.2.6.4 Clinical Examination

Clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For skin lesions, documentation by color photography, including a ruler to estimate size of the lesion, is recommended. Photographs should be retained at the institution.

6.2.6.5 Cytology and Histology

Cytologic and histologic techniques can be used to differentiate between complete and partial response in rare cases (e.g., after treatment to differentiate residual benign lesions and residual malignant lesions in germ cell tumors). Cytologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met response or stable disease criteria.
6.2.6.6 Endoscopy and Laparoscopy

Endoscopy and laparoscopy have not been fully or widely validated, so their use should be limited to validation studies in specialized institutions, and to confirming complete histopathologic response when biopsy specimens have been obtained.

6.2.6.7 Ultrasound

Ultrasound may be used only as an alternative to clinical measurements for superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules, and for confirming complete disappearance of superficial lesions usually assessed by clinical examination.
7. **Study Parameters**

1. Prestudy scans and x-rays used to assess all measurable or non-measurable sites of disease must be done within 4 weeks prior to registration.

2. Prestudy CBC (with differential and platelet count) should be done ≤ 4 weeks before registration.

3. All required prestudy chemistries, as outlined in Section 3, should be done ≤ 4 weeks before registration – unless specifically required on Day 1 as per protocol.

4. The first scan for response should occur 6 weeks after study entry. Assessment for response will then be performed every 6 weeks. If there is a partial or complete response, this must be confirmed at the next scan 6 weeks later.

### Table: Study Parameters

<table>
<thead>
<tr>
<th>Test</th>
<th>Prestudy</th>
<th>Every 3 weeks</th>
<th>Every 6 weeks</th>
<th>Follow up $^{10}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and physical examination</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital signs $^1$</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse Oximetry Measurement</td>
<td>X</td>
<td></td>
<td>As clinically indicated</td>
<td></td>
</tr>
<tr>
<td>Height/Weight</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG Performance Status</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td>X</td>
<td></td>
<td>As clinically indicated</td>
<td></td>
</tr>
<tr>
<td>CBC, differential, platelets $^2$</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Sodium, potassium, BUN, serum creatinine, glucose, calcium, magnesium, phosphorous, SGOT (AST), SGPT (ALT), total bilirubin, alkaline phosphatase, LDH, albumin, amylase, lipase</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR, aPTT $^3$</td>
<td>X</td>
<td></td>
<td>As clinically indicated</td>
<td></td>
</tr>
<tr>
<td>Brain MRI $^4$</td>
<td>X</td>
<td></td>
<td>As clinically indicated</td>
<td></td>
</tr>
<tr>
<td>Chest CT $^{4,9}$</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Abdomen/pelvis CT or MRI $^{4,9}$</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Bone scan $^5$</td>
<td>X</td>
<td></td>
<td>As clinically indicated</td>
<td></td>
</tr>
<tr>
<td>Clinical Tumor Assessment $^6$</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Beta HCG $^7$</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary Assessments $^{12}$</td>
<td>X</td>
<td></td>
<td>As clinically indicated</td>
<td></td>
</tr>
<tr>
<td>cKIT mutation status $^{11}$</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathology Submission $^8$</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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1. Blood pressure measurements should be made using a calibrated electronic device, unless performed in a doctor's office where a manual blood pressure measurement is acceptable.

2. CBCs (with differential and platelet count) which includes WBC, ANC, Platelets, Hgb, and Hct. CBC with differential should be obtained twice weekly if ANC < 1000/mm$^3$ or platelet count < 50,000/mm$^3$ until these cytopenias resolve to grade 1 or less.

3. Patients taking warfarin for therapeutic anticoagulation should have their INR measured weekly for the first cycle, then once per cycle thereafter.

4. Chest, abdomen, and pelvis should be re-imaged every six weeks. CTs should be done with IV and oral contrast. Baseline brain MRI should be done with gadolinium. If MRI is contraindicated, head CT with IV contrast may be substituted.
5. A baseline bone scan is required for patients with known bone metastases, elevated alkaline phosphatase or symptoms raising suspicion of bone metastases. In the case of bone scan, if negative at baseline, it may be deferred until the development of bone pain or a newly increased alkaline phosphatase.

6. Intracutaneous or subcutaneous lesions should be evaluated with digital photography at baseline and at the time of each subsequent tumor assessment. A centimeter-scale ruler must be included in the photographic field on each occasion.

7. For women of childbearing potential, within 2 weeks prior to registration.

8. Submission requirements are outlined in Section 10.
   If tumor will be submitted for central determination of c-KIT mutation status, materials must be submitted to Massachusetts General Hospital-Pathology (MGH) within 5 working days following pre-registration and must meet the following requirements:
   - Tumor blocks or unstained slides with > 20% tumor tissue (> 40% preferred to decrease probability of a false negative) are required for the evaluation of KIT mutation and amplification. Failure to submit the requested materials will render the case ineligible.
   - Tumor tissue is requested from all registered patients who have answered "Yes" to "laboratory research studies or banking."

9. Scans will no longer be required once the patient goes off treatment for any reason.

10. Every 3 months if patient is < 2 years from study entry. Every 6 months if patient is 2-5 years from study entry.

11. If c-KIT mutation status will be determined centrally by MGH, see footnote 8 and Section 10. If cKIT mutation status by Polymerase Chain Reaction (PCR) and sequencing was performed locally, a copy of the report must be submitted to the ECOG-ACRIN Operations Office - Boston as follows:
   a. For patients with known cKIT mutations in exons outlined in Section 3.1.4, submit (with E2607 Source Document Tracking Coversheet, form # 3022) within 5 working days following registration to step 1.
   b. For patients with cKIT mutation status as defined by 3.1.4, the report, the completed Appendix VI form, and the E2607 Source Document Tracking Coversheet (form # 3022) must be submitted within 24 hours following pre-registration.

12. Patients are to 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. See Sections 3.1.10 and 5.4.
8. **Drug Formulation and Procurement**

8.1 **Dasatinib**

8.1.1 Other Names

Sprycel (BMS-354825)

8.1.2 Chemical Name

N-(2-chloro-6-methylphenyl)-2-[(6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl)amino]-5-thiazolecarboxamide, monohydrate.

8.1.3 Molecular Formula

C\textsubscript{22}H\textsubscript{26}ClN\textsubscript{7}O\textsubscript{2}S (Molecular Weight 506.02 daltons)

8.1.4 Classification

Tyrosine kinase inhibitor (c-KIT, PDGFRbeta, BCR-ABL, SRC family (SRC, LCK, YES, FYN), EPHA2)

8.1.5 Mechanism of Action

The KIT pathway is an important mediator of responses to growth signals and angiogenic factors. This pathway is thought to be aberrantly activated in human tumors. Preclinical data suggests the KIT pathway to be important in the following in acral, mucosal, and solar melanomas.

Sprycel is a potent inhibitor of: c-KIT, PDGFRbeta, BCR-ABL, SRC family (SRC, LCK, YES, FYN), EPHA2.

8.1.6 Storage and Stability

Dasatinib tablets should be stored at 25° C (77° F); excursions permitted between 15°-30° C (59°-86° F)

The tablets should be stored in the original package. Dasatinib is a film-coated tablet and has a melting point of 280°-286° C.

8.1.7 Dose Specifics

Patients will receive 70 mg po twice daily, once in the morning and once in the evening with or without food. Tablets should not be crushed or cut. They should be swallowed whole.

8.1.8 Preparation

Dasatinib tablets contain the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The tablet coating consists of hypromellose, titanium dioxide, and polyethylene glycol. If tablets are crushed or broken, pharmacy and clinical personnel should wear disposable chemotherapy gloves. Personnel who are pregnant should avoid exposure to crushed and/or broken tablets.
8.1.9 Drug-Drug Interactions

Dasatinib is a time-dependent inhibitor of CYP3A4 and may decrease the metabolic clearance of drugs that are primarily metabolized by CYP3A4. Drugs that may increase dasatinib plasma concentrations include ketoconazole, itraconazole, erythromycin, clarithromycin, retroviral agents, and telithromycin. Drugs that may decrease dasatinib concentrations include H2 receptor antagonists and proton pump inhibitors. Locally acting antacids (i.e., Maalox, Mylanta) allowed either 2 hours before or 2 hours after dasatinib administration. Drugs that may have their plasma concentrations altered include phenytoin, carbamazepine, phenobarbital, rifampin, and St. John’s wort.

8.1.10 How Supplied

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Dasatinib is available free of charge from Bristol-Myers Squibb and distributed by ALMAC Clinical Services.

Dasatinib will be supplied in two different strengths:

- 20 mg film-coated tablets, 30 tabs/bottle, film-coated tablets, biconvex, round, white to off-white in appearance with “BMS” debossed on one side and “527” on the other side
- 50 mg film-coated tablets, 30 tabs/bottle, film-coated tablets, biconvex, oval, white to off-white in appearance with “BMS” debossed on one side and “528” on the other side

IND Status

The use of Dasatinib in this trial is classified as “off-label” or unapproved use of FDA-approved drugs. When a drug or combination of drugs used in an off-label manner as part of a clinical trial, it is, by rule, considered as an investigational treatment regimen. However, while these treatment regimens are not approved by the FDA, their use is exempt from the requirements for an IND to conduct this study as defined under Title 21 CFR 312.2(b) of the codified FDA regulations.

Drug Availability

Initial Drug Orders for Each Patient: Following submission and approval of the required regulatory documents and patient registration, a supply of Dasatinib may be ordered from ALMAC Clinical Services. Institution personnel must email a completed Sprycel® (Dasatinib) Drug Request Form (See Appendix V) to ALMAC Clinical Services at BMSDasatinibISTProgram@almacgroup.com. The subject line of the email MUST include “SPRYCEL® SUPPLY REQUEST”. All drug orders must include a patient sequence number. No starter supplies are available for this protocol.

Rev. 11/11

The initial shipment will cover a 12 week treatment period (4 cycles). Allow 4-7 business days for shipment of drug from receipt of the Sprycel® (Dasatinib) Drug Request Form by ALMAC Clinical
Services. This form can be downloaded from the ECOG website in WORD format.

**IMPORTANT REORDER INSTRUCTIONS**

Reorders should be emailed directly to BMSDasatinibISTProgram@almacgroup.com for shipment within 4-7 business days. (See Appendix V). The subject line of the email MUST include “SPRYCEL® SUPPLY REQUEST”.

Shipments will be made from Almac Clinical Services on Monday through Thursday for delivery on site Tuesday through Friday. There will be no weekend or holiday delivery of drugs. It is possible that sites may have more than one Dasatinib clinical study ongoing at the same time. It is imperative that only product designated for ECOG-ACRIN E2607 be utilized for this study.

Drug Destruction and Return: At the completion of the study, all unused drugs will be destroyed at the site according to the institution’s policy for drug destruction. Please maintain appropriate records of the disposal, including dates and quantities. Drug Inventory Records:

Investigational Product Records at Investigational Site(s): It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines.

8.1.11 Side Effects

See Section 5.3.

8.1.12 Nursing/Patient Implications

1. Monitor for jaundice
2. Evaluate patient for GI intolerance.
3. Dasatinib can be taken with or without a meal.

8.1.13 References

9. Statistical Considerations

9.1 Previous Study Design

Initially this study was designed to evaluate the response (CR+PR) rate in patients with metastatic melanoma with the subtypes: i) solar, ii) mucosal, iii) acral in KIT+ and KIT- patients. A total of 56 patients were planned to be enrolled in the first stage. Based on the interim analysis result, it was planned to i) open only to KIT+ cases or ii) extend the enrollment to both KIT+ and KIT- cases or iii) terminate the study.

Since this trial was initiated, Klug et al. reported that dasatinib has limited activity in patients with melanoma unselected by KIT mutational status (19). We have reviewed the E2607 data as of August 5, 2010. This analysis included a total of 43 cases of which 36 had the KIT mutation status typed (1 positive, 32 negative and 3 not enough samples). One KIT+ case has died before the response was assessed, but there were only two patients with PRs among KIT- cases. Of the 23 KIT- cases with acral and mucosal subtypes, the response (CR+PR) rate was 9% (2/23). This data review indicated there is minimal treatment benefit in KIT- cases. This led to the study design change indicated below.

9.2 New Study Design (Based on data as of August 5, 2010)

The main changes are as follows: i) screen patients for KIT mutation status (either locally or centrally) and enroll KIT+ cases only, ii) KIT+ mutation rate is low in sun-damaged cases – therefore this subgroup will be eliminated, iii) The Gynecologic Oncology Group will join the study to enhance the accrual of vulvovaginal melanoma cases, iv) The statistical design has been revised with the assumption that the KIT mutation rate is 6-7%.

9.2.1 Accrual

It is assumed that approximately 15 (50%) of the patients to be accrued will have their melanoma’s c-KIT mutation status determined locally. For the remaining patients, it is estimated that approximately 250 patients with acral or mucosal (including vulvovaginal) melanoma subtypes will be screened centrally for KIT mutations. Of these, it is expected that 15 KIT mutation+ subjects will be enrolled in this study. Of the accrued patients, we expect that there will be 12 KIT+ cases with vulvovaginal melanoma and 18 other melanoma cases. Including the pre-screening of 250 cases, enrolling 30 KIT + cases is expected to be completed in 3 years.

9.2.2 Primary Objective

If dasatinib can improve the response rate from 15% to 37% in KIT+ cases, we will conclude this is a promising regimen for KIT+ cases. Note that the main sample size calculation presented in this section is based on the combined ECOG-ACRIN and GOG populations. However, at the end of the study, separate analyses in ECOG-ACRIN and GOG populations will also be performed.
A maximum of 30 (for 28 eligible) patients will be registered with a two-stage accrual design. If dasatinib shows evidence of at least 37% response rate, we would consider this a promising drug for a further study. However to conserve patient resources, we wish to minimize accrual if the response rate is less than 15%.

In the first stage, 15 cases (assuming 14 eligible) will be accrued. If there are at least 3 responses, accrual will continue to 30 (assuming 28 eligible). If there are at least 7 responses this will be considered successful. This design will provide 90% power with a one-sided type I error rate of .10. If the response rate is low (15%), there is 65% chance of stopping the study early.

Given the small percentage of KIT+ rate, the screening process will continue while interim analysis is being conducted.

9.2.3 Secondary Objectives
The duration of response for responders, progression-free survival and safety profile of dasatinib will be evaluated. Descriptive statistics will be provided for this data.

9.3 Safety Monitoring
Interim analyses of toxicity are performed twice yearly for all ECOG-ACRIN studies. Reports of these analyses are sent to the ECOG-ACRIN Principal Investigator or Senior Investigator at the participating institutions. Expedited reporting of certain adverse events is required, as described in Section 5.2.

9.4 Gender and Ethnicity
The combined stage 1 and stage 2 accruals for E2607 is 87 patients. The breakdown of the patient populations by gender and race within these stages are outlined below.

**Stage 1 Accrual**
For the stage 1 accrual of 57 patients on E2607, the accrual in subgroups defined by gender and race is:

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Gender</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
<td>Males</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>35</td>
<td>19</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td><strong>Ethnic Category: Total of all subjects</strong></td>
<td>35</td>
<td>22</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Racial Category</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indian or Alaskan Native</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>31</td>
<td>20</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td><strong>Racial Category: Total of all subjects</strong></td>
<td>35</td>
<td>22</td>
<td>57</td>
<td></td>
</tr>
</tbody>
</table>
Stage 2 Estimated Accrual

Based on preliminary data from E2607 and GOG, the anticipated accrual on stage 2 (cKIT+ mutation status only) in subgroups defined by gender and race is:

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Gender</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic or Latino</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td></td>
<td>12</td>
<td>18</td>
<td>30</td>
</tr>
<tr>
<td><strong>Ethnic Category: Total of all subjects</strong></td>
<td></td>
<td>12</td>
<td>18</td>
<td>30</td>
</tr>
</tbody>
</table>

| Racial Category                          |        |         |       |       |
| American Indian or Alaskan Native        |        | 0       | 0     | 0     |
| Asian                                    |        | 0       | 0     | 0     |
| Black or African American                |        | 0       | 0     | 0     |
| Native Hawaiian or other Pacific Islander|        | 0       | 0     | 0     |
| White                                    |        | 12      | 18    | 30    |
| **Racial Category: Total of all subjects** |        | 12      | 18    | 30    |

The accrual targets in individual cells are not large enough for definitive subgroup analyses. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

Combined Stage 1 (Actual) and Stage 2 (Estimated) Accrual

The anticipated accrual in subgroups defined by gender and race combined from the tables above is:

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Gender</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic or Latino</td>
<td></td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td></td>
<td>47</td>
<td>37</td>
<td>84</td>
</tr>
<tr>
<td><strong>Ethnic Category: Total of all subjects</strong></td>
<td></td>
<td>47</td>
<td>40</td>
<td>87</td>
</tr>
</tbody>
</table>

| Racial Category                          |        |         |       |       |
| American Indian or Alaskan Native        |        | 0       | 0     | 0     |
| Asian                                    |        | 2       | 2     | 4     |
| Black or African American                |        | 2       | 0     | 2     |
| Native Hawaiian or other Pacific Islander|        | 0       | 0     | 0     |
| White                                    |        | 43      | 38    | 81    |
| **Racial Category: Total of all subjects** |        | 47      | 40    | 87    |
10. Pathology Review

NOTE: ECOG-ACRIN requires that all samples submitted from patients participating in this trial be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). See Section 10.2.

From patients for which the c-KIT mutation status of their melanoma has not been determined locally, pathology materials must be submitted for analysis during pre-registration (step 0) to the Massachusetts General Hospital (MGH) within 5 working days following pre-registration. Delays of submission are to be related to the Massachusetts General Hospital via email: ecoq.e2607_tissue@jimmy.harvard.edu.

Tissue submitted should have > 40% tumor, but no less than 20% tumor. Note that submission of tissue with 20-40% tumor increases the risk of false negatives. The submission of inadequate materials(< 20% tumor) for review will delay the turnaround time for reporting results to the institution. Requests for additional materials are to be accommodated as quickly as possible to shorten any delay time.

Direct questions regarding the mandatory tissue submissions may be directed to Tammy Smith (Tel: 617-726-0503, Fax: 617-726-697). However, please do not call the Massachusetts General Hospital Laboratory for results, as testing data cannot be provided over the telephone. Schedule expected patient treatment to account for the turn around time of the assay and distribution of results as expedited processing and analysis is not available.

Specimens from the most recent biopsy or resection of melanoma are requested for the correlative study (Section 11.1) and banking for future studies from all registered patients who consented to allow the use of their tissue for these purposes. If no tumor is available from a metastatic site, residual tumor from the primary site is requested.

Sample submission guidelines for distribution to the pathologist are outlined in Appendix II (Pathology Submission Guidelines).

10.1 The materials required for this protocol are:

10.1.1 Forms and Reports

The following forms and reports are required with all submissions:

- A copy of the surgical pathology report.
- Reports of immunologic studies, if available.
- STS generated shipping manifest (unless STS was unavailable at time of submission)

10.1.2 Biological Material Submission

10.1.2.1 MANDATORY from patients for whom the c-KIT mutation status of the tumor have not been determined locally. Materials are required within 5 working days following pre-registration (Step 0):

- Tissue block of a tumor: metastatic lesion (preferred) or primary tumor
- Sample must have > 20% tumor (greater than 40% preferred).
NOTE: If a tissue block can not be submitted, 1 H&E and fifteen (15) 5μm sections on plus slides are required for the diagnostic review and additional specimens are to be submitted per 10.1.2.3 for the laboratory research studies.

10.1.2.2 Note that patients diagnosed with cutaneous melanoma with chronic sun damage, as of addendum 4, are no longer eligible to participate in this trial.

10.1.2.3 From all patients registered to treatment who answer ‘yes’ to “I agree to participate in the laboratory research studies that are being done as a part of this clinical trial” or “My specimens may be kept for use in research to learn about, prevent, treat or cure cancer.”

If samples were not submitted for central review or if only slides are submitted at pre-registration, the submission of tumor tissue blocks are requested for research (metastatic tissue is preferred but primary tumor tissue will be accepted). If blocks can not be submitted, the following submission alternative is requested:

- Twenty (20) 5μm unstained, uncharged slides
- 1 or more core punches from tumor tissue block, 4mm or larger
- Three 10μm sections, if adequate material is available.

10.1.3 Shipping Procedures

Tumor specimens are to be submitted as outlined below. The appropriate materials will be distributed to central reviewers and laboratory investigators for the analysis described in Sections 10.3 and 11.

10.1.3.1 The required materials for c-KIT mutation analyses must be submitted within one week following pre-registration (step 0) to:

Massachusetts General Hospital
Dr. John Iafrate
c/o Tammy Smith
70 Blossom Street
GRJ-1008
Boston, MA 02114
Ph: 617-726-0503
Fax: 617-726-6974
Email: kvernovsky@partners.org
10.1.3.2 The tumor tissue specimens for the correlative studies or banking are to be submitted within 1 month following patient registration (Step 1) to:

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
1515 Holcombe Blvd
Houston, TX 77030
Phone: Toll Free 844-744-2420 (713-745-4440 Local or International Sites)
Fax: 713-563-6506
Email: eacbpf@mdanderson.org

10.1.4 Site Notification of Central c-KIT Mutation Status Results

If adequate materials are submitted, the c-KIT mutation status will be completed within 10 working days of receipt of materials.

Results will be FAXed to the ECOG-ACRIN Operations Office - Boston and the investigator/study coordinator indicated in the STS. If the information in STS is incorrect, provide the laboratory with the corrected contact information immediately.

It will take 24 hours and up to 72 hours (if weekend or holiday) for ECOG-ACRIN Operations Office - Boston to enter the central review results in the ECOG-ACRIN randomization system. Registration of a patient cannot occur until this information has been entered.

Only those patients harboring c-KIT mutations may register to treatment.

10.2 Sample Tracking System

It is required that all samples submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). The software will allow the use of either 1) an ECOG-ACRIN user-name and password (ECOG-ACRIN sites only), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the samples required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst

Important: Any case reimbursements associated with specimen submissions may not be captured if specimens are not logged into STS. Additionally, please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated shipping manifest must be shipped with all specimen submissions.
Please direct your questions or comments pertaining to the STS to ecoa-
crin.tst@jimmy.harvard.edu.

10.2.1 Study Specific Notes

If STS is unavailable at the time of specimen submission, proceed
with submission of the specimens and retroactively log the specimens
when STS becomes available.

10.3 Central Reviews

Histopathologic evaluation will be performed by a central pathologist, Dr. John
Lafrate, at the Massachusetts General Hospital, providing diagnostic confirmation
and tumor region identification. The KIT mutation status will be performed by
MGH Translational Research Laboratory under the direction of Dr. Darrell
Borger.

Mutational Analysis

Dasatinib-sensitive KIT mutations in the juxtamembrane, kinase I and activation
domains [9-13] will be identified through direct sequencing. Tumor cells will be
enriched through macrodissection using a reference hematoxylin and eosin-
stained slide of an adjacent section. Genomic DNA will be extracted using the
ArchivePure DNA Cell/Tissue Kit (5 Prime, Gaithersburg, MD), according to
manufacturer’s instructions. KIT exons 11, 13, 17 and 18 will amplified through
polymerase chain reaction using the following primers pairs [17]:

**Exon 11** (236 bp) Forward: 5’-CCAGAGTGCTCTAATGACTG-3’,
Reverse: 5’-ACCCAAAAAGGTGACATGGA-3’

**Exon 13** (174 bp) Forward: 5’-CATCAGTTTGCCAGTTGTGC-3’,
Reverse: 5’-ACACGGCTTTACCTCCAATG-3’

**Exon 17** (172 bp) Forward: 5’-TGTATTCACAGAGACTTGGC-3’,
Reverse: 5’-GAAAATAAAAATCCTTTCAG GAC-3’

**Exon 18** (230 bp) Forward: 5’-CATTTCAGCAACAGACGACCAT-3’,
Reverse: 5’-TCTTTGGCAAGGATTTT-3’

The resulting amplicons will be evaluated for mutations using bi-directional
Sanger sequencing using the Big Dye Terminator V1.1 Cycle Sequencing Kit and
the automated ABI 3730 DNA Analyzer (Applied Biosystems, Foster City, CA),
following standard procedures. The following mutations identified in melanoma
will be evaluated [10, 14, 16, 18]: Exon 11 (Y553N, V559A, N566D, L576P), exon
13 (R634W, K642E), exon 17 (D816H), and exon 18 (A829P). A sample will be
considered positive for a KIT mutation if a second round of PCR amplification
and sequencing confirms the mutant sequence. Activating mutations in the BRAF
and NRAS genes (identified through direct sequencing) will be used as an
exclusion event, as activation of this pathway would likely uncouple response to
Dasatinib treatment.

10.4 Banking

Residual material from the blocks submitted will be retained at the ECOG-ACRIN
Central Repository for possible use in future ECOG-ACRIN approved studies.
Any residual blocks will be available for purposes of individual patient management on specific written request. If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study.
11. Correlative Studies

The tissue submissions requested for the correlative studies are outlined in Section 10.

11.1 Predicting Response to Dasatinib and Acral and Mucosal Melanomas

There are no data examining the role of dasatinib in melanoma. Dasatinib has been shown to potently inhibit wild type kit, juxtamembrane domain mutant KIT autophosphorylation, KIT-dependent activation of downstream pathways, as well as PDGFR and SFK’s. Based on preclinical data demonstrating that acral, mucosal, and solar melanomas possess KIT abnormalities, and that PDGFR and SFK’s may also play a key role in the pathogenesis of melanoma, we are proposing that dasatinib may have a therapeutic effect in these subtypes.

The purpose of these correlative studies is to find markers that predict response in the individual patient, in order to ultimately treat only those patients who are more likely to respond. We will perform correlative studies, evaluating potential markers of response, including analyses of KIT, SFK’s and PDGFRA, and correlating our findings with response or resistance to dasatinib. Small cores will be taken from the paraffin embedded tumor blocks submitted to ECOG-ACRIN and placed on glass slides to make tissue microarray. Immunohistochemical staining for KIT (CD 117) and PDGFRA expression can be performed on tissue microarray. We will study differences in marker expression between responders and non-responders, with the goal of developing an assay to specifically predict response to dasatinib.

11.2 KIT Gene Amplification via Fluorescence In Situ Hybridization

KIT gene amplification has been identified in a subset of melanomas and has been associated with increased protein expression and gene mutation [10, 15, 16]. The allelic status of the KIT gene relative to chromosome 4 copy number will therefore be determined using dual-colored fluorescence in situ hybridization (FISH). Probes will consist of two overlapping bacterial artificial chromosomes (BAC) containing KIT sequences (clones# RP11-586A2 and RP11-722F21; Children’s Hospital, Oakland Research Institute, Oakland, CA) and a reference chromosome enumeration probe for the centromeres of chromosome 4 (CEP 4; Abbott Laboratories, Abbott Park, IL). These probes will be differentially labeled in the presence of either SpectrumOrange-dUTP (KIT) or SpectrumGreen-dUTP (CEP 4), using the Nick-Translation Kit according to manufacturer’s instructions (Abbott Laboratories). Target sequences in deparaffinized samples will be unmasked using heat and Digest All-3 (Zymed, San Francisco, CA, USA) pretreatment. The tumor region containing a predominance of neoplastic cells will be identified with an adjacent hematoxylin and eosin-stained slide. This region of the sample will be hybridized with a combination of KIT and CEP 4 probes and subsequently counterstained with 4’,6-diamidino-2-phenylindole (DAPI). A minimum of 50 non-overlapping and morphologically unequivocal malignant cell nuclei, across at least four areas of interest, will be evaluated per patient sample. High polysomy will be defined as ≥ 4 copies of chromosome 4 in ≥ 40% of cells, and gene amplification will be defined by either the presence of tight gene clusters, a gene/chromosome ratio of ≥ 2 or ≥ 15 or more gene copies per cell in ≥ 10% of analyzed cells, according to published guidelines [19, 10]. All amplified
and polysomy cases identified will be independently verified by a single FISH-certified pathologist.

11.3 Sample Inventory Submission Guidelines

Inventories of all samples collected, aliquoted, and used on the above mentioned laboratory correlative studies and diagnostic reviews will be submitted to the ECOG-ACRIN Operations Office - Boston on a monthly basis. Inventories will be submitted electronically in a format dictated by the ECOG-ACRIN Operations Office - Boston.

11.4 Lab Data Transfer Guidelines

The data from the diagnostic reviews will be submitted to the ECOG-ACRIN Operations Office - Boston within one week of conduct of the reviews. The data collected on the above mentioned correlative study will be submitted electronically to the ECOG-ACRIN Operations Office - Boston by the designated laboratories on a quarterly basis. The quarterly cut-off dates are March 31, June 30, September 30, and December 31. Data is due at the ECOG-ACRIN Operations Office - Boston 1 week after these cut-off dates.
12. Records to Be Kept

Please refer to the E2607 Forms Packet for the forms submission schedule and copies of all forms. The E2607 Forms Packet may be downloaded by accessing the ECOG World Wide Web Home Page (http://www.ecog.org). Forms must be submitted to the ECOG-ACRIN Operations Office - Boston, FSTRF, 900 Commonwealth Avenue, Boston, MA 02215 (ATTN: DATA).

This study will be monitored by the CTEP Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office - Boston to CTEP by electronic means.

12.1 Records Retention

This study is being conducted under an IND exemption and is not intended to support any FDA-related filings. However, ECOG-ACRIN requires clinical investigators to retain all trial-related documentation, including source documents, for at least one year from the posting of the final technical report of the outcome of this trial to support any publication of the data.

Please contact the ECOG-ACRIN Operations Office - Boston prior to destroying any source documents.

13. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

14. References


A Phase II Trial of Dasatinib in KIT-Positive Patients with Unresectable Locally Advanced or Stage IV Mucosal, Acral and Vulvovaginal Melanomas

Appendix I

Informed Consent Template for Cancer Treatment Trials (English Language)
[Deleted in Addendum #10]

INFORMED CONSENT INTENTIONALLY REMOVED FROM PROTOCOL DOCUMENT

Appendix I was removed from the protocol document in Addendum #10 and is posted as a separate document on the ECOG website. This was removed from the protocol to comply with NCI formatting guidelines.
Appendix II

Pathology Submission Guidelines

The following items are included in Appendix II:

1. Guidelines for Submission of Pathology Materials  
   (instructional sheet for Clinical Research Associates [CRAs])
2. Instructional memo to submitting pathologists
3. List of Required Materials for E2607
4. ECOG-ACRIN Generic Specimen Submission Form (#2981)
Guidelines for Submission of Pathology Materials

The following items should always be included when submitting pathology materials to the ECOG-ACRIN Central Biorepository and Pathology Facility:

- Institutional Surgical Pathology Report
- Pathology materials (see attached List of Required Material)
- ECOG-ACRIN Generic Specimen Submission Form (#2981)

Instructions:

1. Please provide the following information:
   - Patient's name (last, first)
   - Protocol number
   - Protocol case number (the patient's ECOG-ACRIN sequence number)
   - The institutional identification numbers for the materials provided
   - Affiliate (if appropriate)

2. Complete blank areas of the pathologist's instructional memo and forward it, along with the List of Required Material to the appropriate pathologist.

3. The pathologist should return the required pathology samples and surgical pathology reports, along with the completed additional required information. If any other reports are required, they should be obtained from the appropriate department at this time.

4. Keep a copy of the STS shipping manifest or Specimen Submission Form (#2981) for your records.

5. Double-check that ALL required forms, reports and pathology samples are included in the package to the Central Biorepository and Pathology Facility.

Pathology specimens submitted WILL NOT be processed by the Central Biorepository and Pathology Facility until all necessary items are received.

6. Mail pathology materials to:

   Materials for central determination of c-KIT mutation status, submit within 5 working days of pre-registration:
   - Massachusetts General Hospital
   - Dr. John Iafrate
   - c/o Tammy Smith
   - 70 Blossom Street
   - GRJ-1008
   - Boston, MA 02114

   If you have any questions concerning the above instructions or if you anticipate any problems in meeting the pathology material submission deadline of 5 working days, contact: (617) 726-0503, Kvernovsky@partners.org

   Materials for the laboratory research studies and future research:
   - ECOG-ACRIN Central Biorepository and Pathology Facility
   - MD Anderson Cancer Center
   - Department of Pathology, Unit 085
   - Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
   - 1515 Holcombe Blvd
   - Houston, TX 77030

   Direct questions to the ECOG-ACRIN Central Biorepository and Pathology Facility at Tel: 844-744-2420 or Fax: 713-563-6506 or email eacbpf@mdanderson.org.
List of Required Material

E2607: A Phase II Trial of Dasatinib in KIT-Positive Patients with Unresectable Locally Advanced or Stage IV Mucosal Acral and Vulvovaginal Melanomas

Pre-Treatment

1. Institutional pathology report (must be included with EVERY pathology submission).

2. Reports of immunological stains, if available.

3. Biological specimens:

   • **MANDATORY** from all patients with unknown c-KIT mutation status following Pre-Registration: Tumor block of most recent diagnostic biopsy or melanoma resection. Tissue must have > 20% tumor, with > 40% preferred. Samples < 40% may result in a higher rate of false negatives.

   **NOTE:** Tissue ≤ 20% tumor will be indicated as inadequate and will require submission of additional materials prior to testing or patient will be deemed ineligible.

   • From all patients registered to treatment and consenting to submission of tissue for research studies: Tumor tissue blocks. metastatic tissue is preferred but primary tumor tissue will be accepted, is to be submitted. If tissue blocks were submitted for c-KIT mutation status to MGH (first bullet) additional tissue would be appreciated but not required. However, if only slides were submitted additional materials are required. If blocks can not be submitted, the following submission alternative is requested:

     − Twenty (20) 5μm unstained, uncharged slides
     − One or more core punches from tumor tissue block, 4mm or larger
     − Three 10μm sections, if adequate material is available.

   **NOTE:** Banked tissue blocks may be returned upon written request for purposes of patient management. However, since blocks are being used for laboratory studies, in some cases the material may be depleted, and, therefore, the block may not be returned.
MEMORANDUM

TO: ________________________________ (Submitting Pathologist)

FROM: Stanley Hamilton, M.D., Chair
ECOG-ACRIN Laboratory Science and Pathology Committee

DATE: ________________

SUBJECT: Submission of Pathology Materials for E2607: A Phase II Trial of Dasatinib in KIT-Positive Patients with Unresectable Locally Advanced or Stage IV Mucosal, Acral and Vulvovaginal Melanomas

The patient named on the attached request has been entered onto an ECOG-ACRIN protocol by ________________________________ (ECOG-ACRIN Investigator). This protocol requires the submission of pathology materials for pathology review and laboratory studies.

Keep a copy for your records and return the completed Submission Form, the surgical pathology report(s), the slides and/or blocks and any other required material (see List of Required Material) to the Clinical Research Associate (CRA). The CRA will forward all required pathology material to the ECOG-ACRIN Central Biorepository and Pathology Facility.

Blocks and slides submitted for this study will be retained at the ECOG-ACRIN Central Repository for future studies. Paraffin blocks will be returned upon written request for purposes of patient management.

Please note: Since blocks are being used for laboratory studies, in some cases the material may be depleted, and, therefore, the block may not be returned.

Results of the diagnostic review will not be distributed to you upon completion of the review.

If you have any questions regarding this request, please contact the Central Biorepository and Pathology Facility at 844-744-2420 or email eacbpf@mdanderson.org.

The ECOG-ACRIN CRA at your institution is:

Name: ________________________________
Address: ________________________________
Phone: ________________________________

Thank you.
Institution Instructions: This form is to be completed and submitted with all specimens ONLY if the Sample Tracking System (STS) is not available. **Use one form per patient, per time-point.** All specimens shipped to the laboratory must be listed on this form. Enter all dates as MM/DD/YY. Keep a copy for your files. Retroactively log all specimens into STS once the system is available. **Contact the receiving lab to inform them of shipments that will be sent with this form.**

**Protocol Number** ____________________________  **Patient ID** ____________________________  **Patient Initials** Last ______ First ______

**Date Shipped** ____________________________  **Courier** ___________________________________  **Date CRA will log into STS** ____________________________

**Shipped To (Laboratory Name)** __________________________________________________________

**FORMS AND REPORTS:** Include all forms and reports as directed per protocol, e.g., pathology, cytogenetics, flow cytometry, patient consult, etc.

<table>
<thead>
<tr>
<th>Required fields for all samples</th>
<th>Additional fields for tissue submissions</th>
<th>Completed by Receiving Lab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Type (fluid or fresh tissue, include collection tube type)</td>
<td>Surgical or Sample ID</td>
<td>Lab ID</td>
</tr>
<tr>
<td>Quantity</td>
<td>Collection Date and Time 24 HR</td>
<td>Anatomic Site (e.g., primary, mets, normal)</td>
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Fields to be completed if requested per protocol. Refer to the protocol-specific sample submissions for additional fields that may be required.

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<tr>
<th>Leukemia/Myeloma Studies:</th>
<th>Diagnosis</th>
<th>Intended Treatment Trial</th>
<th>Peripheral WBC Count (x1000)</th>
<th>Peripheral Blasts %</th>
<th>Lymphocytes %</th>
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<tbody>
<tr>
<td>Study Drug Information:</td>
<td>Therapy Drug Name</td>
<td>Date Drug Administered</td>
<td>Start Time 24 HR</td>
<td>Stop Time 24HR</td>
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<td>Caloric Intake:</td>
<td>Date of Last Caloric Intake</td>
<td>Time of Last Caloric Intake 24HR</td>
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**CRA Name** ____________________________  **CRA Phone** ____________________________  **CRA Email** ____________________________

Comments

9/12/14
Appendix III

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the ECOG web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

________________________________________________________________________

[ PATIENT NAME ] [ DATE ]
[ PATIENT ADDRESS ]

Dear [ PATIENT SALUTATION ],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the help of people like you who participate in clinical trials, we will achieve our goal of effectively treating and ultimately curing cancer.

We believe you will receive high quality, complete care. Your physician and research staff will maintain very close contact with you. This is important so as to allow your physician to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of [ INSTITUTION ] and the ECOG-ACRIN Cancer Research Group, we thank you again and look forward to helping you.

Sincerely,

[ PHYSICIAN NAME ]
A Phase II Trial of Dasatinib in KIT-Positive Patients with Unresectable Locally Advanced or Stage IV Mucosal, Acral and Vulvovaginal Melanomas

Appendix IV

Patient Pill Diary

<table>
<thead>
<tr>
<th>Day</th>
<th>Time Morning Dose Taken</th>
<th>Dose Amount</th>
<th>Time Evening Dose Taken</th>
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Appendix V
Sprycel® (Dasatinib) DRUG REQUEST Form

Please mark ONE of the following boxes:

- INITIAL DRUG SHIPMENT suggested quantity - 10 BOTTLES OF 50MG AND 4 BOTTLES OF 20MG
- RESUPPLY DRUG SHIPMENT suggested quantity - TWO MONTH SUPPLY FOR ALL ON-GOING AND PLANNED PATIENTS

All dates should be in dd-mmm-yyyy format

<table>
<thead>
<tr>
<th>CA180-</th>
<th>BMS Protocol Number:</th>
<th>Site Number:</th>
<th>Date of Request:</th>
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</table>

Investigator Name:
Investigator Address (Please include contact name):
Phone:
E-mail:

Product Requested:
- Sprycel® 20 mg
- Sprycel® 50mg

# of Bottles Requested:
# of Patients on Dose:
# of Bottles on Shelf

The Investigator Site is advised to apply protocol labels to the commercial drug without covering any pertinent information, i.e. lot number/expiry date.

STORAGE INSTRUCTIONS
These supplies should be stored at 15°C to 25°C. Product excursions of 40°C for up to 5 days and down to -20°C for up to 5 days during storage at sites are acceptable.

Transmission of this Form to Almac Souderton PA serves as assurance that all required regulatory and contractual documentation for this Site/Study is complete. By submission for Re-Supply requests, Site assures their site remains in good regulatory standing.

Please e-mail this document with the subject heading
“CA180 Sprycel® SUPPLY REQUEST” to the following:
PaLogistics.ClinicalServices@Almacgroup.com

Contact Mike Harrison, Joshua Lindauer, or Sarah Fanning at (215) 660-8500 with any questions pertaining to the transmission of this order form.
Appendix VI

E2607 Central Reviewer Approval of Locally Determined c-KIT Mutation Status

Approval of the mutation status from Dr. Lawrence (Dr. Kirkwood) is required prior to pre-registration if:
1. Melanoma’s c-KIT mutations status assessed locally
2. The result is cKIT mutation positive but:
   • There is NOT a mutation in exon 9, 11, 13, 17 or 18 of the c-KIT gene
   OR
   • It is uncertain, from the report, whether the mutation is applicable

PART I - COMPLETED BY SITE:
ECOG-ACRIN E2607 Patient ID: __________________________
Patient Initials (L,F): ________________________
Date of c-KIT Testing: ________________________
Site Contact Name: ________________________________________
Site Contact E-mail: _______________________________________
Site Contact FAX: ________________________________________
To obtain approval, complete Part I then, within 24 hours following Pre-registration, submit the form
and the redacted c-KIT report to the ECOG-ACRIN Operations Office - Boston either by:
1. Faxing to 617-582-8578, ATTN: Pre-Registration/E2607. Indicate on the report the protocol number
   (E2607), the patient’s initials and patient’s ECOG-ACRIN patient ID number.
OR
2. Available to ECOG-ACRIN sites ONLY: Scan and upload the documents via the ECOG Data
   Transfer WebApp https://webapps.ecog.org/DataTransfer/
   Documents must be named:
   • E2607-PtID#-Form (e.g. E2607-12345-Form) and
   • E2607-PtID#-Report (e.g. E2607-12345-Report)

PART II - COMPLETED BY REVIEWER:
☒ Patient is not eligible
☒ Patient’s melanoma harbors an applicable c-KIT+ mutation
   Approved c-KIT mutation: ________________________________
   Indicate reviewer: Dr. Don Lawrence _____ or Dr. John Kirkwood _____
Reviewer Signature: _______________________________________
Date of Approval: _______________________________________
REVIEWER INSTRUCTIONS: Upon completion of the review, complete Part II then:
1. Enter the patient’s eligibility into the ECOG Prestudy WebApp. If the WebApp is not available, Fax
to 617-582-8578
2. Fax the completed form to the site contact listed in Part I

NOTE: Retain a copy of this form in the patient’s chart.