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Abbreviated Title: Das-Ganit in Rhabdomyosarcoma

TITLE: A Phase I/II Trial of the Insulin-Like Growth Factor 1 Receptor (IGF-1R) Antibody AMG479 (Ganitumab) in Combination with the Src Family Kinase (SFK) Inhibitor Dasatinib in Patients with Embryonal and Alveolar Rhabdomyosarcoma

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PRÉCIS

Background:

- Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma of childhood. The annual incidence in the United States is 4-7 cases per million children under 15 years, which represents 250 new cases per year.[1] Two major histologic subtypes exist: embryonal rhabdomyosarcoma (ERMS) and alveolar rhabdomyosarcoma (ARMS), the latter of which carries a particularly poor prognosis.[2]
- Over-expression of both the type 1 IGF receptor (IGF-1R) and its ligands has been observed in multiple malignancies, including pediatric sarcomas, and abnormal activation of this pathway contributes to sarcoma development and progression.[3-5] Downstream signaling cascades of IGF-1R further regulate tumor cell proliferation, survival, and metastasis through the MAPK/ERK and PI3K/mTOR pathways.[6] In the majority of RMS, IGF-1R is highly expressed.[7, 8]
- Monoclonal antibodies targeting IGF-1R interfere with ligand binding and decrease the expression of the receptor on cell surfaces by internalization and degradation of the receptor.[9-12] A number of these have been tested in the clinical setting. Results from a phase II trial using monotherapy with monoclonal antibodies against IGF-1R resulted in clinically meaningful responses in about 10-15% of patients with RMS. However, the vast majority of these responses were short-lived with a rapid onset of resistance.[13, 14]
- YES is a member of the SRC family tyrosine kinases (SFKs), non-receptor tyrosine kinases that function in a number of signaling pathways necessary for cell growth, differentiation and survival.[15, 16] Preclinical work suggests involvement of YES in a number of solid tumor types, including colon carcinoma, oral squamous cell carcinoma, glioma, pancreatic cancer, mesothelioma, and RMS.[17-22]
- Recently, the Helman lab published preclinical work showing that in both embryonal and alveolar RMS models, blockade of IGF-1R results in YES activation and that YES activation is associated with resistance to IGF-1R blockade. In addition, combination blockade of IGF-1R and YES in vitro results in downregulation of phospho-AKT in some cell lines. Treatment blocking both IGF-1R and YES results in enhanced growth inhibition of multiple cell lines of both embryonal and alveolar RMS in vitro and in vivo.[23]

Objectives:

- Phase I: To determine the safe dose of dasatinib when given with ganitumab in patients with relapsed or refractory embryonal or alveolar RMS.
- Phase II: To determine if the use of ganitumab plus dasatinib is able to be associated with a modest fraction of patients who experience an objective clinical response (CR and PR) as defined by RECIST criteria. In addition, a second primary objective will estimate the fraction that is without progression at 4 months.

Eligibility:

- Patients must have a diagnosis of relapsed or refractory embryonal or alveolar RMS, be able to swallow tablets, have archival tissue available.
- Patients must have adequate performance status and adequate major organ function and have recovered from acute toxicity of all prior therapies.

Design:

- This is an open label, multi site, phase I/II study designed to determine if ganitumab given in combination with dasatinib in children and adults with relapsed or refractory embryonal or alveolar RMS for whom no curative options exist.
- In the phase I portion, using a standard 3 + 3 design, limited dose escalations will be performed to define the maximum tolerated dose (MTD) or the highest safe dose tested of dasatinib when given in combination with ganitumab in this patient population.
- In the phase II component, sixteen (16) evaluable patients, including up to 6 patients from the phase I portion treated at the selected phase II dose, will be enrolled to rule out a 5% fraction with a clinical response in favor of a 30% fraction with a clinical response, using a one sided 0.10 significance level exact test for a binomial proportion. In practice, the fraction of the 16 patients that have objective responses will be determined and reported along with 80% and 95% confidence intervals. If there are 3 objective responses in 16 evaluable patients, the lower one-sided exact 90% confidence interval is 7.1%, thus ruling out 5%.
- It is anticipated that approximately 10-15 patients per year may be accrued onto this trial. Thus, 2 to 3 years is expected to completed accrual.
- In all patients, mechanisms of response and resistance will be assessed by analyzing archival tissue for expression of IGF-1R, insulin receptor, IGF-2 expression and phospho-YES expression, and through genomic sequencing (on protocol 10-C-0086). Genomic sequencing of tumor cells from tissue relative to non-tumor cells from whole blood will be profiled to identify the genomic variances that may contribute to response or disease progression and provide an understanding of molecular abnormalities. RNA sequencing will be conducted to provide expression data and give relevance to DNA mutations; Quantitative proteomics analysis will be conducted on all patients to determine the exact amounts of specific proteins and/or to confirm expression of genes that are correlative of response and disease progression. Genomic and transcriptomic analysis will be conducted on patients who consent to protocol 10-C-0086, Comprehensive Omics Analysis of Pediatric Solid Tumors and Establishment of a Repository for Related Biological Studies. All genomic, transcriptomic, and proteomic molecular analyses will be retrospective and exploratory.
- In patients who agree to undergo biopsy of their tumor, provided the tissue is easily accessible and can be biopsied safely with minimal morbidity, mechanisms of response and resistance will be assessed by analyzing biopsy tissue expression of IGF-1R, insulin receptor, IGF-2 expression and phospho-YES expression, and through genomic sequencing.

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1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objectives

1.1.1.1 Phase I: To determine the safe dose of dasatinib when given with ganitumab in patients with relapsed or refractory embryonal or alveolar RMS.

1.1.1.2 Phase II: To determine if the use of ganitumab plus dasatinib is able to be associated with a modest fraction of patients who experience an objective clinical response (CR and PR) as defined by RECIST criteria. In addition, a second primary objective will estimate the fraction that is without progression at 4 months.

1.1.2 Secondary Objectives

1.1.2.1 To assess the PFS in patients receiving this combination.

1.1.2.2 To determine the fraction of patients with stable disease >= 6 months as defined by RECIST criteria in patients receiving this combination.

1.1.2.3 To describe the toxicity and confirm the tolerability of the combination of ganitumab and dasatinib in patients with relapsed or refractory RMS.

1.1.3 Exploratory Objectives

1.1.3.1 To determine the genomic and proteomic profile of subjects' tumors to identify gene mutations, gene amplifications, RNA-expression levels, and protein-expression levels. Correlations between genomic/proteomic profiles and efficacy outcomes will be assessed.

The following specific objectives will be explored using genomic/proteomic profiles:

1.1.3.2 To retrospectively analyze archival tissue for quantitation of IGF-1R and to correlate tumor responses with the presence of target.

1.1.3.3 To examine IGF-1R expression, phospho-YES, insulin receptor expression and IGF-2 expression in tumor tissue obtained from biopsy samples.

1.1.3.4 To conduct genomic analysis of archival and relapse biopsy samples and compare them to germline samples. For these studies, patients will be co-enrolled on the pediatric omics study (10-C-0086).

2 BACKGROUND AND RATIONALE

2.1 INHIBITING THE INSULIN-LIKE GROWTH FACTOR TYPE 1 RECEPTOR (IGF1-R) IN RHABDOMYOSARCOMA (RMS):

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma of childhood. The annual incidence in the United States is 4-7 cases per million children under 15 years, which represents 250 new cases per year.[1] Two major histologic subtypes exist: embryonal rhabdomyosarcoma (ERMS) and alveolar rhabdomyosarcoma (ARMS), the latter of which carries a particularly poor prognosis. Patients with metastatic or recurrent disease are essentially incurable with a 5-year

overall survival of less than 20%, and outcomes have only minimally improved over the past several decades.[2] Thus, new therapies for RMS are critically needed.

The insulin-like growth factor (IGF) system plays an important role in the biology of many cancers, and for many years, a research focus of the Helman lab in the Pediatric Oncology Branch (POB) at the NCI has been to develop an understanding of IGF signaling in pediatric sarcomas. Over-expression of both the type 1 IGF receptor (IGF-1R) and its ligands has been observed in multiple malignancies, including pediatric sarcomas, and abnormal activation of this pathway contributes to sarcoma development and progression.[3-5] Downstream signaling cascades of IGF-1R further regulate tumor cell proliferation, survival, and metastasis through the MAPK/ERK and PI3K/mTOR pathways.[6] In the majority of RMS, IGF-1R is highly expressed. A study by Cao et al. examined 9 tumor samples from patients with ARMS and ERMS and found that 5 of these (roughly 60%) highly expressed IGF-1R.[7] Another study of archival tumor tissue reported that 90% of pediatric RMS tumors highly expressed IGF-1R by immunohistochemistry.[8] Thus, inhibition of IGF-1R is a potentially important therapeutic target in RMS.

Monoclonal antibodies targeting IGF-1R interfere with ligand binding and decrease the expression of the receptor on cell surfaces by internalization and degradation of the receptor.[9-12] A number of these have been tested in the clinical setting. Results from a phase II trial using monotherapy with monoclonal antibodies against IGF-1R resulted in clinically meaningful responses in about 10-15% of patients with RMS. However, the vast majority of these responses were short-lived with a rapid onset of resistance. Specifically, a study of R1507, a monoclonal antibody against IGF-1R, in patients with relapsed or refractory sarcomas (RMS, osteosarcoma, synovial sarcoma and soft-tissue sarcoma) reported that in the RMS subset, 1 of 36 (3%) patients (embryonal subtype) had a PR by WHO criteria and an additional 3 of 36 (8%) patients (all alveolar subtype) had a decrease in tumor size that was greater than 50% noted at 6 weeks, but had disease progression at the 12 week time point and responses could thus not be confirmed. One additional RMS patient (3%) achieved a PR at 18 weeks that was not confirmed thereafter.[13] An additional phase II study that used cixutumumab, another monoclonal antibody against IGF-1R, in patients with previously treated advanced or metastatic soft-tissue sarcomas or Ewing family of tumors reported a 12 week PFS for RMS patients.[14]

The development of agents targeting IGF-1R has been abandoned by pharmaceutical companies due to the lack of clinical benefit in adult cancers.[24-26] Because of the promising clinical activity in pediatric sarcomas, particularly Ewing sarcoma, the NCI (CTEP) was able to negotiate a CRADA with Amgen to manufacture the Amgen IGF-1R inhibitor (AMG479) for a phase II trial with the Children's Oncology Group (COG). This study is a randomized phase II trial evaluating the addition of ganitumab to multiagent chemotherapy for patients with newly diagnosed metastatic Ewing sarcoma. Through this CRADA, ganitumab would also be available for this study.

Work done by the Helman lab in mouse xenograft models of alveolar and embryonal RMS revealed a phenomenon similar to that observed in the clinical trials. Mice treated with h7C10, another monoclonal antibody against IGF-1R, showed a progression free period of about 9 weeks, compared to 3 weeks in control animals. Evaluation of the tumor samples from treated mice after regrowth showed persistent down-regulation of IGF-1R, but a rebound in AKT

phosphorylation, suggesting that resistance was not due to loss of activity of the antibody against IGF-1R, but rather the result of a bypass resistance pathway.[7]

2.2 YES ACTIVATION AS A BYPASS RESISTANCE PATHWAY TO IGF-1R INHIBITION:

YES is a member of the SRC family tyrosine kinases (SFKs), non-receptor tyrosine kinases that function in a number of signaling pathways necessary for cell growth, differentiation and survival.[15, 16] Preclinical work suggests involvement of YES in a number of solid tumor types, including colon carcinoma, oral squamous cell carcinoma, glioma, pancreatic cancer, mesothelioma, and RMS.[17-22] In RMS, YES is highly expressed in both ERMS and ARMS cell lines, xenografted tumors, and human tumors, although the precise mechanism through which it functions remains to be described. Recently, the Helman lab published preclinical work showing that in both embryonal and alveolar RMS models, blockade of IGF-1R results in YES activation and that YES activation is associated with resistance to IGF-1R blockade. In addition, combination blockade of IGF-1R and YES in vitro results in downregulation of phospho-AKT in some cell lines. Treatment blocking both IGF-1R and YES results in enhanced growth inhibition of multiple cell lines of both embryonal and alveolar RMS in vitro and in vivo. Specifically, in vivo experiments showed that mice in groups receiving vehicle, R1507 or dasatinib alone reached an endpoint volume of 3000 mm^3 by days 39, 45 and 69 (alveolar RMS) and days 69, 78 and 90 (embryonal RMS), while mice receiving the combination had an average tumor size of only 500 mm^3 at the end of the experiments (days 69 (alveolar) and 90 (embryonal)).[23] This inhibition occurs at concentrations that are achievable in humans. The average dasatinib plasma concentration at once daily dosing at 60 mg/m^2 (33 nM) exceeds the IC_{50} of dasatinib in combination with R1507 (10 nM) in RMS cell lines.[23, 27] For R1507 the minimum plasma concentration on a once per week dosing schedule (3300 μM) exceeds the IC_{50} (100 nM) in RMS cell lines.[23, 28] These data provide the rationale for the clinical evaluation of the combination of IGF-1R and YES blockade in RMS.

2.3 RATIONALE FOR COMBINING IGF-1R INHIBITION AND YES/SFK INHIBITION IN RMS IN A PHASE I/II STUDY:

Clinical data demonstrate that the activity of IGF-1R antibody therapy in RMS is limited by a rapid onset of acquired resistance. Based on preclinical data showing that YES mediates this resistance in some embryonal and alveolar RMS and preclinical data demonstrating that the combination of IGF-1R inhibition with YES inhibition overcomes this resistance resulting in sustained inhibition of RMS growth [23], we are proposing a phase I/II study of the combination of ganitumab and dasatinib. As preclinical data do not suggest a difference in response between ERMS and ARMS [23], and due to the relative rarity of RMS, we will not stratify this study to separate the histologies.

Inhibition of IGF-1R by ganitumab occurs at concentrations that are achievable in humans.[29] *In vitro* RMS cell growth inhibition by dasatinib occurs at concentrations that are achievable in humans.[23, 27] However, there are no human studies that report on the concentrations needed to inhibit YES phosphorylation in rhabdomyosarcoma. In addition, while the combination of these specific agents has not been evaluated clinically, IGF-1R antibodies have been combined with multiple agents at full dose and have been well tolerated. Further, these two agents do not have

serious overlapping toxicities and there is an unmet need for better therapies for patients with embryonal and alveolar RMS, particularly in the setting of metastatic disease or relapse.

2.4 DASATINIB

Dasatinib (BMS-354825), an aminothiazole analogue, is an orally administered (PO) protein tyrosine kinase (PTK) inhibitor with specificity for five kinases/kinase families that have been strongly linked to multiple forms of human malignancies.[30-32] These targets include: BCR-ABL, c-SRC, c-KIT, PDGFβ receptor, and EPHA2. *In vivo* and *in vitro* studies have established that dasatinib demonstrates potent antiproliferative activity in a wide spectrum of cancer cell lines/types, and clinical results suggest anticancer activity of dasatinib in chronic myelogenous leukemia (CML) and solid tumor patients.[33-36]

Dasatinib potently and selectively inhibits the five oncogenic PTKs/kinase families by competing with ATP for the ATP-binding sites in the kinases: SRC family kinases (IC_{50}: SRC = 0.55 nM, LCK = 1.1 nM, YES = 0.41 nM, FYN = 0.2 nM); BCR-ABL (<3 nM); c-KIT (13 nM); EPHA2 (17 nM) and PDGFβ receptor (28 nM).[32] The agent was found to be less potent against unrelated PTKs and several serine/threonine kinases. Dasatinib also demonstrates potent inhibition of VEGF- and bFGF-driven proliferation of human umbilical vein endothelial cells (HUVECs), with IC_{50} values of 43 and 248 nM, respectively.

BCR-ABL, a constitutively active cytoplasmic tyrosine kinase, is present in >90% of all patients with CML and in 15-30% of adult patients with acute lymphoblastic leukemia (ALL). The inhibition of BCR-ABL by imatinib, another PTK inhibitor, is effective in the management of CML thus providing proof-of-concept for targeting PTKs. However, resistance to imatinib therapy associated with BCR-ABL gene mutation/over-expression and activation of selected SRC kinases has been increasingly encountered.[37] Dasatinib has activity in a number of imatinib-resistant tumors,[38-42] in addition to being 500-fold more potent than imatinib in inhibiting BCR-ABL. The ability of dasatinib to inhibit imatinib-resistant forms of BCR-ABL is presumed to be due to its relaxed binding requirements because, unlike imatinib which binds only to the inactive conformation of the BCR-ABL kinase, dasatinib binds to both the active and inactive conformations.[43]

2.4.1 Nonclinical Studies

2.4.1.1 Efficacy

Dasatinib inhibits growth of multiple BCR-ABL-dependent leukemic cell lines and also shows activity against 14 of 15 imatinib-resistant BCR-ABL kinase mutants.[41] Inhibition of CML cell lines established from patients who were resistant to imatinib therapy has also been reported.[36] Dasatinib potently inhibits wild-type (IC_{50}: 1-10 nM) and mutant (IC_{50}: 10-100 nM) KIT kinases in M07E cells and human mast cell leukemia cell lines, respectively.[34] Also of note, dasatinib selectively killed primary neoplastic bone marrow mast cells from patients with systemic mastocytosis while sparing other hematopoietic cells.[44]

Dasatinib demonstrated antiproliferative activity in a wide-spectrum of solid tumor types, including mastocytoma, prostate, and breast cell lines with IC_{50} values ranging from 5.4-103 nM.[32] The agent also inhibited stem cell factor-driven proliferation of three small cell lung

cancer (SCLC) cell lines with IC_{50} values in the range of 114-220 nM and showed activity in head and neck squamous cell carcinoma and non-small cell lung cancer cell lines.[45]

When dasatinib was administered twice daily (BID) on a 5-days-on/2-days-off schedule for a total of 14 to 25 days at doses of 10-50 mg/kg/dose, *in vivo* antitumor activity of dasatinib was seen in prostate, colon, breast, and pancreatic xenograft models.[32] Similarly, dasatinib was effective against K562 and imatinib-resistant K562-R human CML xenografts in SCID mice at doses as low as 2.5-5 mg/kg/day.[42] In combination with docetaxel, dasatinib produced antitumor effects against PC3 human prostate carcinoma xenografts that were substantially better than the effects of either single agent alone.[32]

Dasatinib at 20 or 50 mg/kg inhibited the T-cell proliferation response in mice following the transfer of lymphocytes from allogeneic donor mice.[32] In addition, treatment of mice with dasatinib 25 mg/kg BID inhibited the graft-versus-host response in a non-vascularized model of murine heart transplant. The 5-days-on/2-days-off regimen almost completely eliminated immunosuppressive activity in this model.

SRC kinase is known to play a major role in osteoclast function. In short-term studies, dasatinib acted as a potent inhibitor of bone resorption as measured by its ability to reduce the release of ^{45}calcium into the culture medium by fetal rat long bones *in vitro* (IC_{50} = 2 nM). Dasatinib also inhibited parathyroid hormone (PTH)-stimulated release of ^{45}calcium in a dose-dependent manner with an apparent IC_{50} of 2 nM. At 5 nM, dasatinib completely blocked PTH-stimulated bone resorption in thyro-parathyroidectomized rats. The therapeutic utility of dasatinib in the treatment of cancer-related hypercalcemic syndromes has not been fully explored, and the long-term effects of dasatinib on bone physiology are also unknown.

2.4.1.2 Nonclinical Pharmacokinetic and Pharmacodynamic Studies

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

The value of phospho-SRC as a biomarker of dasatinib efficacy has been explored in nonclinical studies.[46] In nude mice bearing subcutaneous PC-3 tumors (human prostate), measurement of phospho-SRC by western blot in tumor and peripheral blood mononuclear cells (PBMCs) following treatment with a single dose of dasatinib (15 or 50 mg/kg) produced similar results in both tissues. Levels of phospho-SRC were maximally inhibited at 3 hours post dose, then recovered partially between 7 and 17 hours and returned to the basal level by 24 hours after agent administration. These results were quantitated by image scanning and compared to efficacy results when the agent was administered PO BID at 15-50 mg/kg/dose for 14 days on a 5-days-on/2-days-off schedule. Efficacy and phospho-SRC inhibition appeared to correlate, and this pharmacodynamic model permitted the authors to predict that the plasma concentration of

dasatinib required to produce 90% inhibition of phospho-SRC would be 164 nM and 91 nM in PC-3 tumor and PBMCs, respectively. Studies to evaluate the clinical utility of phospho-SRC as a biomarker are ongoing.

2.4.1.3 Toxicology

A range of toxicology studies have been conducted to support the oral administration of dasatinib in humans. The oral studies indicated that dasatinib induced reversible toxicities of the gastrointestinal (GI) and lymphoid systems in rats and monkeys, and of the hematopoietic system in rats. Embryofetal development studies in rats and rabbits indicated that dasatinib caused embryolethality or skeletal malformations at doses that did not cause maternal toxicity, suggesting that it is a selective developmental toxicant. An in vitro cytogenetics study in CHO cells indicated that it was clastogenic at concentrations >5 μg/mL, a level not achievable in vivo. The agent is nongenotoxic and did not show significant potential for undesirable functional activity in in vitro receptor/ion channel binding and enzyme assays. In vitro potassium channel current (HERG/IKr) and Purkinje fiber assays suggested that dasatinib could potentially prolong cardiac ventricular repolarization (QT interval), and a single-dose cardiovascular study in monkeys demonstrated that the agent at a dose of 10 mg/kg caused a minimal increase in blood pressure for approximately 2 hours post dose. There were no drug-related neurologic observations in rats or monkeys. Dasatinib was found to be phototoxic in an in vitro assay in mouse fibroblasts.

2.4.2 Clinical Experience

Over 2000 subjects have received dasatinib, the majority with CML refractory or intolerant to imatinib.[32] Studies conducted in healthy volunteers include the following: PK; formulation comparisons; the effect of food; drug interactions; and supportive care. Data are available from 11 phase I and phase II studies in patients with CML, Philadelphia chromosome-positive (Ph+) ALL, or solid tumors using different dosage regimens and designed to determine PK, pharmacodynamics, safety, and efficacy in these populations.

Dasatinib is a multi-target tyrosine kinase inhibitor that targets SFKs, including YES. Dasatinib has been approved for the treatment of certain forms of CML and ALL. In adults with CML, the recommended dosing is 100 mg/day (approximately equivalent to 60 mg/m^2/day).[27] In a phase I study in pediatric patients, the recommended dosing was 85 mg/m^2/dose twice daily for patients with solid tumors. The dose-limiting toxicities in this study were headache and diarrhea. Several patients who received multiple courses of dasatinib experienced pleural effusions.[27] In combination studies, 100 mg/day of dasatinib has been the dose when used with gemcitabine or CCNU in adults.[47, 48] This is the dose we propose for this combination study. The most common toxicities that have been reported with combination use of dasatinib in patients with non-hematologic malignancies are nausea, fatigue, transaminitis, and cytopenias. Rare pleural effusions and rash have also been reported.[27, 33] Dasatinib is available in tablet sizes of 5 mg, 20 mg, 50 mg, 70 mg, 80 mg and 100 mg.

2.4.2.1 Pharmacokinetics

Pharmacokinetic (PK) studies were conducted using a single 100 mg dose of dasatinib administered to healthy volunteers in four different formulations: 50 mg clinical tablets x 2, 5 mg clinical tablets x 20, 20 mg commercial tablets x 5, and 50 mg commercial tablets x 2. The

PK profile of the agent was similar in all four formulations. The PK profile of dasatinib was also assessed in CML and Ph+ ALL patients providing data which showed that the PK parameters in the patient population appear to be similar to that in the healthy volunteers. The agent was absorbed rapidly following oral administration; peak plasma concentrations were achieved in 0.5-3 hours and dose-related increases in plasma concentrations were observed. The mean terminal half-life ($t_{1/2}$) of dasatinib was 4 hours. Dosing interval exposures and $t_{1/2}$ values were comparable regardless of whether the agent was administered on a once daily or twice daily (BID) 5-day-on/2-day-off schedule, or BID continuously.

A phase I study has been initiated in solid tumor patients to determine the effect of the CYP3A4 inhibitor ketoconazole on dasatinib PK. In a study of 18 patients with solid tumors, 20 mg of dasatinib once daily coadministered with 200 mg of ketoconazole twice daily increased the dasatinib C_{max} and AUC by four- and five-fold, respectively.

2.4.2.2 Efficacy

A phase I study treated patients with CML in chronic phase (CP) or advanced disease (accelerated phase or blast crisis) or Ph+ ALL who were intolerant or resistant to imatinib.[38, 49] Dasatinib was administered once daily at doses ranging from 15 to180 mg/day or BID at doses ranging from 25 to 50 mg for 5-7 consecutive days each week. Complete hematologic response was documented in 37 of 40 CP patients (92%) and the rate was similar with both schedules (once daily or BID). Fourteen CP patients (35%) achieved a complete cytogenetic response and four (10%) experienced partial responses. In 44 patients with advanced CML or Ph+ ALL, 31 major hematologic responses were documented (70%). Cytogenetic responses were documented in 25 advanced CML or ALL patients, including complete responses in 11 patients.

A phase I study has been conducted in patients with refractory solid tumors in order to evaluate the safety, tolerability, and the pharmacologic profile of dasatinib.[33] Patients received escalating doses (25 to 120 mg) of dasatinib without food administered BID for 5 consecutive days every week followed by 2 days of rest (5D2 schedule), or on a continuous daily dosing (CDD) schedule. There were no objective responses on CT scans, but stable disease (SD) was observed in 11 patients (16%), including three gastrointestinal stromal tumor (GIST) patients. These 11 were comprised of seven (21%) of 33 patients on the 5D2 schedule and four (12%) of 34 patients on the CDD schedule. The median duration of SD was 3.6 months (range 1.7 – 23.6 months). The investigators noted that the clinical benefits of the agent in a subset of imatinib-resistant GIST patients have been encouraging.

In solid tumors, the recommended phase II dose for dasatinib in adult patients was found to be 120 mg BID on the 5D2 schedule, or 70 mg BID on the CDD regimen.[33] In pediatric patients with solid tumors, the recommended phase II dose for dasatinib was found to be 85 mg/m^2 BID.[27] In October 2010, dasatinib was approved by the FDA for treatment of chronic, accelerated, and blast phase CML and Ph+ ALL with resistance or intolerance to imatinib. Results from two phase 3 dose-optimization studies supported starting doses of 100 mg once/day for CP CML and 140 mg once/day for imatinib-resistant accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL. A randomized phase 3 trial comparing dasatinib to imatinib led to FDA approval of dasatinib (100 mg once/day) for first-line therapy of newly diagnosed CML.

2.4.3 Safety

Myelosuppression, probably attributable to suppression of the Ph+ clone, was the most frequent adverse event (AE) in the phase I study in CML or Ph+ ALL, while the most significant AE was grade 3/4 thrombocytopenia (28%).[32] Severe myelosuppression was reversible and easily managed with a short dose interruption; about 60% of patients required interruption of treatment, and the myelosuppression generally resolved within 3 months, often in association with a cytogenetic response.[38] Twenty-five percent of leukemia patients required a dose reduction. In the phase I study in solid tumor patients, hematologic AEs were uncommon: two patients on the 5D2 schedule with grade 1 or 2 anemia developed grade 3 anemia while on study drug, whereas on the CDD schedule one patient developed grade 4 neutropenia and another grade 3 anemia.[33]

Non-hematologic AEs from the two phase I trials include GI intolerance (primarily diarrhea, nausea, and vomiting), GI hemorrhage, fatigue, dyspnea, anorexia, dehydration, fluid retention, pleural and pericardial effusion, a moderate increase in QTcF (with no QTcF >500 msec), elevated creatinine, depression, and tumor lysis syndrome. In addition to these AEs, dasatinib treatment has the potential to produce skin rashes, other respiratory events, and CNS hemorrhage. While neither immunosuppression nor osteoclast function abnormalities (*e.g.*, osteoporosis) were observed in these short-term studies, SRC kinase inhibitors have the potential to cause these types of events.

As of September 2010 in the overall population of 2840 subjects, a total of 740 (26%) deaths were reported in adult dasatinib-treated subjects with CML or Ph+ ALL. Of these 740 deaths, 296 occurred within 30 days of the last dose of study therapy. Of the 740 deaths, 380 (51%) were due to disease progression and 11 (1.5%) have been positively attributed to study drug toxicity.

2.4.3.1 Potential Drug Interactions

Dasatinib is primarily metabolized by CYP3A4 and therefore, potent inhibitors of this enzyme are contraindicated.[32] Dasatinib is also a significant inhibitor of this hepatic enzyme but a weak inhibitor of other cytochrome enzymes, and the agent does not induce CYP3A4. Thus, dasatinib may decrease the clearance of drugs that are significantly metabolized by the CYP3A4 enzyme, and caution should be used with concurrent use of such drugs or substances. In a study in cancer patients, concomitant use of a potent CYP3A4 inhibitor (ketoconazole) produced >5-fold increase in exposure to dasatinib, while healthy subjects treated concurrently with dasatinib and a potent CYP3A4 inducer experienced a 5-fold decrease in dasatinib exposure. When the CYP3A4 substrate simvastatin was studied in combination with dasatinib, increased simvastatin exposure resulted, indicating the necessity of caution when dasatinib is administered with CYP3A4 substrates with a narrow therapeutic margin (*e.g.,* cyclosporine).

2.5 GANITUMAB

Ganitumab is a fully human monoclonal antibody directed against IGF-1R that exerts its antitumor effect by inhibiting IGF1R activation through blockade of ligand binding (IGF-1 and IGF-2) to the extracellular domain of IGF-1R, and induction of receptor internalization and degradation, without cross-reacting with the insulin receptor. Blockage of ligand binding inhibits cell survival and proliferative signals and, consequently, suppresses tumor cell growth and invasion. Inhibition of IGF1R signaling with ganitumab provides a potential mechanism for

inhibiting tumor growth either alone or in combination with other anticancer therapy.[50]

The drug has high affinity for IGF-1R, with a K_D of 0.3 nM. The IC_{50} for blocking IGF-1R phosphorylation in the presence of IGF-1 or IGF-2 is 0.6 nM.[50]

2.5.1 Non-clinical studies

2.5.1.1 Efficacy

In vitro studies demonstrated high-affinity binding of ganitumab to human (dissociation constant (51) = 0.30 nM), cynomolgus monkey (K_d = 0.15 nM), rat (K_d = 0.25 nM), and mouse (K_d = 0.30 nM) IGF1R. Ganitumab inhibited the interaction of IGF1R with both of its natural ligands (IGF-1 and IGF-2) equally without cross-reacting with the insulin receptor. Ganitumab inhibited IGF-1- and IGF-2-mediated IGF1R activation, Akt activation, and DNA synthesis in cells engineered to express IGF1R and in human cancer cell lines. As monotherapy, ganitumab demonstrated activity in human sarcoma, breast carcinoma, colon carcinoma, ovarian carcinoma, and pancreatic carcinoma xenograft models. The activity of ganitumab in vivo was driven by ligand blockade and receptor down-regulation, which resulted in apoptosis and/or lower rates of cellular proliferation. In a number of tumor xenograft models, ganitumab also enhanced the antitumor activity of chemotherapeutic agents, such as irinotecan, gemcitabine, and cyclophosphamide, and targeted agents, such as rapamycin, panitumumab, and erlotinib. The treatment of mice with ganitumab led to increased serum levels of IGF 1, insulin-like growth factor binding protein 3 (IGFBP-3), and growth hormone and to decreased peripheral blood neutrophils.[50]

2.5.1.2 Nonclinical Pharmacokinetic and Pharmacodynamic Studies

Exposure to ganitumab increased approximately dose-proportionally after single and multiple IV or intraperitoneal administrations in normal cluster of differentiation 1 (CD-1) mice, Sprague-Dawley rats (0.12 to 120 mg/kg), and in cynomolgus monkeys (0.1 to 100 mg/kg). Antibodies to ganitumab were observed in rats and cynomolgus monkeys, with apparent increased drug clearance in some of the antibody-positive animals after IV administration of ganitumab. Terminal elimination half-life ($t_{1/2, z}$) values ranged from 4 to 6 days in cynomolgus monkeys in the absence of anti-ganitumab antibodies. Toxicokinetics of ganitumab did not markedly differ between male and female animals.[50]

2.5.1.3 Toxicology

A comprehensive package of toxicology studies was performed, including repeated-dose IV toxicity studies of up to 6 months in the rat and 9 months in the cynomolgus monkey, safety pharmacology studies (neurobehavioral and cardiovascular/respiratory in the rat and monkey, respectively), maternal and embryo-fetal developmental study in the pregnant rat, and tissue cross-reactivity studies in tissue sections from humans and the preclinical species. The Sprague-Dawley rat and cynomolgus monkey were selected as the nonclinical toxicology species because the in vitro potency and functional activity of ganitumab in rats and monkeys is similar to the potency in humans. Ganitumab administration primarily affected body weight, food consumption, clinical pathology parameters, liver, kidney, thymus, and reproductive organs in rats and/or monkeys. No adverse effects were noted in safety pharmacology studies that

evaluated cardiovascular (electrocardiogram parameters including corrected QT interval [QTc]), CNS, and respiratory effects of ganitumab at doses up to 300 mg/kg.[50]

2.5.2 Clinical Experience

In a phase I study in 53 adults with advanced solid tumors, a dose of 20 mg/kg given IV once every 2 weeks was deemed tolerable (MTD was not reached), though biochemical blockade was achieved at levels of 12 mg/kg IV every 2 weeks. Four of 23 patients treated at the 20 mg/kg dose level developed Grade 3 thrombocytopenia. The only other Grade 3 toxicities noted across dose levels were arthralgia (n=1); diarrhea (n=1); and fatigue (n=1). Hyperglycemia and hypothyroidism were also reported.[52] An adult phase II study with patients with Ewing family tumors and desmoplastic small round cell tumors used a dose of 12 mg/kg given IV once every 2 weeks and reported similar toxicities, most commonly fatigue, thrombocytopenia, and hyperglycemia.[53] When used in combination with other agents including conatumumab, gemcitabine, panitumumab, erlotinib, and sorafenib, doses of AMG479 between 12 mg/kg and 20 mg/kg IV every 2 weeks have been tolerated in adults. Frequent toxicities in the combination studies include fatigue, nausea and vomiting. Frequent grade 3 toxicities in these combination studies included neutropenia, thrombocytopenia and hyperglycemia.[54-57] The combination of ganitumab (12 mg/kg IV every 2 weeks) to gemcitabine improved 6-month overall survival in patients with advanced pancreatic cancer in a phase II trial,[58] though a randomized phase 3 trial testing this combination in advanced pancreatic cancer was stopped early when futility stopping rules were met.

The pharmacokinetic profile of ganitumab appears to differ somewhat between adult patients with various solid tumors and adult patients with Ewing sarcoma and DSRCT treated on a phase II trial.[53] Specifically, patients on this phase II trial treated with 12 mg/kg every 2 weeks had lower trough concentrations after their first and third doses of ganitumab compared to patients with relapsed solid tumors treated on 2 other studies with this same dose and schedule. The mean ± SD trough concentration after Cycle 1 was 17.5 ± 8.52 µg/mL for EWS/DSRCT vs. 22 ± 11 µg/mL and 26.1 ± 12.5 µg/mL for other solid tumors. The mean ± SD trough concentration after Cycle 3 was 15.9 ± 33.6 µg/mL for EWS/DSRCT vs. 27 ± 15.9 µg/mL and 42.2 ± 18.5 µg/mL for other solid tumors.[50] 22 of 29 patients (75%) with EWS/DSRCT had ganitumab trough concentrations > 10 µg/mL after a single dose of 12 mg/kg.[53]

2.5.3 Rationale for Proposed Ganitumab Starting Dose

While a pediatric phase I clinical trial of ganitumab has not been performed, several points suggest that proceeding with the proposed pediatric and adult study based on the adult experience with this drug is reasonable. First ganitumab is currently being used in a randomized Phase II trial conducted by COG in combination with a standard chemotherapy backbone of vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide in pediatric patients with newly diagnosed metastatic Ewing Sarcoma (activation data 12/8/2014; NCT02306161). Second, IGF-1R monoclonal antibodies as a class have been well tolerated in both adults and children. Finally, of the compounds in this class in which adult and pediatric phase I studies have been performed, the recommended pediatric dose has not been lower than the adult dose. For example, the recommended pediatric phase II dose of IMC-A12 is 9 mg/kg weekly [59], which compares favorably to the adult recommended phase II dose of 6 mg/kg weekly.[60] Likewise, for

dalotuzumab, the recommended pediatric phase II dose (900 mg/m^2 IV every 3 weeks) was similar to the recommended adult phase II dose.[61] Third, the dose used in this study is below the maximum dose evaluated and deemed tolerable in the adult single agent phase I study.

The starting dose of ganitumab for this study will be 18 mg/kg. This dose was selected for several reasons. First, biochemical blockade of IGF-1R signaling is observed at serum concentrations > 10 µg/mL.[29] Blockade of IGF-1R epitope binding on neutrophils also begins to saturate at serum concentrations of 10 µg/mL.[50] Trough serum concentrations in excess of this target trough concentration value of 10 µg/mL are anticipated using 18 mg/kg, extrapolating from the experience from the phase II trial of young adults with relapsed Ewing sarcoma treated with 12 mg/kg. These trough serum concentrations compare favorably with the IC_{50} of ganitumab in 2 Ewing sarcoma cell lines of 1.6 and 3.7 nanomolar (0.54 µg/mL and 0.23 µg/mL).[62] In *in vivo* studies of ganitumab against mouse Ewing sarcoma xenografts, activity was noted at doses of ganitumab that yield steady state serum concentrations of 4.7 µg/mL.[62] Second, experience with ganitumab and other IGF-1R monoclonal antibodies have demonstrated clinical activity in patients with Ewing sarcoma at doses below maximal evaluated dose levels of 20 mg/kg.[53, 59] For example, the phase II trial of ganitumab in patients with relapsed Ewing sarcoma used 12 mg/kg IV every 2 weeks.[53] Third, combination studies have evaluated doses of 12-20 mg/kg every 2 weeks.[58] Fourth, given the risk of thrombocytopenia that has been observed with IGF-1R monoclonal antibodies,[12, 52, 59] use of maximal studied doses of ganitumab (20 mg/kg) may not be feasible in combination with other agents.

2.6 PROPOSED TRIAL:

2.6.1 Dose Selection for Phase I/II Design

This is a phase I/II trial to test the combination of ganitumab and dasatinib in patients with refractory or relapsed embryonal or alveolar rhabdomyosarcoma. The ganitumab dose for both the phase I and phase II components will be 18 mg/kg IV every 2 weeks, starting on day 0, based on published data indicating that this dose inhibits the target and is tolerable in combination with other therapies (see section **2.5.3**). The starting dasatinib dose will be 60 mg/m^2 daily, which is the dose that has historically been used in combination with other therapies. For cycle 1, dasatinib dosing will begin on day -7 to preemptively inhibit YES prior to ganitumab dosing. For subsequent cycles, both agents will begin on day 0. Based on *in vitro* data generated in RMS cell lines, it is expected that this dose will produce concentrations high enough to inhibit the target. However, given the dearth of data on inhibition of YES with dasatinib in human tumors and the fact that in solid tumor studies, the recommended phase II doses were significantly higher both for adult and pediatric patients, we propose a phase I dose escalation from 60 mg/m^2/dose once daily (maximum 100 mg/day) to 60 mg/m^2/dose BID (maximum 70 mg BID). This higher dose is still below the recommended phase II dose in pediatric patients with solid tumors, and equivalent to the recommended phase II dose in adult patients with solid tumors.[27, 32]

The design will be a phase I lead in using a standard 3 + 3 design. Limited dose escalations will be performed to define the maximum tolerated dose (MTD) or the highest safe dose tested of dasatinib when given in combination with ganitumab in this patient population (see section **5.1.1** for details). In the phase II component, sixteen (16) evaluable patients, including up to 6 patients from the phase I portion treated at the selected phase II dose, will be enrolled.

Once the recommended phase II dose of dasatinib in combination with ganitumab (18 mg/kg) is determined, enrollment on the phase II portion of the trial will commence. We expect that the 18 mg/kg dose of ganitumab will be tolerated. However, we will limit enrollment to 6 patients initially to assess the toxicity of this combination at the recommended dose, since these two agents have not been assessed in combination previously. Provided ≤1/6 patients experience toxicities clearly attributable to ganitumab, the remainder of the patients will be treated using the ganitumab dose of dose of 18 mg/kg. If 2 or more of the initial 6 patients experience toxicity requiring a dose modification and the toxicities can be clearly attributed to ganitumab only, the ganitumab dose will be reduced to 12 mg/kg for all subsequent patients.

2.6.2 Patient Selection

Ideally, this trial would select patients with tumors that express IGF-1R. However, there are a number of issues that make prospective identification of these patients impractical. IHC, which could be performed as a pre-enrollment evaluation, has not been shown to reliably demonstrate IGF-1R expression. The preferred method to detect IGF-1R expression is with selection reaction monitoring (SRM) mass spectrometry and this will be done retrospectively in this trial. However, it is not feasible to perform this testing and obtain results prior to enrollment of each patient. Given that, tumor IGF-1R expression will not be an eligibility criteria. Based on published data, we expect the majority of patients to express IGF-1R on their tumors. Once the retrospective data on IGF-1R expression is available it will be analyzed and if a significant number of patients are identified to have no IGF-1R expression, we will consider amending the trail to enroll more patients.

2.6.3 Endpoint Selection

Historically, pediatric phase II trials have used tumor shrinkage based on RECIST or WHO criteria as a measure of response. However, a number of targeted agents have received FDA approval recently based on prolongation of survival or progression free survival, without evidence of a substantial number of RECIST responses. We hypothesize that improved progression free survival (PFS) may be a more meaningful measurement of clinical activity of targeted agents for our population.

An analysis of 85 patients with RMS enrolled on 7 negative phase II COG trials revealed that 88% of patients on those trials experienced disease progression by 4 months and 93% progressed by 6 months.[63-69] Upon review of the aforementioned studies, 4/7 (irinotecan, vinorelbine, rebeccamycin analogue, docetaxel) stated in their eligibility requirements that patients who had undergone more than 2 prior regimens were ineligible. For the remaining 3 studies (oxaliplatin, topotecan, ixabepilone), the median number of prior regimens was 2. Additionally, the oxaliplatin study analyzed the number of prior regimens patients had received and found no significant difference in the number of prior treatments between responders and non-responders. It would be unlikely that patients would be referred for enrollment on our trial immediately after their first relapse. This trial uses only targeted agents, and most centers first attempt salvage with a regimen using a cytotoxic backbone in first relapse or primary refractory rhabdomyosarcoma. Thus, we expect the majority of patients enrolling will have been treated with 2 or more prior therapies, making them more refractory and likely to have an expected PFS of 12% or less at 4 months.

Since our goal is to identify active agents that could be integrated into therapy at earlier time points, for example in the upfront setting, standard objective response measurements in the setting of relapse and refractory disease may be inadequate methods to detect activity of these agents in aggressive tumors such as rhabdomyosarcoma. Hence, we have selected co-primary endpoints of objective clinical response (CR and PR) as defined by RECIST criteria and the 4-month disease stabilization fraction (see section **13**).

3 PATIENT SELECTION

3.1 ELIGIBILITY CRITERIA

3.1.1 Inclusion Criteria

3.1.1.1 Patients of any age must have histologically or cytologically confirmed embryonal or alveolar rhabdomyosarcoma (RMS) confirmed by the Laboratory of Pathology, NCI or by the Department of Pathology and Laboratory Medicine, CHLA.

3.1.1.2 Patients must have measurable disease as per RECIST (version 1.1).

3.1.1.3 Patients must be able to undergo appropriate imaging studies to monitor tumor response.

3.1.1.4 Archival tissue of tumors (slides or blocks (blocks preferred) must be available for analysis. If tissue is not available, patients willing to undergo a pre-treatment biopsy may enroll.

3.1.1.5 Prior Therapies:

- There is no maximum number of prior medical therapies.
- There must be no curative or life prolonging treatments available.
- Patients who have received other IGF-1R antibodies or inhibitors are eligible, as long as an appropriate washout period has elapsed (see below).
- Participants must have had their last fraction of external beam radiation therapy that is local and palliative at least 2 weeks prior to enrollment (except for radiation therapy to the lungs as noted below), and had their last substantial bone marrow radiation at least 6 weeks prior to enrollment.
- Participants must have had their last radiation therapy of the lungs at least 8 weeks prior to enrollment.
- Participants must have had their last dose of temozolomide at least 4 weeks prior to enrollment; their last dose of other cytotoxic chemotherapy at least 3 weeks prior to enrollment; their last dose of biological therapy, such as biological response modifiers (e.g., cytokines), immunomodulatory agents, vaccines, differentiating agents, used to treat their cancer at least 7 days prior to enrollment, their last dose of a monoclonal antibody the shorter of 3 half- lives or 28 daysprior to enrollment, and their last dose of any investigational agent at least 4 weeks prior to enrollment.

- Participants must have recovered from the acute toxic effects of prior therapy to a grade 1 (CTCAE v.5.0) level prior to enrollment (does not apply to alopecia).

3.1.1.6 Age. There are no age limits for this study, but patients must have the ability to swallow tablets.

3.1.1.7 ECOG performance status ≤2 or Karnofsky >50% (if ≥ 16 years of age); or children < 16 years old must have a Lansky performance of ≥50% (see **Appendix 1**).

3.1.1.8 Patients must have normal organ and marrow function as defined below:

– absolute neutrophil count	≥1,000/mcL
– platelets	≥75,000/mcL
– total bilirubin	≤1.5X upper limit of normal (ULN), with exception of patients with Gilbert syndrome
– ALT	≤ 3.0X ULN
– creatinine	within normal institutional limits
	OR
– creatinine clearance	≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.
– Normal blood glucose for age	

3.1.1.9 Hematologic parameters for patients undergoing biopsy **only**: Patients should have INR ≤1.4 and PTT ≤ 40 seconds (unless due to lupus anticoagulant). In patients not meeting these parameters, clearance by hematology will be required prior to undergoing a biopsy.

3.1.1.10 Cardiac Function: QTcF < 480 msec (Fridericia correction), and ejection fraction (EF) ≥ 50%

3.1.1.11 Contraception

The effects of these agents on the developing human fetus are unknown. For this reason, men and women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 4 months after completion of administration of either agent. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

Negative pregnancy test is required for women of childbearing potential.

3.1.1.12 Ability of subject or Legally Authorized Representative (LAR) to understand and the willingness to sign a written informed consent document.

3.1.1.13 Patients will be strongly encouraged to participate in 10-C-0086. If a patient does not agree to enroll on 10-C-0086, germline genetic analysis will not be performed.

3.1.2 Exclusion Criteria

3.1.2.1 Patients who are receiving any other investigational agents.

3.1.2.2 Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.1.2.3 History of allergic reactions attributed to compounds of similar chemical or biologic composition to dasatinib or ganitumab or other agents used in study.

3.1.2.4 Patients who require concurrent treatment with any medications or substances that are potent inhibitors or inducers of CYP3A4 are ineligible. (See **Appendix 2** for lists of specifically prohibited medications or substances.)

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list or medical reference text such as the Physician's Desk Reference. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product. (See **Appendix 3**)

3.1.2.5 Patients who require concurrent treatment with antithrombotic and/or anti-platelet agents (*e.g.*, warfarin, heparin, low molecular weight heparin, aspirin, and/or ibuprofen).

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

3.1.2.7 Patients with a history of radiation pneumonitis.

3.1.2.8 Patients may not have any clinically significant cardiovascular disease including the following:

- myocardial infarction or ventricular tachyarrhythmia within 6 months
- 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.) should 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 should be excluded from the study.

3.1.2.9 Uncontrolled intercurrent illness including, but not limited to, the following: ongoing or active infection; history of significant bleeding disorder, including congenital (von Willebrand's disease) or acquired (anti-factor VIII antibodies) disorders; large pleural

effusions; or psychiatric illness/social situations that would limit compliance with study requirements.

3.1.2.10 Patients with known pre-existing diabetes mellitus will be excluded because of the risk of hyperglycemia with ganitumab.

3.1.2.11 Pregnant women are excluded from this study because animal studies with dasatinib have shown embryolethality and fetal skeletal alterations at non-toxic maternal doses. Because there is an unknown but potential risk for adverse events in nursing human infants secondary to treatment of the mother with dasatinib, breastfeeding should be discontinued if the mother is treated with dasatinib.

3.2 SCREENING EVALUATION

3.2.1 Clinical Evaluation (within 7 days of enrollment)

3.2.1.1 History and Physical Examination:

A complete history and physical examination, (including vital signs with blood pressure, pulse, respiratory rate, temperature, and oxygen saturation), and a description of signs and symptoms is required.

3.2.1.2 Height, Weight and Body Surface Area:

For patients < 18 years old, the BSA should be calculated from measurement of weight and height on the same day by the standard formula in use at the NCI:

$$BSA=\frac{Weight\ (kg)^{0.425} * Height\ (cm)^{0.725}}{139.315}$$

3.2.1.3 Tanner Stage (pediatric patients)

3.2.1.4 Performance status determination

3.2.2 Laboratory studies

The following laboratory studies will be performed within 7 days of enrollment.

3.2.2.1 β-HCG pregnancy test on all women of child-bearing potential

3.2.2.2 Hematology: complete blood count, differential, platelet count, PT, PTT.

3.2.2.3 Chemistries: BUN, creatinine, electrolytes (sodium, potassium, chloride, CO2), calcium, magnesium, phosphorus, uric acid, total protein, albumin, LDH, and glucose.

3.2.2.4 Fasting triglycerides, cholesterol (total, HDL, LDL)

3.2.2.5 HbA1C.

3.2.2.6 Hepatic Panel: Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, (Direct Bilirubin, if total bilirubin is elevated)

3.2.2.7 Urinalysis

3.2.3 Electrocardiogram (ECG)

ECG with Calculation of QTcF using Fridericia's correction (QTcF = QT/ $\sqrt[3]{RR}$). Electrocardiograms will be evaluated by suitably qualified personnel for the presence of QTcF prolongation or other abnormalities, in particular, any changes in the T-wave morphology that would suggest a higher likelihood for the development of any arrhythmia.

3.2.4 Echocardiogram

3.2.5 Imaging studies

Imaging studies of disease sites must be performed within 4 weeks prior to initiating protocol therapy. If more than 4 weeks have elapsed between the date imaging studies to determine eligibility were obtained and the start date of treatment, then repeat imaging studies must be obtained prior to initiating protocol therapy.

4 RECRUITMENT AND REGISTRATION

4.1 RECRUITMENT STRATEGIES

This study will be posted on NIH websites and on NIH social media forums. The following recruitment strategies will also be employed to elicit potential candidates for this trial:

1. Listed on www.clinical trials.gov;
2. Listed in the CHLA flyer for physicians in southern California
3. In addition, patients from POB, NIH adult clinics and CHLA who are eligible for participation will be offered participation in this study

Prior to distribution of any recruitment materials, such materials will be submitted to the NIH Intramural IRB for review.

4.2 REGISTRATION PROCEDURES

4.2.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require IND sponsors to select qualified investigators. NCI policy requires all persons participating in any NCI-sponsored clinical trial to

register and renew their registration annually. To register, all individuals must obtain a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (*i.e.*, clinical site staff requiring write access to Oncology Patient Enrollment Network (OPEN) or Rave or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	**IVR**	**NPIVR**	**AP**	**A**
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov.

4.2.2 Site Registration

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. Assignment of site registration status in the

CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site

4.2.2.1 Requirements for 10003 Site Registration

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted.)

4.2.2.2 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission

When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

4.2.2.3 Checking Site Registration Status

You can verify your site registration status on the members' section of the CTSU website.

- 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

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.2.3 Patient Registration

4.2.3.1 IWRS

Patient Enrollment will be facilitated using the Interactive Web Response System (IWRS). IWRS is a web-based registration system available to users on a 24/7 basis. On a successful registration, IWRS will assign a patient number and assign the treatment. Patient enrollment data entered by Registrars in IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave. IWRS will provide a printable confirmation of registration and treatment information. Please print this confirmation for your records.

- Users must have a valid CTEP-IAM account (*i.e.*, CTEP username and password) to access the IWRS system.
- Users defined with the Registrar role will have the ability to register patient in the study.
- Users defined with the Client Administrator role will have the ability to manage accrual limits, open and close treatment assignments as well as approve slot reservations, if applicable to the study.

4.2.3.2 OPEN / IWRS

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available to users on a 24/7 basis. It is integrated with the CTSU Enterprise System for regulatory and roster data interchange and with the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. Patient enrollment data entered by Registrars in OPEN / IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave.

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

4.2.4 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

- Have a valid CTEP-IAM account (*i.e.*, CTEP username and password).
- To enroll patients: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type.
- Have regulatory approval for the conduct of the study at their site.

Prior to accessing OPEN/IWRS, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- If applicable, all patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form.

4.2.5 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab 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.

4.3 LOCAL REGISTRATION FOR NCI CCR

Authorized staff must register the eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agent. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

4.3.1 For Participating Site Registration

Registration will be a two part process as patients are screened on this protocol. A protocol registration form will be supplied by the CCR study coordinator and updates will be provided as needed. To initially register a subject, after the participant has signed consent, complete the top portion of the form and send to CCR study coordinator. Once eligibility is confirmed, after completion of screening studies, complete the remainder of the form which is the eligibility checklist, indicating that the patient is being registered for treatment and send to CCR study coordinator. In addition, source documents supporting the eligibility criteria must be sent to the CCR study coordinator. The CCR study coordinator will notify you either by e-mail or fax that the protocol registration form has been received which will include the unique patient/subject ID number. Questions about eligibility should be directed to the CCR study coordinator or PI. Questions related to registration should be directed to the CCR study coordinator.

Subjects that do not meet screening criteria should be removed from the study following the procedure in section **5.6**.

4.3.2 Treatment Assignment Procedures

4.3.2.1 Cohorts

Number	Name	Description
1	Dose Escalation Cohort (Phase I)	Patients (minimum 2 years of age and above) with embryonal or alveolar RMS and measurable disease.
2	Dose Expansion Cohort (Phase II)	Patients (minimum 2 years of age and above) with embryonal or alveolar RMS and measurable disease.

3	Previosly Treated Dose Expansion Cohort (Phase II)	Patients (minimum 2 years of age and above) with embryonal or alveolar RMS and measurable disease previously treated in the Phase I portion of this study.

4.3.2.2 Arms

Number	Name	Description
1	Phase I	Combination of ganitumab and dasatinib with limited dose escalation of dasatinib
2	Phase II	Combination of ganitumab and dasatinib at the MTD (or highest safe dose)

4.3.2.3 Arm Assignment

The treatment assignment is open-label and non-randomized (i.e., patients in Cohort 1 are directly assigned to Arm 1 and patients Cohort 2 and Cohort 3 are directly assigned to Arm 2).

4.4 GENERAL GUIDELINES

Following registration, patients should begin protocol treatment within 7-10 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5 TREATMENT PLAN

5.1 AGENT ADMINISTRATION

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in section **7**. Appropriate dose modifications are described in section **6**. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

5.1.1 Dose Escalation/De-escalation Schedules

During the Phase I portion of the study, patients will receive dasatinib and ganitumab at the following dose levels:

Phase I Dose Escalation Schedule for Dasatinib		
Dose Level	**Dose of dasatinib**	**Dose of ganitumab**
Level -1	40 mg/m^2 once daily (maximum dose of 100 mg/day) on days -7	18 mg/kg every 2 weeks, beginning on day 0

	through day 27 during cycle 1, and then days 0-27 for subsequent cycles (28 day cycles).	
Level 1	60 mg/m^2 once daily (maximum dose of 100 mg/day) on days -7 through day 27 during cycle 1, and then days 0-27 for subsequent cycles (28 day cycles).	18 mg/kg every 2 weeks, beginning on day 0
Level 2	60 mg/m^2 BID (maximum dose of 70 mg BID) on days -7 through day 27 during cycle 1, and then days 0-27 for subsequent cycles (28 day cycles).	18 mg/kg every 2 weeks, beginning on day 0

During the Phase II portion of the study, patients will receive dasatinib and ganitumab at level 1, as described below. See section **5.1.3** for further details on de-escalation.

Phase II Potential Dose De-escalation Schedule for Ganitumab further details in section **2.6.1** and section **5.1.3**		
Dose Level	Dose of dasatinib	Dose of ganitumab
Level -1	Dasatinib MTD determined during phase I	12 mg/kg every 2 weeks, starting on day 0
Level 1	Dasatinib MTD determined during phase I	18 mg/kg every 2 weeks, starting on day 0

5.1.2 Dasatinib administration

For all dose levels in the phase I and II portions, dasatinib will begin on day -7 for cycle 1 and day 0 for subsequent cycles. For the phase I portion, dose escalation will proceed in cohorts of 3–6 patients, starting at dose Level 1. The MTD is the dose level at which no more than 1 of up to 6 patients experience DLT during the first cycle of treatment, and the dose below that at which at least 2 (of ≤6) patients have DLT as a result of the drug. If a patient did not experience DLT and did not finish treatment in cycle 1, he or she will only be evaluable for the dose escalation portion of the study if they received both ganitumab doses and ≥85% of the dasatinib doses in cycle 1. Patients who have not met these criteria will be replaced in the dose level. If ≥2 out of a maximum of 6 patients experience DLT at dose Level 1, the dose of dasatinib will be de-

escalated to dose Level -1. If 0-1 out of a maximum of 6 patients have DLT at dose Level -1, this will be considered the MTD. If 2 or more out of a maximum of 6 patients experience DLT at dose Level -1, the accrual will be suspended pending discussions with the Sponsor and NIH Intramural IRB regarding how to proceed with the combination therapy.

Dose escalation will follow the rules outlined in the Table below.

Number of Patients with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter up to 3 patients at the next dose level
$\geq$ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Up to three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter up to 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Up to three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
$\leq$1 out of 6 at highest dose level below the maximally administered dose	This is the MTD and is generally the recommended phase II dose. At least 6 patients must be entered at the recommended phase II dose.

The dose determined to be MTD, or the highest dose evaluated if no MTD is established will be the dose and schedule administered in the Phase II portion of the study. Patients who received the MTD during Phase I will be included in the analysis of the Phase II objectives.

See the dosing nomogram in **Appendix 4**.

During cycle 1, patients will be observed in the clinic, day hospital or hospital for 2 hours after the first dose of dasatinib is taken.

Dasatinib tablets may be taken with or without food as desired, but should be swallowed with at least 8 ounces (240 mL) of water. A light meal is not required, but may improve gastric tolerance for dasatinib. Tablets must be swallowed whole and may not be broken. If vomiting

occurs within 30 minutes of swallowing the tablet(s), the dose may be replaced if the tablets can be seen and counted. Four weeks (28 days) constitutes one cycle of treatment, with the exception of cycle 1, which lasts five weeks (35 days). Treatment continues until one of the criteria in section **5.3** applies.

Patients will be provided with a Medication Diary for dasatinib (Appendix 5, Appendix 6, Appendix 7, and **Appendix 8**), instructed in its use, and asked to bring the diary with them to each appointment. A new copy of the Medication Diary will be given to patients whose dose is reduced due to adverse events.

If tablets are accidentally crushed or broken, caregivers should wear disposable chemotherapy gloves. Pregnant women should avoid exposure to crushed and/or broken tablets.

5.1.3 Ganitumab Administration

Patients receive ganitumab intravenously on an outpatient basis once every 2 weeks on a continuous dosing schedule starting on day 0 (1 cycle is 28 days), at a dose of 18 mg/kg per dose which is below the MTD determined in the pediatric phase I trial and is the same dose being used in a current COG phase II trial for metastatic Ewing sarcoma (AEWS1221) in combination with a standard chemotherapy backbone of vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide. We thus do not expect that the 18 mg/kg dose of ganitumab will not be tolerated. However, in addition to toxicity assessment for the phase I dose escalation with dasatinib, toxicity from ganitumab will be assessed after the first 6 patients have been enrolled at the phase II dasatinib dose, since these two agents have not been assessed in combination previously. Provided ≤1/6 patients experience toxicities clearly attributable to ganitumab, the remainder of the patients will be treated using the ganitumab dose of dose of 18 mg/kg. If 2 or more of the initial 6 patients experience toxicity requiring a dose modification and the toxicities can be clearly attributed to ganitumab only, the ganitumab dose will be reduced to 12 mg/kg for all subsequent patients.

The first dose of ganitumab should be administered over an hour. Maximum infusion duration is 120 minutes. Vital signs should be recorded 30-60 minutes before the dose, 30 minutes (+/- 10 mins) into the infusion and after the infusion (+/- 10 mins). Temperatures should be taken orally. If a temperature is not taken orally and is found to be elevated, it should be repeated with an oral reading. During cycle 1, patients will be observed in the clinic, day hospital or hospital for at least 1 hour after the first dose of ganitumab is given.

5.1.4 Criteria for starting subsequent treatment cycles

Patients who complete a treatment cycle (28 days) may receive another cycle if:

- Disease Status: If imaging is done, the patient has stable disease or has experienced a PR or CR, (see Section **11.1.4**).
- Toxicity: Patients who experienced dose-limiting toxicity in the previous cycle should have the dose modified as per Section **6**.
- Conditions for discontinuation of protocol treatment or off-study criteria (Sections **5.3** and **5.5**) have not been met.

5.2 GENERAL CONCOMITANT MEDICATION AND SUPPORTIVE CARE GUIDELINES

There is a potential for interaction of dasatinib with other concomitantly administered drugs. Therefore, all prescription and over-the-counter medications as well as herbal treatments or alternative medicines must be fully documented in the Case Report Form (CRF; including indication and dates of administration).

5.2.1 Agents that induce or inhibit CYP3A4

Agents or substances that strongly induce or inhibit CYP3A4 are prohibited during dasatinib treatment because the patient's exposure to dasatinib is significantly affected by such materials. For CYP3A4 inhibitors, a washout period of >7 days is required prior to starting dasatinib. The washout period should be based on the half-life of the particular CYP 3A4 inhibitor which can be substantially longer than 7 days in some cases (e.g., amiodarone). The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected P450 isoenzymes. See **Appendix 2** for a list of specifically prohibited CYP3A4 inhibitors and inducers.

Other inhibitors, inducers, and substrates of CYP3A4 may affect dasatinib metabolism, and restriction of their use is recommended. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list or medical reference text such as the Physician's Desk Reference.

Patients should be advised not to consume substantial quantities of grapefruit or grapefruit juice during dasatinib treatment.

5.2.2 Agents to avoid or agents prohibited

Because systemic antacids (H_2 inhibitors, proton pump inhibitors) decrease dasatinib absorption, patients who require antacids should use short-acting, locally-active agents (*e.g.*, Maalox®, Mylanta® *etc*.). However, these agents should not be taken within either 2 hours before or 2 hours after the dasatinib dose.

Use of agents with proarrhythmic potential is not permitted during the study, and a washout period of ≥7 days is required prior to starting dasatinib. The washout period should be based on the half-life of the particular proarrhythmic agent which can be substantially longer than 7 days in some cases (*e.g.*, amiodarone). See **Appendix 2: Substances Prohibited During Dasatinib Treatment** for a list of proarrhythmic agents that are specifically prohibited during dasatinib treatment. A comprehensive list of agents with the potential to cause QTc prolongation can be found at http://torsades.org.

Thrombocytopenia and hemorrhagic events can occur with dasatinib treatment. For this reason, patients may not take anticoagulants or medications that inhibit platelet function while on study including therapeutic warfarin or heparin. All such medications must have been stopped ≥7 days prior to starting dasatinib to allow an appropriate washout period. If the patient requires any surgical (including dental) procedure while on study, dasatinib should be stopped 1 day before the procedure and not reinstituted until 1 to 2 days afterward or until adequate hemostasis is achieved.

5.2.3 Support for hypocalcemia

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

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

5.2.4 Antiemetics and Anti-diarrheals

The nausea, vomiting, and diarrhea that may occur with dasatinib administration can generally be managed through the use of appropriate supportive measures (anti-emetics - *e.g.,* 5-HT_3 antagonists, benzodiazepines, prochlorperazine, and anti-diarrheal medications - *e.g.*, loperamide).

Given the risk of hyperglycemia with ganitumab, the use of corticosteroids as an antiemetic is strongly discouraged. Corticosteroids should only be considered as an antiemetic if a patient has poorly controlled nausea without corticosteroids. Sporadic use of corticosteroids as premedication for transfusions is allowed.

5.2.5 Diuretics

Fluid retention, including pleural effusions, should be controlled by early institution of diuresis (*e.g.,* furosemide, 20-40 mg PO daily and/or spironolactone, 25-50 mg PO, titrated to symptoms). Pleural effusions that remain or become symptomatic despite diuresis should be managed with thoracentesis. Steroid treatment may also be effective for pleural effusion. Chest discomfort may be related to a pericardial effusion; and an echocardiogram should be performed to investigate this possibility in such cases.

5.2.6 Supportive care for inflammation

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

5.2.7 Other supportive measures

Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary.

Growth factors that support platelet or white cell number or function can only be administered for culture proven bacteremia or invasive fungal infection. The PI or protocol AI should be notified before growth factors are initiated.

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) include dyspnea, fatigue, hypoxia, and edema. Since other medical conditions may also cause these symptoms, non-invasive procedures (including echocardiogram) should be done first to rule out more the common etiologies of these symptoms, such as pleural effusion, pulmonary edema, anemia, and lung infiltration.

Right heart catheterization can confirm the diagnosis of PAH. Hypertension is "pre-capillary" and not a consequence of left heart failure or chronic lung disease if there is normal pulmonary capillary wedge pressure (<15 mm Hg) but elevated pulmonary artery pressure (mean pulmonary artery pressure >25 mm Hg). Since PAH may be reversible upon discontinuation of dasatinib, a diagnostic approach of interruption of dasatinib treatment may be considered at the discretion of the treating physician; however, if PAH is confirmed, dasatinib should be permanently discontinued.

5.3 DURATION OF THERAPY (OFF TREATMENT)

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s). Patients required to permanently discontinue one agent due to toxicity may continue treatment with the other agent until other off treatment criteria are met,
- Treatment of both agents has been held for a period of 6 weeks, for any reason,
- Patient decides to withdraw from the treatment, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.4 DURATION OF FOLLOW UP

Patients removed from treatment for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. In addition, patients will be followed for at least 30 days after the last dose of investigational agents and until disease progression, whichever occurs last. Refer to section **10** for specific follow up requirements.

5.5 CRITERIA FOR REMOVAL FROM STUDY

Patients will be removed from study when any one of the following criteria is met. The reason for study removal and the date the patient was removed must be documented in the Case Report Form. Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy.

- Completed study follow-up period
- Participant requests to be withdrawn from study
- Death

5.6 LOCAL OFF PROTOCOL TREATMENT AND OFF-STUDY PROCEDURE

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off protocol treatment and when a subject is taken off-study. A Participant Status Update Form from the website (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov.

5.6.1 Participating sites

The Participant Status Update Form will be supplied by the CCR study coordinator. Send the completed form to the CCR study coordinator.

6 DOSING DELAYS/DOSE MODIFICATIONS

6.1 DEFINITION OF DOSE LIMITING TOXICITY (DLT) (PHASE I) AND TREATMENT LIMITING TOXICITY (TLT) (PHASE II)

Toxicity will be evaluated and treatment limited by the toxicities defined below (see also sections **6.2** through **6.6** for more information). This study will utilize the CTEP Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 for toxicity and Adverse Event grading and reporting. An adverse event must be judged to be possibly, probably, or definitely related to dasatinib, ganitumab or the combination to be considered a dose limiting toxicity (DLT) or treatment limiting toxicity (TLT).

Dose limiting toxicities (DLT) (Phase I) and treatment limiting toxicities (TLT) (phase II) are defined as:

- Any toxicity of grade 3 or higher, with the specific **exceptions** of:
  - Grade 3 nausea and vomiting of < 5 days duration
  - Grade 3 ALT/AST that return to levels that meet initial eligibility criteria within 7 days of study drug interruption and that do not recur upon re-challenge with study drug.
  - Grade 3 fever or infection < 5 days duration.
  - Grade 3 hypophosphatemia, hypokalemia, hypocalcemia and/or hypomagnesemia responsive to supplementation, or that are isolated events
  - Grade 3 neutropenia or thrombocytopenia
  - Grade 3 and grade 4 infusion reactions (not considered DLTs because they are not dose related)
- Grade 2 hemorrhage/bleeding/coagulopathy (without thrombocytopenia)
- QTcF prolongation ≥ 550 msec
- Any toxicity of grade 2 or greater that is considered intolerable to the patient, and cannot be controlled with standard supportive measures.

Treatment will be held until toxicity improves to less than or equal to grade 1 or baseline.

Depending on attribution of toxicity, treatment can be restarted with a dose reduction of the agent that caused the toxicity, or reduction of both agents if the toxicity cannot clearly be attributed to either one. Dose reductions of dasatinib will be performed by a dosing nomogram with detailed instructions on dose reduction (See **Appendix 4** and section **6.7**). Dose reductions of ganitumab will be as per section **6.6**.

Adverse events (AEs) should be treated with the appropriate maximum supportive care, and dose reductions should be clearly documented in the case report form.

Patients will be withdrawn from the study treatment if they fail to recover to CTCAE grade 0-1 or tolerable grade 2 (or within 1 grade of starting values for pre-existing laboratory abnormalities) from a treatment-related toxicity within 14 days OR they experience agent-related adverse events requiring dose modification despite one previous dose reduction of ganitumab (*i.e.*, would require a second dose reduction) or two previous dose reductions of dasatinib (*i.e.*, would require a third dose reduction) unless the investigator and CTEP senior investigator agree that the patient should remain on the study treatment because of evidence that the patient is/may continue deriving benefit from continued study treatment. Patients required to permanently discontinue one agent due to toxicity may continue treatment with the other agent until off treatment criteria are met (section **5.3**). If both agents have been held for a period of 6 weeks for any reason, patients will be removed from the study.

6.2 ADVERSE EVENTS ATTRIBUTED TO GANITUMAB

During participation in this study, patients who experience DLT or TLT attributable to ganitumab, or to both agents, may have the dose of ganitumab reduced to 12 mg/kg[2].

We do not expect that the 18 mg/kg dose of ganitumab will not be tolerated. However, in addition to toxicity assessment for the phase I dose escalation with dasatinib, toxicity from ganitumab will be assessed after the first 6 patients have been enrolled at the phase II dasatinib dose. If 2 or more of those patients who experience toxicity requiring a dose modification and the toxicities can be clearly attributed to ganitumab only, the ganitumab dose will be reduced to 12 mg/kg for all subsequent patients.

6.3 HEMATOLOGIC ADVERSE EVENTS ATTRIBUTED TO DASATINIB OR GANITUMAB

Event	AE Grade or Observation	Dose modification
Neutropenia	Grades 1-3	Maintain dose
	Grade 4 [1]	Hold both agents until ≤ grade 3, then reduce dasatinib per Section **6.7** AND ganitumab to 12 mg/kg/dose and resume treatment
Thrombocytopenia	Grades 1-3	Maintain dose

	Grade 4 [1]	Hold both agents until ≤ grade 3, then reduce dasatinib per Section 6.7 AND ganitumab to 12 mg/kg/dose and resume treatment
[1]If Grade 4 neutropenia or Grade 4 thrombocytopenia recur or persist for more than 2 weeks, patients should be removed from study treatment and bone marrow evaluation considered.		

6.4 PNEUMONITIS ATTRIBUTED TO DASATINIB AND GANITUMAB

This patient population may have been treated with thoracic radiation prior to enrollment on this study for management of primary tumor (e.g., chest wall primary site) or metastatic disease (e.g., whole lung radiation for patients with lung metastasis). Ganitumab treatment may increase the risk or severity of pneumonitis, although the extent of this potential interaction is not fully known. Dasatinib has also been associated with pneumonitis, both with concurrent lung radiation and without radiation.

It is important to be vigilant for the development of pneumonitis in patients treated with ganitumab. Oxygen saturation evaluation at time of protocol mandated physical examinations is required. Additional evaluations in patients who have been treated with lung radiation who present with unexplained cough, dyspnea, or physical exam findings on lung auscultation should be considered.

Pneumonitis will be managed according to local practice, individualized to each patient's clinical scenario:

Grade 1: Patients with Grade 1 pneumonitis (asymptomatic) should be monitored according to local practice for potential worsening to higher grade pneumonitis (symptomatic).

Grade 2 or higher: Prompt initiation of steroid therapy is critical and treatment should not be delayed in cases of suspected pneumonitis. A typical approach to Grade 2 and higher radiation pneumonitis includes a protracted course (2-4 weeks) of high dose corticosteroids (methylprednisolone or prednisone) followed by a taper. Prophylaxis for pneumocystis pneumonia (PCP) is required for patients receiving > 20 mg prednisone daily for 4 weeks or longer. Consultation with pulmonology is strongly encouraged for these patients.

Sites are to report symptomatic grade 2 or higher pneumonitis in an expedited manner via CTEP-AERS and through routine reporting.

Dose modifications for dasatinib and ganitumab are as follows:

Pneumonitis Grade (per CTCAE, under *Pneumonitis*)	**Action**
Grade 1	• Monitor closely for worsening symptoms. • Continue dasatinib and ganitumab.
Grade 2	• Initiate steroid therapy as indicated. • Strongly encourage consultation with pulmonologist. • Hold dasatinib and ganitumab until resolution to grade 1. • If pneumonitis resolves to tolerable grade 2 or less within 14 days, retreatment may be considered once it has returned to grade 1, if the patient has not met off-study criteria. Discussion with the Sponsor is required before retreatment can occur. If retreatment is permitted[1], dasatinib will be resumed per dosing in Appendix 4 and Section 6.6 and ganitumab will be resumed at 12 mg/kg.
Grade 3	• Initiate steroid therapy as indicated. • Consultation with pulmonologist. • Hold ganitumab until resolution to grade 1. • If pneumonitis resolves to tolerable grade 2 or less within 14 days, retreatment may be considered once it has returned to grade 1, if the patient has not met off-study criteria. Discussion with the Sponsor is required before retreatment can occur. If retreatment is permitted[1], dasatinib will be resumed per dosing in Appendix 4 and Section 6.6 and ganitumab will be resumed at 12 mg/kg.
Grade 4	• Initiate steroid therapy as indicated. • Consultation with pulmonologist. • Discontinue dasatinib and ganitumab permanently.
*For patients who have already been retreated at a dose reduced dose for pneumonitis, **if pneumonitis of any grade recurs, dasatinib and ganitumab will be permanently discontinued.**	

In most cases, patients who develop pneumonitis will be receiving treatment with both ganitumab and dasatinib. In the event that a patient develops pneumonitis before ganitumab is introduced (during week 1 of therapy), initiation of ganitumab must first be discussed with the Sponsor.

6.5 ADDITIONAL ADVERSE EVENTS ATTRIBUTED TO DASATINIB

Event	**AE Grade or Observation**	**Dose modification**
Hemorrhage/Bleeding/ Coagulopathy	Grade 1	No interruption in treatment; maintain current dose. Monitor as clinically indicated

Event	AE Grade or Observation	Dose modification
(without thrombocytopenia)	Grade 2	Hold dasatinib until AE resolved to ≤ grade 1; reduce dose to next lower dose level, and continue treatment. If grade 2 or greater hemorrhage/ bleeding recurs following dose reduction, stop dasatinib and remove patient from study treatment. Follow up per protocol (section **5.4**) if patient is removed from the study treatment.
	Grade 3 or 4	Discontinue treatment and follow up per protocol (see section **5.4**).
QTcF Prolongation	>480 but <550 msec	Review patient's concomitant medications for QT interval-prolonging agents. Correct any electrolyte abnormalities. Continue dasatinib at current dose level and repeat ECG.
	≥550 msec	Stop dasatinib and any other QT interval-prolonging agents immediately. Correct any electrolyte abnormalities, then *1.* If there is a plausible explanation for AE other than dasatinib treatment, resume dasatinib at current dose level. *2.* If dasatinib **may have contributed** to the AE: • Reduce 2 dose levels and restart dasatinib. • If QTcF remains <480 msec after 14 days at reduced dose, increase one dose level and continue dasatinib.

6.6 ADDITIONAL ADVERSE EVENTS ATTRIBUTED TO GANITUMAB

6.6.1 Hyperglycemia

For patients who develop hyperglycemia based on random, non-fasting glucose levels, discontinue use of corticosteroids before modifying ganitumab dose. If hyperglycemia occurs without use of corticosteroids, fasting glucose level should be checked. If elevated, ganitumab therapy modifications should be as follows:

Hyperglycemia Grade (per CTCAE, under *Hyperglycemia*)	**Action**
Grade 1	Continue ganitumab.
Grade 2	Continue ganitumab. Consider consultation with Pediatric Endocrinologist.
Grade 3 **or** Urine glucose > 0.1 g/dL	• Initiate insulin therapy or oral diabetic agent* as indicated. • Hold ganitumab until resolves to ≤ Grade 2 without glycosuria. • Resume ganitumab at same dose IF patient is asymptomatic, AND serum glucose is consistently < 250 mg/dL (≤ Grade 2) without glycosuria AND resolution to < Grade 2 has occurred within 2 weeks of interruption. The patient may continue to receive concomitant insulin or an oral diabetic agent for the management of hyperglycemia while receiving ganitumab. • If Grade 3 hyperglycemia recurs despite a stable dose of insulin or oral diabetic agent OR if resolution to consistent levels < Grade 2 requires more than 2 weeks of interruption, subsequent doses should be administered with a reduced dose of 12 mg/kg/dose.
Grade 4	• Initiate insulin therapy as indicated. • If associated with diabetic ketoacidosis or hyperosmolar nonketotic syndrome, discontinue ganitumab permanently. Otherwise, use the following instructions. • Hold ganitumab until resolves to ≤ Grade 2. • Resume ganitumab with a reduced dose of 12 mg/kg/dose IF patient is asymptomatic, AND serum glucose is consistently < 250 mg/dL (≤ Grade 2) without glycosuria AND resolution to ≤ Grade 2 has occurred within 2 weeks of interruption. The patient may continue to receive concomitant insulin or an oral diabetic agent for the management of hyperglycemia while receiving ganitumab. • If resolution to consistent levels < Grade 2 requires more than 2 weeks of interruption OR if Grade 4 toxicity recurs after re- challenge with 12 mg/kg, then discontinue ganitumab permanently.

*** Recommended guidelines for use of oral diabetic agents:**
Initiation of treatment for hyperglycemia should occur under the guidance of a pediatric endocrinologist. Metformin may be used per endocrinologist's recommendations.

Other oral anti-hyperglycemic agent may be used at the discretion of the pediatric endocrinologist. Insulin therapy should be directed by specialists in pediatric diabetes with the goal of normal fasting blood sugars <126mg/dL **and HgbA1C < 8%.**

6.6.2 Infusion Reactions

For patients who have allergic or acute infusion reactions, therapy modifications based on grade should be as follows. Guidelines for emergency management of infusion reactions are recommendations and institutional standard practice may be used as an alternative.

Grade	Action
Grade 1 Transient flushing or rash, drug fever between 37.5 °C and 38.0 °C (99.5 °F - 100.4 °F) taken orally	• Slow infusion rate by 50% and monitor patient for worsening of condition. Maximum infusion duration is 120 minutes.
Grade 2 Rash, flushing, urticaria, dyspnea, drug fever ≥ 38.0 °C (≥100.4 °F) taken orally	• Stop infusion; symptom control (diphenhydramine hydrochloride **1 mg/kg** (max 50 mg) IV, acetaminophen 10- 15 mg/kg (max 650 mg) for fever, and oxygen if needed). • Resume infusion at 50% of the prior rate once the reaction has decreased to ≤ Grade 1. Monitor patient for worsening condition. Maximum infusion duration is 120 minutes. • For subsequent dose, premedicate with diphenhydramine hydrochloride **1 mg/kg** (max 50 mg) IV. • If Grade 1-2 infusion reactions reoccur with subsequent dose, add dexamethasone **0.2 mg/kg** (max 10 mg) IV or equivalent to premedications above. (Only dose interruption/discontinuation, but not dose reduction, is required for allergic/infusional reactions.)
Grade 3 Symptomatic bronchospasm with or without urticaria, allergy-related edema/ angioedema, hypotension	• Stop infusion immediately. • Administer diphenhydramine hydrochloride **1 mg/kg** (max: 50 mg) IV, dexamethasone **0.2 mg/kg** (max: 10 mg) IV (or equivalent), bronchodilators for bronchospasms, and other medications as medically indicated. Hospital admission should be considered. • Discontinue ganitumab treatment permanently.
Grade 4 Anaphylaxis	• Stop infusion immediately • Administer diphenhydramine hydrochloride **1 mg/kg** (max 50 mg) IV, dexamethasone **0.2 mg/kg** (max 10 mg) IV (or equivalent), and other anaphylaxis medications as indicated. Epinephrine or bronchodilators should be administered as indicated. Hospital admission for observation may be indicated. • Discontinue ganitumab treatment permanently.

6.6.3 Ototoxicity

Given the rarity of baseline hearing loss and low risk of ototoxicity in the setting of IGF-1R inhibition, this protocol does not include serial audiograms. If a patient develops symptoms of ototoxicity, such as tinnitus or hearing loss, then an audiogram should be obtained. If Grade 3 or 4 hearing loss occurs, ganitumab should be held and not resumed without consultation with the Sponsor.

6.6.4 Cardiac Toxicity

The following ganitumab modifications will apply:

Asymptomatic decrease in the ejection fraction to < 50% / decrease in the left ventricular shortening fraction to < 27%: hold ganitumab, correct any existing electrolyte or micronutrient deficiencies, and repeat tests in 1 week. If abnormality persists after 1 week, discontinue ganitumab permanently. If abnormality resolves after 1 week, continue ganitumab at current dose. If ganitumab needs to be held more than once due to transient decreases in left ventricular systolic dysfunction, discontinue ganitumab permanently. Missed doses of ganitumab due to decreases in EF will not be made up.

Grade 3 (symptomatic) left ventricular systolic dysfunction: hold ganitumab and resume ganitumab only if symptoms resolve and LV/SF recover to ≥ 50% / 27% within 4 weeks. If Grade 3 toxicity recurs, discontinue ganitumab permanently.

Grade 4 left ventricular systolic dysfunction: discontinue ganitumab permanently.

6.6.5 Other Non-Hematologic Toxicities Associated with Ganitumab

For all other toxicities, the following dose modification guidelines should be followed:

Grade	Action
Grade 1	Continue ganitumab.
Grade 2	Continue ganitumab.
Grade 3	• Unlikely or unrelated to ganitumab: Continue ganitumab. Possibly, probably, or definitely related: Hold ganitumab until resolves to ≤ Grade 2. If toxicity resolves within 2 weeks of interruption, then resume ganitumab with a reduced dose of 12 mg/kg/dose.
Grade 4	• Unlikely or unrelated to ganitumab*: Hold ganitumab until resolves to ≤ Grade 2, then resume ganitumab at full dose. • Possibly, probably, or definitely related: Discontinue ganitumab.

*If Grade 4 toxicity is pre-existing or is specifically attributable to tumor, ganitumab should not be held. Examples include tumor-related pain, paralysis due to spinal cord compression, and blindness due to parameningeal tumor.

6.7 DASATINIB DOSE MODIFICATIONS FOR TOXICITY

6.7.1 For Daily Dosing

Current Dose (Daily)	Reduced Dose (Daily)	% Decrease
100 MG PER DOSE	70 MG PER DOSE	30
95 MG PER DOSE	65 MG PER DOSE	32
90 MG PER DOSE	65 MG PER DOSE	28
85 MG PER DOSE	60 MG PER DOSE	29
80 MG PER DOSE	55 MG PER DOSE	31
75 MG PER DOSE	50 MG PER DOSE	33
70 MG PER DOSE	50 MG PER DOSE	28
65 MG PER DOSE	45 MG PER DOSE	31
60 MG PER DOSE	40 MG PER DOSE	33
55 MG PER DOSE	40 MG PER DOSE	27
50 MG PER DOSE	35 MG PER DOSE	30
45 MG PER DOSE	30 MG PER DOSE	33
40 MG PER DOSE	40 MG PER DOSE ON M, W, TH, SAT, SUN	28
35 MG PER DOSE	25 MG PER DOSE	29
30 MG PER DOSE	20 MG PER DOSE	33
25 MG PER DOSE	20 MG PER DOSE ON M, TU, W, TH, F, SAT	31
20 MG PER DOSE	20 MG PER DOSE ON M, W, TH, SAT, SUN	28

6.7.2 For BID Dosing

Current Dose (BID)	Reduced Dose (BID)	% Decrease
70 MG PER DOSE	50 MG PER DOSE	28
65 MG PER DOSE	45 MG PER DOSE	31
60 MG PER DOSE	40 MG PER DOSE	33
55 MG PER DOSE	40 MG PER DOSE	27
50 MG PER DOSE	35 MG PER DOSE	30
45 MG PER DOSE	30 MG PER DOSE	33
40 MG PER DOSE	40 MG PER DOSE ON M, W, TH, SAT, SUN	28
35 MG PER DOSE	25 MG PER DOSE	29
30 MG PER DOSE	20 MG PER DOSE	33
25 MG PER DOSE	20 MG PER DOSE ON M, TU, W, TH, F, SAT	31
20 MG PER DOSE	20 MG PER DOSE ON M, W, TH, SAT, SUN	28

6.8 DOSING DELAYS

Missed doses of dasatinib will not be made up.

All efforts will be made to adhere to the ganitumab schedule. However, if patients are unable to receive ganitumab on the prescribed day due to reasons unrelated to study drug toxicity (eg. an inpatient hospitalization at an outside hospital for reasons unrelated to the study agents), the dose may be administered within a window of 72 hours prior to or after the scheduled date. The subsequent dose of ganitumab would be given per the original schedule.

Patients scheduled for elective radiotherapy of the lungs should hold ganitumab at least two months prior to radiation.

7 SPONSOR SAFETY REPORTING

7.1 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (section 7.1) and the characteristics of an observed AE (section 7.2) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

7.2 COMPREHENSIVE ADVERSE EVENTS AND POTENTIAL RISKS LIST(S) (CAEPRS)

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

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2937 patients.* Below is the CAEPR for Dasatinib (BMS-354825, Sprycel).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.7, September 10, 2018[1]

Adverse Events with Possible Relationship to Dasatinib (BMS-354825, Sprycel) (CTCAE 5.0 Term) [n= 2937]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 3)***
	Febrile neutropenia		
CARDIAC DISORDERS			
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction	
	Pericardial effusion		

Adverse Events with Possible Relationship to Dasatinib (BMS-354825, Sprycel) (CTCAE 5.0 Term) [n= 2937]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
GASTROINTESTINAL DISORDERS			
	Abdominal distension		
	Abdominal pain		***Abdominal pain (Gr 3)***
	Anal mucositis		
	Constipation		
Diarrhea			***Diarrhea (Gr 3)***
	Dyspepsia		
	Gastrointestinal hemorrhage[2]		
	Mucositis oral		
Nausea			***Nausea (Gr 3)***
	Rectal mucositis		
	Small intestinal mucositis		
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	General disorders and administration site conditions - Other (superficial edema)		***General disorders and administration site conditions - Other (superficial edema) (Gr 2)***
	Generalized edema		
	Non-cardiac chest pain		
	Pain		
INFECTIONS AND INFESTATIONS			
	Infection[3]		***Infection[3] (Gr 3)***
INVESTIGATIONS			
	Alanine aminotransferase increased		

Adverse Events with Possible Relationship to Dasatinib (BMS-354825, Sprycel) (CTCAE 5.0 Term) [n= 2937]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Aspartate aminotransferase increased		
		Electrocardiogram QT corrected interval prolonged	
Neutrophil count decreased			***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	Weight gain		
	Weight loss		
	White blood cell decreased		***White blood cell decreased (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Hypocalcemia		
	Hypokalemia		
	Hypophosphatemia		***Hypophosphatemia (Gr 3)***
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
		Growth suppression[4]	
		Musculoskeletal and connective tissue disorder - Other (epiphyses delayed fusion)[4]	
		Musculoskeletal and connective tissue disorder - Other (osteopenia)[4]	
Myalgia			***Myalgia (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		

Adverse Events with Possible Relationship to Dasatinib (BMS-354825, Sprycel) (CTCAE 5.0 Term) [n= 2937]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Headache			***Headache (Gr 3)***
		Intracranial hemorrhage	
		Leukoencephalopathy	
		Reversible posterior leukoencephalopathy syndrome	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
		Gynecomastia[4]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
Dyspnea			***Dyspnea (Gr 3)***
	Laryngeal mucositis		
	Pharyngeal mucositis		
Pleural effusion			***Pleural effusion (Gr 3)***
	Pneumonitis		
		Pulmonary hypertension	
	Tracheal mucositis		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
		Erythema multiforme	
	Pruritus		
	Rash acneiform		
Rash maculo-papular			***Rash maculo-papular (Gr 2)***
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	
VASCULAR DISORDERS			
	Flushing		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be

obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

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

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

[4]Effects on growth and development have been observed in pediatric patients and may include epiphyses delayed fusion, osteopenia, growth retardation, and gynecomastia.

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

Adverse events reported on Dasatinib (BMS-354825, Sprycel) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Dasatinib (BMS-354825, Sprycel) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia)

CARDIAC DISORDERS - 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; Dry eye; Eye disorders - Other (optic nerve neuritis); Periorbital edema

GASTROINTESTINAL DISORDERS - Anal fissure; Ascites; Colitis; Dry mouth; Dysphagia; Esophagitis; Flatulence; Gastritis; Gastrointestinal disorders - Other (enteritis); Gastrointestinal disorders - Other (oral soft tissue disorder); Gastrointestinal disorders - Other (tongue eruption); Gastrointestinal ulcer[5]; 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

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising

INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; Cardiac troponin T increased; CD4 lymphocytes decreased; CPK increased; Creatinine increased; Electrocardiogram T wave abnormal; GGT increased; Investigations - Other (bone densitometry); 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; Muscle cramp; Musculoskeletal and connective tissue disorder - Other (muscle stiffness); Musculoskeletal and connective tissue disorder - Other (nuchal rigidity); Musculoskeletal and connective tissue disorder - Other (tendonitis); Myositis; Osteoporosis; Pain in extremity; Rhabdomyolysis

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

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

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

RENAL AND URINARY DISORDERS - Acute kidney injury; Proteinuria; Urinary frequency

REPRODUCTIVE SYSTEM AND BREAST DISORDERS – Irregular menstruation

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

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

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

Note: Dasatinib (BMS-354825, Sprycel) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.2.2 Comprehensive Adverse Events and Potential Risks list (CAEPR) **for Ganitumab (AMG 479, NSC 750008)**

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 334 patients.* Below is the CAEPR for Ganitumab (AMG 479).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.1, March 26, 2019[1]

Adverse Events with Possible Relationship to Ganitumab (AMG 479) (CTCAE 5.0 Term) [n= 334]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
EAR AND LABYRINTH DISORDERS			
		Hearing impaired[2]	
GASTROINTESTINAL DISORDERS			
	Diarrhea		***Diarrhea (Gr 2)***
	Nausea		***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***

Adverse Events with Possible Relationship to Ganitumab (AMG 479) (CTCAE 5.0 Term) [n= 334]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
Infusion related reaction[3]			***Infusion related reaction[3] (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	Lymphocyte count decreased		
	Neutrophil count decreased		***Neutrophil count decreased (Gr 3)***
	Platelet count decreased		***Platelet count decreased (Gr 3)***
	White blood cell decreased		***White blood cell decreased (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			

Adverse Events with Possible Relationship to Ganitumab (AMG 479) (CTCAE 5.0 Term) [n= 334]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Anorexia		***Anorexia (Gr 2)***
Hyperglycemia			***Hyperglycemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Myalgia		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Pneumonitis[4]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash[5]		***Rash[5] (Gr 2)***

[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]Middle to high range sensorineural hearing loss has been reported in patients treated with monoclonal antibodies to Insulin-like Growth Factor-1 Receptor (IGF-1R).

[3]Infusional reactions may include chills, fever, hypotension, dyspnea, arthralgia, joint swelling, headache, dizziness, and cardiac arrhythmia (e.g., atrial fibrillation, tachycardia).

[4]The rate and severity of radiation-associated pneumonitis may be increased in patients who receive ganitumab shortly before or after radiation to the lungs.

[5]Rash includes rash, rash acneiform, rash maculo-papular, skin lesions, and pruritus.

Adverse events reported on ganitumab (AMG 479) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that ganitumab (AMG 479) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Febrile neutropenia

CARDIAC DISORDERS - Atrial fibrillation; Cardiac disorders - Other (diastolic dysfunction); Heart failure; Myocardial infarction

ENDOCRINE DISORDERS - Hypothyroidism

EYE DISORDERS - Cataract; Keratitis

GASTROINTESTINAL DISORDERS - Abdominal pain; Anal fistula; Anal mucositis; Constipation; Dysphagia; Esophagitis; Gastrointestinal disorders - Other (enteritis); Mucositis oral; Oral pain; Pancreatitis; Rectal fistula; Rectal hemorrhage; Small intestinal obstruction; Typhlitis

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Malaise; Non-cardiac chest pain; Pain

HEPATOBILIARY DISORDERS - Hepatobiliary disorders - Other (hepatic function abnormal); Hepatobiliary disorders - Other (jaundice cholestatic)

INFECTIONS AND INFESTATIONS - Anorectal infections; Infections and infestations - Other (pneumococcal infection); Lung infection; Myelitis; Sepsis; Skin infection; Soft tissue infection; Urinary tract infection

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Vascular access complication

INVESTIGATIONS - Alkaline phosphatase increased; Creatinine increased; Ejection fraction decreased; Investigations - Other (electrocardiogram abnormal); Weight loss

METABOLISM AND NUTRITION DISORDERS - Acidosis; Dehydration; Hyperkalemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Bone pain; Generalized muscle weakness

NERVOUS SYSTEM DISORDERS - Radiculitis; Reversible posterior leukoencephalopathy syndrome; Seizure; Stroke; Syncope; Transient ischemic attacks; Tremor

PSYCHIATRIC DISORDERS - Agitation

RENAL AND URINARY DISORDERS - Acute kidney injury; Urinary tract obstruction

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Cough; Epistaxis; Hypoxia; Pleural effusion; Respiratory, thoracic and mediastinal disorders - Other (respiratory hemorrhage)

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Palmar-plantar erythrodysesthesia syndrome; Skin ulceration

VASCULAR DISORDERS - Hematoma; Hypertension; Thromboembolic event (venous)

Note: Ganitumab (AMG 479) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.3 ADVERSE EVENT CHARACTERISTICS

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**

  AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, section **7.1.1**) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.4 EXPEDITED ADVERSE EVENT REPORTING

7.4.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

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

7.4.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating

physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

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

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

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

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

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

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

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

Effective Date: May 5, 2011

7.5 ROUTINE ADVERSE EVENT REPORTING

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must <u>also</u> be reported in routine study data submissions.**

7.5.1 Protocol Specific Additional Instructions and Reporting Exceptions

CTEP-AERS 24-hour Notification is required for ≥ Grade 2 pneumonitis.

7.6 SECONDARY MALIGNANCY

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

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

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

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

7.7 SECOND MALIGNANCY

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

8 NIH INTRAMURAL RESEARCH REPORTING

8.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found here.

8.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING/IRB REPORTING

8.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found here. Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

8.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found here.

8.3 NCI CLINICAL DIRECTOR REPORTING (FOR NCI SITE ONLY)

Problems expeditiously reported to the OHSRP/IRB in iRIS will also be reported to the NCI Clinical Director. A separate submission is not necessary as reports in iRIS will be available to the Clinical Director.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email to the Clinical Director unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to Dr. Dahut at NCICCRQA@mail.nih.gov within one business day of learning of the death.

8.4 NCI GUIDANCE FOR REPORTING EXPEDITED ADVERSE EVENTS FOR MULTI-CENTER TRIALS

Report events to the Reviewing IRB as per its policy. Please also notify the coordinating center PI and study coordinator of your submission at the time you make it.

9 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 GENOMICS, TRANSCRIPTOMICS AND PROTEOMICS MOLECULAR ANALYSIS

Proteomic, genomic and transcriptomic molecular profiling will be conducted by NantOmics.

Proteomic molecular profiling is mandatory for study participation. Patients will be strongly encouraged to participate in genomic and transcriptomic molecular profiling under POB protocol 10-C-0086, Comprehensive Omics Analysis of Pediatric Solid Tumors and Establishment of a Repository for Related Biological Studies. CHLA patients will be given the option to enroll remotely on 10-C-0086 at the time of their enrollment on this study. They will be contacted by an NCI investigator to discuss participation. Only patients who consent to 10-C-0086 will have tumor tissue and whole blood samples collected and sent to NantOmics for genomic and transcriptomic analysis. If patients do NOT consent to genomic and transcriptomic molecular

profiling under protocol 10-C-0086, their samples will be sent to NantOmics for proteomic analysis only.

Collection of FFPE tumor tissue and whole blood at screening/baseline is preferred for the molecular analysis. In the event the tissue cannot be collected at screening/baseline, a historic FFPE tissue block of the specimen taken ≤ 6 months from the date of the screening visit is the second preferred option. In the event this is not available, an archival tissue may be used.

In the event that there is not sufficient tissue to perform all desired analyses, priority will be given to performing NantOmics proteomics first, followed by NantOmics genomics and transcriptomics, followed by NCI protocol 10-C-0086 exploratory studies.

9.1.1 Rationale

Genomic sequencing of tumor cells relative to non-tumor cells from whole blood will be profiled to identify the genomic variances that may contribute to response or disease progression and provide an understanding of molecular abnormalities. RNA sequencing will be conducted to provide expression data and give relevance to DNA mutations. Quantitative proteomics will be conducted to determine the exact amounts of specific proteins and to confirm expression of genes that are correlative of response and disease progression. All genomic, transcriptomic, and proteomic molecular analysis will be retrospective.

9.1.2 Sampling

Genomics and proteomics molecular profiling will be performed on formalin-fixed, paraffin embedded (FFPE) tumor tissue and whole blood (subject matched normal comparator against the tumor tissue) by next-generation sequencing and mass spectrometry-based quantitative proteomics.

9.1.3 Sampling Times

9.1.3.1 Archival Tumor Tissue

Tumor tissues and whole blood will be obtained at baseline.

9.1.3.2 Biopsies

In consenting participants (when biopsies can be performed safely without additional risk of morbidity), biopsies will be performed to explore mechanisms of response, and resistance will be assessed by analyzing biopsy tissue expression of IGF-1R, insulin receptor, IGF-2, and phospho-YES, and through genomic and proteomic analysis. Optional biopsies will be taken at enrollment, during week 1 of treatment and at the time of progression. Biopsies will be formalin-fixed and paraffin embedded.

Specimens will be batched and performed retrospectively.

9.1.4 General Information for Collection of Tumor Tissues and Whole Blood

Tumor tissue and whole blood samples are to be collected according to the NantOmics Sample Collection Manual, or instruction cards included in the Tissue Specimen Kit and Blood Specimen Kit. The kits include the materials necessary to collect and ship FFPE tumor tissue samples and whole blood samples.

NCI investigators are responsible for obtaining the subject's written Informed Consent Form for genomic and transcriptomic analysis (on protocol 10-C-0086); the NCI investigators are to confirm that the written informed consent was obtained before submitting genomic samples.

The investigational site(s) are responsible for completing the protocol # 10003 Clinical Trial Requisition Form with the following information:

- Clinical Site Information
- Patient Information
- Specimen Information
- Specimen Collection Information

The investigational site(s) will return a hard copy of the completed Clinical Trial Requisition Form with the kit shipment per the instructions provided on the form. An electronic copy of this form may be downloaded from the study portal (NantOmics).

Fresh biopsies will be formalin-fixed and paraffin-embedded for molecular profiling. Detailed specimen requirements and procedural instructions for FFPE tumor tissue samples and whole blood samples are provided in the CTEP #10003 NantOmics Sample Collection Manual.

9.1.5 Genomic and Proteomic Analysis of Tumor Tissue and Whole Blood

A single FFPE tumor tissue block is preferred for the extraction of tumor DNA, tumor RNA, and tumor protein (see **Table 1** below). A whole blood sample is required for the extraction of subject normal DNA. Refer to the NantOmics Sample Collection Manual for details. Tumor tissue and whole blood will be processed in the NantOmics, LLC CLIA-registered and CAP accredited/CLIA certified laboratories.

Table 1: Schedule of Collection for Molecular Profiling

Molecular Profiling	**Baseline**
Whole blood (normal comparator against tumor)	
1 PAXgene Blood DNA tube (2.5 mL)[a]	✓
Formalin-fixed, paraffin-embedded tumor tissue block[b]	
A minimum tissue surface area of 25 mm^2, 75 µm thick, with at least 30% malignant tissue	✓

[a] Whole blood to be collected at baseline only for genomic sequencing. Requires 2.5 mL of subject's whole blood in 1 PAXgene Blood DNA tube, provided in the Blood Specimen Kit (see CTEP #10003 NantOmics Sample Collection Manual).

[b] FFPE tissue blocks to be collected at baseline for genomic sequencing, RNAseq, and proteomic analysis. A single block meeting the minimum requirements for genomics and proteomics is required. FFPE tissue blocks to be collected per local pathology laboratory procedures; detailed specimen and procedural instructions are provided in the CTEP #10003 NantOmics Sample Collection Manual.

9.1.6 Genomic and Proteomic Analysis Results

The individual subject's summary report of cancer-related genomic and proteomic data can be provided to the investigator upon request after the individual subject has completed or discontinued the clinical study. Procedural instructions for requesting the cancer-related genomic and proteomic summary report are provided in the CTEP #10003 NantOmics Sample Collection Manual.

9.2 BIOMARKER STUDIES

From the whole-genome sequencing, RNA transcriptomic, and quantitative proteomic profiling, evaluation of biomarkers in tumors and blood samples will include but will not be limited to the following biomarkers:

Biomarker Name[a] AND Lead PI and Site	**Assay (CLIA: Y/N)**	**Use (Integral, Integrated, or Exploratory) AND Purpose [b]**	**Tissue/Body Fluid Tested and Timing of Assay**	**M/O**	**Funding Source(s) [c]**
IGF-1R expression NantOmics	Targeted MS: IGF- 1R CLIA: Y	Exploratory Response assessment	Archival tumor tissue At enrollment	M	NCI/POB
IGF-1R expression NantOmics	Targeted MS: IGF- 1R CLIA: Y	Exploratory Response assessment	Biopsied tumor tissue At enrollment, during week 1 of treatment, and at progression	O	NCI/POB
Insulin receptor expression NantOmics	Targeted MS: IR CLIA: N	Exploratory Response assessment	Archival tumor tissue At enrollment	M	NCI/POB
Insulin receptor expression NantOmics	Targeted MS: IR CLIA: N	Exploratory Response assessment	Biopsied tumor tissue At enrollment, during week 1 of treatment, and at progression	O	NCI/POB
IGF-2 expression NantOmics	Targeted MS: IGF-2 CLIA: N	Exploratory Response assessment	Archival tumor tissue At enrollment	M	NCI/POB
IGF-2 expression NantOmics	Targeted MS: IGF-2 CLIA: N	Exploratory Response assessment	Biopsied tumor tissue At enrollment, during week 1 of treatment, and at progression	O	NCI/POB

Biomarker Name[a] **AND Lead PI and Site**	**Assay** **(CLIA: Y/N)**	**Use (Integral, Integrated, or Exploratory) AND Purpose [b]**	**Tissue/Body Fluid Tested** **and Timing of Assay**	**M/O**	**Funding Source(s) [c]**
Phospho-YES expression NantOmics	Targeted MS: pSFK CLIA: N	Exploratory Response assessment	Archival tumor tissue At enrollment	M	NCI/POB
Phospho-YES expression NantOmics	Targeted MS: pSFK CLIA: N	Exploratory Response assessment	Biopsied tumor tissue At enrollment, during week 1 of treatment, and at progression	O	NCI/POB

The following exploratory biomarker studies will be conducted on archival tissue obtained at the time of enrollment.

1. IGF-1R expression
2. Insulin receptor expression
3. IGF-2 expression
4. Phospho-YES expression

In consenting participants when biopsies can be performed safely without additional risk of morbidity, biopsies will be performed to explore mechanisms of response, and resistance will be assessed by analyzing biopsy tissue expression of IGF-1R, insulin receptor, IGF-2 expression and phospho-YES expression, and through genomic sequencing. Biopsies will be taken at enrollment, during week 1 of treatment and at the time of progression.

Specimens will be batched and performed retrospectively.

9.2.1 Proteomics

There are two key components to the quantitative proteomics approach, which allows for the quantitation of targeted proteins from formalin-fixed paraffin-embedded (FFPE) tumor biopsies.

Liquid Tissue® (LT) Technology

NantOmics uses a proprietary non-contact method of laser microdissection that isolates and collects only the tumor cells of interest for analysis. The accuracy and precision of microdissection ensures that the collected sample is highly enriched for active tumor cells, limiting the presence of necrotic, stromal, or normal cells. The microdissected FFPE tumor tissue is then subjected to Liquid Tissue® processing to solubilize the tumor tissues. The patented Liquid Tissue® technology ensures that formalin cross-links are reversed and all of the proteins in the tumor tissue are solubilized.

Mass Spectrometry-based Selected Reaction Monitoring (SRM) Technology

The solubilized tumor tissue is then subjected to multiplexed SRM analysis using stable isotope-labeled internal standard peptides for accurate quantitation. Quantitative mass spectrometry

represents an emerging clinical method, which is highly specific, reproducible, objectively quantitative, and has reduced sensitivity to pre-analytical variation. In addition, mass spectrometry-based proteomic analysis of FFPE tissue is capable of multiplexing analysis of up to 100 analytes from a small amount of tissue.

9.2.1.1 Sample requirements for proteomics analyses

Refer to NantOmics Sample Collection manual for sample requirements and collection instructions.

Ship samples and the Requisition form, as outlined in the NantOmics Sample Collection manual, to:

NantOmics
Attention: Sample Receipt
9600 Medical Center Drive
Suite 300
Rockville, MD 20850
USA

9.3 SAMPLE STORAGE, TRACKING AND DISPOSITION

Blood and tissue collected during the course of this study will follow NIH guidelines for the research use of human samples and OHSRP Issues to Consider in the Research Use of Stored Data or Tissues. At the NIH Clinical Center, samples will be ordered and tracked in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without IRB notification and an executed MTA.

All tumor samples obtained for research, not directly transported for study analysis, will be transported to Dr. Figg's laboratory to be barcoded. Dr. Figg's laboratory will need the patient's Medical Record Number, name, protocol, date, time, and site of tissue, and a description of the type of tissue (normal versus tumor) to issue a label for the sample.

Please e-mail Dr. Figg's lab at NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact Dr. Figg's lab at NCIBloodcore@mail.nih.gov.

All samples sent to the Blood Processing Core (BPC) will be barcoded, with data entered and stored in the LABrador (aka LabSamples) utilized by the BPC. This is a secure program, with access to LABrador limited to defined Figg lab personnel, who are issued individual user accounts. Installation of LABrador is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen. All Figg lab personnel with access to patient information annually complete the NIH online Protection of Human Subjects course.

LABrador creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without LABrador access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

9.3.1 Sample Storage and Destruction

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80°C according to stability requirements. These freezers are located onsite in the BPC and offsite at NCI Frederick Central Repository Services in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in LABrador (aka LabSamples). All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the BPC. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If, at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested).

Sample barcodes are linked to patient demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the LABrador (aka LabSamples). It is critical that the sample remains linked to patient information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate results with these variables.

If the patient withdraws consent the participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of section **8.2**.

9.4 SAMPLES FOR GENETIC/GENOMIC TESTING

Subjects on this study will be asked to co-enroll on 10-C-0086: Comprehensive Omics Analysis of Pediatric Solid Tumors and Establishment of a Repository for Related Biological Studies. Patients who consent to participate in 10-C-0086 will undergo blood sampling at baseline and prior to each cycle as detailed in the study calendar, as well as genomic analysis as described below.

This companion protocol may include the following analyses: analysis for mutations or Single Nucleotide Variants (SNVs) in tumors and germline DNA, comparative genomics hybridization, whole genome, exome, and transcriptome sequencing of tumor and germline DNA, messenger and microRNA sequencing and expression analysis, epigenetic studies including whole methylome analysis using next generation sequencing, metabolomics study of tumor, global mass spectroscopy-based protein and phospho-protein analysis.

In addition, NantOmics will run Genomic analysis.

9.4.1 Sequencing

1. Whole Genome Sequencing (WGS) will be done at average depth of 30x for normal samples, and an average depth of 60x for tumor samples. RNA sequencing (RNA-Seq) will be performed on tumor samples to obtain approximately 240 million reads across two technical replicates to assure reproducibility.
2. NantOmics lab has experience sequencing tumor DNA extracted from formalin-fixed, paraffin embedded (FFPE) blocks and slides, fresh frozen tissue, and purified DNA. The FFPE failure rate is approximately 10%, with most failures occurring when the blocks provided have little to no tumor content remaining. NantOmics requests matched normal sample of all patients, and can handle multiple sample types including whole blood, saliva, buccal swabs, and purified DNA.
3. Using standard methods, sequencing reads are aligned and duplicate marked, followed by indel realignment and base quality recalibration. NantOmics cancer analytical pipeline takes tumor and matched-normal alignments (BAM format) to call point mutations, small indels, copy number and allele fraction, and structural variants at all scales. Filtering is performed on all variants to reduce false positives while being permissive enough to avoid removing variants of interest. Copy number and allele fraction are integrated to determine regions that exhibit similar copy number and allelic bias, e.g. necessary to discover regions of copy neutral loss-of-heterozygosity (CN-LOH) located inside a region of normal copy number. Using these relative copy number estimates and allele fraction, NantOmics estimates tumor purity and ploidy, and use that to inform more accurate copy number estimates and mutation clonality. They perform local assembly using both unmapped and mapped reads aligned near each putative structural variant to precisely locate (base precision) where the structural variant occurred in the tumor genome. All variants identified are annotated for any effect they may have to gene(s) or their isoforms.

9.4.2 Sample requirements for genomics analyses

9.4.2.1 Tumor tissue

Refer to NantOmics Sample Collection manual for sample requirements and collection instructions and **Appendix 9** if sending samples from a participating site.

9.4.2.2 Blood sample

Refer to NantOmics Sample Collection manual for sample requirements and collection instructions and **Appendix 9** if sending samples from a participating site.

10 STUDY CALENDAR

Baseline evaluations, including cardiac studies, are to be conducted within 1 week prior to start of protocol therapy. Imaging studies of disease must be done ≤4 weeks prior to the start of therapy.

For labs indicating a specific day to be drawn (for example, day 14), labs may be drawn on the day indicated in the table, or up to 2 days earlier.

STUDIES TO BE OBTAINED	Screening	Baseline	During Cycle 1	During Subsequent Cycles	At End of Therapy[1]	Off Therapy[11]
History, physical exam[a], vital signs, including oxygen saturation	X	X	Weekly starting from day -7	At days 0 and 14 of each subsequent cycle	X	Monthly
Tanner stage	X	X		Only if change from baseline	X	
Height, weight, BSA	X	X		At start of each subsequent cycle	X	
Performance Status[2]	X	X		Only if change from baseline	X	
CBC, differential, platelets[3]	X	X	Weekly starting from day -7	Weekly for cycles 2 and 3, then every other week thereafter	X	Monthly
BUN, creatinine, sodium, potassium, chloride, CO2, calcium, magnesium, phosphorus, uric acid, LDH	X	X	Weekly starting from day -7	Prior to each subsequent cycle	X	Monthly
Serum glucose[4]	X	X	Weekly starting from day -7	Weekly for cycles 2 and 3, then every other week thereafter	X	Monthly
HgbA1C[5]	X	X	As indicated[5]	As indicated[5]	As indicated[5]	

STUDIES TO BE OBTAINED	Screening	Baseline	During Cycle 1	During Subsequent Cycles	At End of Therapy[1]	Off Therapy[11]
Hepatic panel: Alkaline phosphatase, ALT, AST, Total bilirubin (Direct bilirubin if total is elevated)	X	X	Weekly starting from day -7	Prior to each subsequent cycle	X	Monthly
Total protein, albumin	X	X	Weekly starting from day -7	Prior to each subsequent cycle	X	Monthly
Fasting triglycerides, Cholesterol (Total, HDL, and LDL)	X	X		Prior to each subsequent cycle	X	Monthly
Urinalysis	X	X	Weekly starting from day -7	Prior to each subsequent cycle	X	Monthly
PT, INR (in patients undergoing biopsy)	X	X	Within 24 hours prior to biopsy		Within 24 hours prior to biopsy	
EKG	X	X		Prior to each subsequent cycle		Monthly
Echocardiogram	X	X		Prior to cycle 2,3,5,7 etc.		Monthly
Disease Evaluation[6]	X	X		Prior to cycle 3, 5, 7, etc.	X	Every 2 months
Pregnancy Test[7]	X	X		Prior to each subsequent cycle		
Unstained slides or block (required at study entry)	X	X				
Molecular Profiling (see section **9.1.5**)		X				
Research Blood (10 cc EDTA or Streck tube if at NIH)[8]		X		Prior to each subsequent cycle		
Research Blood (10 cc Cell-Free DNA BCT		X		Prior to each subsequent cycle		

STUDIES TO BE OBTAINED	Screening	Baseline	During Cycle 1	During Subsequent Cycles	At End of Therapy[1]	Off Therapy[11]
tube if outside NIH)[9]						
Optional Biopsy[10]		X	During week 1		X	
NIH Advance Directives Form[12]		X				

[1] Should be performed, if possible, when the patient comes off treatment regardless of the reason.
[2]**Appendix 1**; prior to cycle 1 and then only required to be recorded if there is a change in performance status during the study.
[3] If patients develop Grade 4 neutropenia then CBC should be checked every 3 to 4 days until recovery to grade 3.
[4]Also obtain for symptoms of polyuria or polydipsia or as otherwise clinically indicated.
[5]HgbA1C should be obtained at baseline and if the patient develops hyperglycemia requiring treatment and then every 3 months until hyperglycemia resolves and treatment is no longer required.
[6] Imaging studies of each site of disease with appropriate modality.
[7] Patients of childbearing potential require a negative pregnancy test prior to starting treatment and must use an acceptable method of birth control. Abstinence is an acceptable method of birth control.
[8]Only perform in patients consented to 10-C-0086 (Omics). Deliver immediately to Donna Bernstein.
[9] Only perform in patients consented to 10-C-0086 (Omics). Ship immediately to Donna Bernstein per guidelines in **Appendix 9**.
[10]Should be performed at end of therapy only if patient comes off treatment due to progression.
[11]Off-therapy studies are required only for patients who are removed by the PI due to drug toxicity or side effects. All patients will be followed for at least 30 days after the last dose of investigational agents and until disease progression, whichever is last.
[12]As indicated in section **15.3**, all subjects enrolled at NIH and ≥ age 18 will be offered the opportunity to complete an NIH advance directives form. This should be done preferably at baseline but can be done at any time during the study as long as the capacity to do so is retained. The completion of the form is strongly recommended, but is not required.
[a] A complete standard physical examination will be performed at baseline; subsequent physical exams will be targeted based on signs and symptoms of presenting patient.

11 MEASUREMENT OF EFFECT

11.1 RESPONSE CRITERIA

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).[70] Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with dasatinib and ganitumab.

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded

and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all

scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published.[71-73] In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.[74]

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-

PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.				

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

11.1.5 Duration of Response

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

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

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

11.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

12 STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7 (Adverse Events: List and Reporting Requirements).

12.1 STUDY OVERSIGHT

This protocol is monitored at several levels, as described elsewhere in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

For a Phase 1/2 trial, enrollment to the Phase 2 portion of the trial will not begin until a protocol amendment has been submitted which summarizes the Phase 1 results, the recommended Phase 2 dose, and the rationale for selecting it. The amendment must be reviewed and approved by CTEP before enrollment to the Phase 2 portion can begin.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave..

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in section **8.2**.

12.2 DATA REPORTING

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (check at https://ctepcore.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Rave Read-Only, Rave CRA (Lab Admin), Rave SLA or Rave Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or Rave CRA (Lab Admin) role, the user must hold a minimum of an AP registration type. To hold the Rave Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin)

using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

12.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted on an 18-36 months basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 Responsibility for Data Submission

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

An End of Study CRF is to be completed by the PI, and is to include a summary of study endpoints not otherwise captured in the database, such as (for phase 1 trials) the recommended phase 2 dose (RP2D) and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-

semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

12.3 DATA SHARING PLANS

12.3.1 Human Data Sharing Plan

What data will be shared?

I will share human data generated in this research for future research as follows:

- Coded, linked data in an NIH-funded or approved public repository.
- Coded, linked data in BTRIS (automatic for activities in the Clinical Center)
- Identified or coded, linked data with approved outside collaborators under appropriate agreements.

How and where will the data be shared?

Data will be shared through:

- An NIH-funded or approved public repository: clinicaltrials.gov.
- BTRIS (automatic for activities in the Clinical Center)
- Approved outside collaborators under appropriate individual agreements.
- Publication and/or public presentations.

When will the data be shared?

- Before publication.
- At the time of publication or shortly thereafter.

12.3.2 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases according to the plan described in protocol 10-C-0086 in compliance with the NIH Genomic Data Sharing Policy.

13 STATISTICAL CONSIDERATIONS

13.1 PHASE I

The primary objective of the phase I component of this study is to determine the safe dose of dasatinib when given with ganitumab in patients with relapsed or refractory embryonal or alveolar RMS. This trial uses a limited dose-escalation design to establish the MTD, or highest safe dose of dasatinib. The starting dose level will be 60 mg/m^2 once daily (maximum dose of 100 mg/dose once daily) on days -7 through day 27 during cycle 1 (35 days), and then days 0-27 for subsequent cycles (28 day cycles). This will be followed by one dose escalation to 60 mg/m^2 BID (maximum dose of 70 mg/dose BID) on days -7 through day 27 during cycle 1, and then days 0-27 for subsequent cycles. The MTD is defined as the dose level immediately below the level at which ≥33% of patients in a cohort experience a DLT. The MTD will be defined based on toxicities observed during the first treatment cycle in order to capture toxicities during 28 days of administration of both agents. Any patient who receives one or more doses and experiences a DLT will be considered evaluable for definition of the MTD. If a patient did not experience DLT and did not finish treatment in cycle 1, he or she will only be evaluable for the dose escalation portion of the study if they received both ganitumab doses and ≥85% of the dasatinib doses in cycle 1. Patients who have not met these criteria will be replaced in the dose level. If ≥2 out of a maximum of 6 patients experience DLT at dose Level 1, the dose of dasatinib will be de-escalated to dose Level -1. If 0-1 out of a maximum of 6 patients have DLT at dose Level -1, this will be considered the MTD. If 2 or more out of a maximum of 6 patients experience DLT at dose Level -1, the accrual will be suspended pending discussions with the Sponsor and NIH Intramural IRB regarding how to proceed with the combination therapy. Dose escalation and de-escalation rules are specified in section **5.1.1**. Patients who receive dasatinib at the MTD (or highest safe dose) and ganitumab during the phase I portion of the study will be included in the evaluation of the phase II objectives.

Toxicities related to the combination therapy will be analyzed and reported descriptively

13.2 PHASE II

The primary objective of the phase II component of the trial is to determine if the use of ganitumab plus dasatinib is able to be associated with a modest fraction of patients who experience an objective clinical response (CR or PR) by RECIST. In addition, a second primary objective will estimate the fraction that is without progression at 4 months and, secondarily, to be able to obtain an approximate estimate of the progression free survival (PFS) of the patients.

The phase II component of the trial will be conducted using a single stage design with 16 evaluable patients. With this number, there would be 90% power to rule out a 5% fraction with a clinical response in favor of a 30% fraction with a clinical response, using a one sided 0.10 significance level exact test for a binomial proportion. In practice, the fraction of the 16 patients that have objective responses will be determined and reported along with 80% and 95% confidence intervals. If there are 3 objective responses in 16 evaluable patients, the lower one-sided exact 90% confidence interval is 7.1%, thus ruling out 5%.

Because the staging evaluations for this trial will take place at approximately 8 week intervals and patients typically progress very rapidly, a Kaplan-Meier curve may potentially be somewhat

imprecise with respect to its presentation of PFS, especially at early time points. Thus, the determination of progression or not at the 4-month evaluation will be the preferred co- primary endpoint for the trial rather than PFS. The information obtained on PFS as well as 4 month progression or not will be reported and considered for use in interpreting the results of this study and may be used to guide any subsequent evaluations.

This study will also address a set of secondary and exploratory objectives.

With the understanding of it limitations, in addition to determining the fraction that are without progression by 4 months, a Kaplan-Meier curve will be constructed as a secondary outcome to at least approximately illustrate the PFS as a function of time, recognizing the limited opportunities to assess the actual time of progression relative to an anticipated rapid progression time.

Toxicities related to the combination therapy will be analyzed and reported descriptively by dose level, grade and attribution.

In all patients, mechanisms of response and resistance will be assessed by analyzing archival tissue for expression of IGF-1R, insulin receptor, IGF-2 expression and phospho-YES expression, and through genomic sequencing (in patients participating in 10-C-0086). In patients for whom tumor biopsies can be obtained successfully, mechanisms of response and resistance will be assessed by analyzing biopsy tissue expression of IGF-1R, insulin receptor, IGF-2 expression and phospho-YES expression, and through genomic sequencing (in patients participating in 10-C-0086).

13.3 SAMPLE SIZE/ACCRUAL RATE

The phase I portion of the study may enroll up to 12 subjects to establish MTD or highest safe dose. Sixteen evaluable patients are required to evaluate the objectives in the phase II component. Up to 6 patients from the phase I component who receive study drugs at the MTD or highest safe dose will be included in the analysis of the 16 patients in the phase II component. Therefore, the maximum patient accrual, allowing for replacement of inevaluable patients (up to 4) as well as to account for screen failures (up to 14), is expected to be 12 + 10 + 4+14, for a total enrollment of 40 patients.

It is anticipated that approximately 10-15 patients per year may be accrued onto this trial. Thus, 2 to 3 years is expected to completed accrual. If the actual accrual is slower, we would consider opening the trial at additional sites to improve the accrual rate.

14 COLLABORATIVE AGREEMENTS

14.1 CTEP COLLABORATIVE AGREEMENT (CRADA, CTA, CSA)

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in

addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

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

14.2 MULTI-INSTITUTIONAL GUIDELINES

14.2.1 IRB Approvals

The PI will provide the NIH Intramural IRB with a copy of the participating institution's approved yearly continuing review. Registration will be halted at any participating institution in which a current continuing approval is not on file at the NIH Intramural IRB.

14.2.2 Amendments and Consents

The CCR PI will provide the NIH Intramural IRB with copies of all amendments, consents and approvals from each participating institution.

15 HUMAN SUBJECTS PROTECTIONS

15.1 RATIONALE FOR SUBJECT SELECTION

Subjects of both genders and from all racial and ethnic groups are eligible for this trial if they meet the eligibility criteria outlined in section **3.1**. No groups are being excluded from participation in the trial. Efforts will be made to extend the accrual to a representative population, but in a small pilot trial which will accrue a maximum of 16 patients, a balance must be struck between the need to evaluate safety and efficacy, and the need to explore gender, racial, and ethnic aspects of clinical research. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

Projected accrual table:

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	

DOMESTIC PLANNED ENROLLMENT REPORT					
American Indian/ Alaska Native	0	1			1
Asian	1	2			3
Native Hawaiian or Other Pacific Islander	0	0			0
Black or African American	4	6			10
White	8	13	2	3	26
More Than One Race	0	0	0	0	0
Total	13	22	2	3	40

15.2 PARTICIPATION OF CHILDREN

There is no limit to the age of participants in this trial. Children who meet eligibility criteria for this trial will be offered entry in the study. Children will be evaluated and cared for by physicians trained in pediatrics and pediatric oncology, and will be followed in a Pediatric Oncology clinic. The clinical and research staff in the Pediatric Oncology Branch and CHLA have extensive experience caring for patients of younger ages in administering complex research therapies.

15.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT (NIH CCR ONLY—PARTICIPATING SITES SHOULD FOLLOW THEIR INSTITUTIONAL POLICY)

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section **15.4**), all subjects enrolled at NIH who are ≥ age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation as needed for the following: an independent assessment of whether an individual has

the capacity to provide consent; assistance in identifying and assessing an appropriate surrogate when indicated; and/or an assessment of the capacity to appoint a surrogate. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in NIH HRPP SOP 14E for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

15.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

The primary risk to patients, including adults who may lose their ability to consent, participating in this research study is from toxicities related to the investigational agents (ganitumab and dasatinib) as described in the protocol, section 7. The primary objective of this study is to determine if the use of ganitumab plus dasatinib is able to be associated with a modest fraction of patients who experience an objective clinical response (CR and PR) as defined by RECIST criteria. In addition, a second primary objective will estimate the fraction that is without progression at 4 months. Patients will thus be treated with therapeutic intent and response to the therapy will be closely monitored. Treatment options for these patients are very limited, as most patients will have received all prior effective therapies. The potential benefits from this therapy are disease stabilization, tumor shrinkage, and a reduction in symptoms caused by rhabdomyosarcoma. Therefore, this protocol involves greater than minimal risk to the patients entered, but presents the potential for direct benefit to individual subjects.

Pediatric patients: This trial will be open to children under 18 years of age. Given the potential for clinical benefit, participation of children in this study meets 45 CFR 46.405- Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child subjects involved in the research.

15.5 CONSENT AND ASSENT PROCESS AND DOCUMENTATION

The investigational nature and research objectives of this trial, the procedures and treatments involved and their attendant risks and discomforts and benefits, and potential alternative therapies will be carefully explained to the patient or the patient's parents or guardian if he/she is a child, and a signed informed consent document will be obtained prior to entry onto the study.

The PI or an associate investigator on the trial at each site will obtain consent. The PI or associate investigator will meet with the patient, or the patient's parents or guardian, and other family members to discuss the protocol treatment and alternative options in detail. It will be stated clearly that participation in the research study is voluntary and that participants can withdraw from the study without losing benefits they would otherwise be entitled to. The patient and family members will be encouraged to ask questions, and additional meetings to discuss the treatment options will be arranged as necessary.

The investigators are requesting a waiver from the IRB to allow only one parent to sign the informed consent to enter a child on the protocol. Because many patients must travel to the NIH or CHLA from long distances at substantial expense, requiring both parents to be present for the consent process could be a financial hardship for many families. When guardianship status of the child is uncertain, documentation of custody status must be obtained.

In situations where there is joint custody of a child, both parents must sign consent. If only one parent can be present at NIH or CHLA, the other parent's consent can be obtained by telephone via the procedure described in section **15.5.2**.

Where deemed appropriate by the clinician and the child's parent(s) or guardian, the child will also be included in all discussions about the trial and age-appropriate language will be used to describe the procedures and tests involved in this study, along with the risks, discomforts and benefits of participation. Written assent will not be obtained from children as the study holds out the prospect of direct benefit that is important to the health and well-being of the child and is available only in the context of the research. Verbal assent will be obtained as appropriate for children ages $\geq$ 7. The child will sign the appropriate line in the consent document to attest to assent. Children under the age of 7 will not be required to provide assent as they typically do not have the cognitive ability to fully understand the nature of research. The consent/assent process will be documented in the child's medical record, including the assessment of the child's ability to provide assent (verbal versus written) as applicable. All children will be contacted after they have reached the age of 18 to determine whether they wish to continue on the trial and informed consent will be obtained from them at that time.

15.5.1 Consent for minors when they reach the age of majority

When a pediatric subject reaches age 18, continued participation (including ongoing interactions with the subject or continued analysis of identifiable data) will require consenting of the now adult with the standard protocol consent document to ensure legally effective informed consent has been obtained. We request waiver of informed consent for those individuals who become lost to follow up after all efforts to reach the subject have failed. We also request waiver of informed cosent for individuals who have been taken off study prior to reaching the age of majority.

Requirements for Waiver of Consent consistent with 45 CFR 46.116 (d):

(1) The research involves no more than minimal risk to the subjects.

   a. Analysis of samples and data from this study involves no additional risks to subjects.

(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects.

   a. Retention of these samples or data does not affect the welfare of subjects.

(3) The research could not practicably be carried out without the waiver or alteration.

   a. Considering the length of time between the minor's last contact with the research team and their age of majority, it will likely be very difficult to locate them again. A significant reduction in the number of samples analyzed is likely to impact the quality of the research.

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

   a. We only request a waiver of consent for those subjects who have been lost to follow-up or who have been taken off study prior to reaching the age of majority.

15.5.2 Telephone consent

This procedure may be used for initial consent in the event that both parental signatures are required as referenced above. This procedure may also be used for re-consent in the event that a patient needs to re-consent because of changes to the consent document. The informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent.

The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone.

A fully executed copy will be returned via mail for the subject's records.

The informed consent process will be documented in the medical record.

16 PHARMACEUTICAL INFORMATION

16.1 DASATINIB (IND# 120449, NSC# 732517)

Other names: BMS-354825, Sprycel®

16.1.1 Chemical Name:

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

16.1.2 Mechanism of Action:

Dasatinib is a potent, broad spectrum ATP-competitive inhibitor of 5 critical oncogenic tyrosine kinase families: BCR-ABL, SRC family kinases, c-KIT, ephrin (EP) receptor kinases, and PDGFβ receptor. Overexpression or activation of these kinases plays critical roles in the etiology of various cancer types.

16.1.3 Molecular Formula:

$C_{22}H_{26}ClN_7O_2S \cdot H_20$ **MW:** Dasatinib monohydrate: 506.02 daltons

16.1.4 Approximate Solubility:

Dasatinib's solubility ranged from 18.42 mg/mL at pH 2.6 to < 0.001 mg/mL at pH 7.

16.1.5 How Supplied:

BMS supplies and CTEP, NCI, DCTD distributes dasatinib. Dasatinib is available in the following tablet/bottle sizes:

- 5 mg round, plain white film-coated tablets.
- 20 mg biconvex round, white to off-white film-coated tablets. The tablet is debossed with "20" on one side and "527" on the other side.
- 50 mg biconvex oval, white to off-white film-coated tablets. The tablet is debossed with "50" on one side and "528" on the other side.

Inactive ingredients include lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate. The film-coating contains hypromellulose, titanium dioxide, glycerol triacetate (in the 5 mg), and polyethylene glycol (in the 20 mg tablets and 50 mg tablets).

Tablets are supplied in high-density polyethylene (HDPE) bottles with desiccant and cotton. The bottles are heat-induction sealed with child-resistant caps.

16.1.6 Storage:

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

16.1.7 Stability:

Stability studies are ongoing.

16.1.8 Route of Administration:

Oral. Tablets may be taken with or without food. They should be swallowed whole and not crushed or broken.

16.1.9 Potential Drug Interactions

Dasatinib is primarily metabolized by the human CYP3A4 enzyme; therefore, potent CYP3A4 inducers and inhibitors are prohibited on dasatinib trials.

Concomitant use of dasatinib and a CYP3A4 substrate may increase exposure to the CYP3A4 substrate. Therefore, caution is warranted when dasatinib is co-administered with CYP3A4 substrates of narrow therapeutic index.

Systemic antacids (both H_2 receptor antagonists and proton pump inhibitors) are prohibited on dasatinib trials. Locally acting antacids can be given up to two hours prior or two hours following dasatinib administration.

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

Due to the possibility of CNS, gastrointestinal, cardiac, and cutaneous hemorrhage, use caution in patients who require medications that inhibit platelet function or anticoagulants.

16.1.10Special Handling:

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

16.2 GANITUMAB (IND# 120449, NSC# 750008)

16.2.1 Other Names:

AMG 479

16.2.2 Classification:

Monoclonal antibody

16.2.3 M.W.:

146 kilodaltons (kD)

16.2.4 Mode of Action:

Ganitumab exerts its anti-tumor activity by blocking ligand binding (IGF-1 and IGF-2) and inducing receptor internalization and degradation without cross-reacting with the insulin receptor.

16.2.5 Description:

Fully human recombinant IgG1 monoclonal antibody targeting IGF-1R

16.2.6 How Supplied:

Ganitumab will be supplied by NantBio and distributed by the PMB, CTEP, NCI as a sterile, clear, colorless liquid with 70 mg/mL (210 mg/3 mL or 700 mg/10 mL) vial of ganitumab. The single-use vials also contain the following excipients; 10 mM sodium acetate, 5% w/v sorbitol, 0.004% w/v polysorbate 20, pH 5.2. *Once the 700 mg vial size is available, the 210 mg vial size will no longer be available for this trial.*

16.2.7 Preparation:

The prescribed dose of ganitumab should be further diluted in 0.9% sodium chloride to a concentration between 3 mg/mL and 20 mg/mL.

16.2.8 Storage:

Store at 2°C to 8°C. Do not shake or freeze. Protect from light.

16.2.9 Stability

Once the ganitumab is injected into the infusion bag, the infusion must be completed within 8 hours. The total time between removal of ganitumab intact vials from the refrigerator and completion of infusion must not exceed 24 hours.

Vials contain no preservatives and any solution remaining in the vials after the dose is prepared should be discarded.

16.2.10 Route*(s)* of Administration

Intravenous infusion.

16.2.11 Method of Administration

The infusion line should be thoroughly flushed with saline before and after administration of ganitumab to avoid mixing with other drug products or IV solutions.

The first dose should be administered over 60 ± 10 minutes without premedication. If well tolerated, subsequent infusions may be administered over 30 minutes, at the investigator's discretion. Infusion times can be extended to a maximum of 120 minutes for subjects unable to tolerate the 60 minute infusion. Doses over 2100 mg should be infused over 120 minutes.

16.3 AGENT ORDERING AND AGENT ACCOUNTABILITY

16.3.1 Agent Ordering

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

In general, sites may order initial agent supplies when a subject is being screened for enrollment onto the study.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

16.3.2 Agent Inventory Records –

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

16.3.3 Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB coordinator via email.

16.3.4 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: PMBRegPend@ctep.nci.nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm

- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account: https://eapps-ctep.nci.nih.gov/iam/
- CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

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18 APPENDICES

18.1 APPENDIX 1: PERFORMANCE STATUS CRITERIA

PERFORMANCE STATUS CRITERIA Karnofsky and Lansky performance scores are intended to be multiples of 10					
Karnofsky (>16 years of age)		**Lansky (≤16 years of age)**		**ECOG**	
Score	Description	Score	Description		
100	Normal, no complaints, no evidence of disease	100	Fully active, normal.	0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.		
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly	1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.		
60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.	2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.		
40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.	3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.		
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.	4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.		

18.2 APPENDIX 2: SUBSTANCES PROHIBITED DURING DASATINIB TREATMENT

CYP3A4 Inhibitors:

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

CYP3A4 Inducers:

- aminoglutethimide, primidone, rifabutin, rifampin, St. John's wort
- carbamazepine, nevirapine, oxcarbazepine, rifapentine
- fosphenytoin, pentobarbital, phenobarbital, phenytoin

Agents with Proarrhythmic Potential

- quinidine, procainamide, disopyramide, amiodarone, sotalol, ibutilide, dofetilide
- erythromycins, clarithromycin
- chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide
- cisapride, bepridil, droperidol, methadone, arsenic, chloroquine, domperidone, halofantrine, levomethadyl, pentamidine, sparfloxacin, lidoflazine

Because the lists of these agents are constantly changing, your prescribers should consult a frequently-updated list or medical reference text such as the Physician's Desk Reference to see if any medicine they want to prescribe is on a list of drugs to avoid.

18.3 APPENDIX 3: INFORMATION ON POSSIBLE DRUG INTERACTIONS

Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

The patient _____ is enrolled on a clinical trial using the experimental agent **dasatinib and ganitumab**. *This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.*

Dasatinib interacts with many drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or herbal supplements such as St. John's wort.

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you and keep the attached information card in your wallet**. These are the things that you and they need to know:

Dasatinib interacts with (a) certain specific enzyme(s) in your liver.

- The enzyme(s) in question is/are ***CYP3A4 Inhibitor*** (because it may increase your blood level of dasatinib) and ***CYP3A4 Inducer*** (because dasatinib is broken down by this enzyme in order to be cleared from your body)
- **Dasatinib** must be used very carefully with other medicines that need these liver enzymes to be effective or to be cleared from your system.
- Other medicines may also affect the activity of the enzyme.
    - Substances that increase the enzyme's activity ("inducers") could reduce the effectiveness of the drug, while substances that decrease the enzyme's activity ("inhibitors") could result in high levels of the active drug, increasing the chance of harmful side effects.
    - Dasatinib may affect the heart's electrical activity (QTc prolongation).
    - Use caution when administering dasatinib with other potential QTc-prolonging medications.
    - Because antacids (H2 inhibitors, proton pump inhibitors) decrease your ability to absorb dasatinib, antacids should be limited to short-acting, locally-active agents (e.g., Maalox®, Mylanta® etc.). However, these agents should not be taken within either 2 hours before or 2 hours after the dasatinib dose.
    - Substances that effect platelet function should be avoided such as aspirin, nonsteroidal anti-inflammatory drugs (like motrin, ibuprofen), some antibiotics, some cardiovascular and lipid-lowering drugs, some antidepressants. It is important that you discuss any new drugs (prescription or over the counter) with your doctor before starting.
- You and healthcare providers who prescribe drugs for you must be careful about

adding or removing any drug in this category.

- Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered ***CYP3A4 Inhibitor*** or ***CYP3A4 Inducer.*** Examples of these medicines are listed on the next page.
- Because the lists of these agents are constantly changing, your prescribers should consult a frequently-updated list or medical reference text such as the Physician's Desk Reference to see if any medicine they want to prescribe is on a list of drugs to avoid.
- Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small and located above or below the brand name, and printed in the ingredient list. Find the generic name and determine, with the pharmacist's help, whether there could be an adverse interaction.
- Be careful:
  - If you take acetaminophen regularly: You should not take more than 3.25 grams a day if you are an adult. Read labels carefully! Acetaminophen is an ingredient in many medicines for pain, flu, and cold.
  - If you drink grapefruit juice or eat grapefruit: Avoid these until the study is over.
  - If you take herbal medicine regularly: You should not take St. John's wort while you are taking **Dasatinib**.

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is _____ and he or she can be contacted at_____

INFORMATION ON POSSIBLE DRUG INTERACTIONS	
You are enrolled on a clinical trial using the experimental agent **dasatinib and ganitumab.** This clinical trial is sponsored by the NCI. These drugs may interact with drugs that are processed by your liver. Because of this, it is very important to: ➢ Tell your doctors if you stop taking regular medicine or if you start taking a new medicine. ➢ Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, pharmacist) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	**Dasatinib** interacts with a specific liver enzyme called **CYP3A4**, and must be used very carefully with other medicines that interact with this enzyme. ➢ Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of **CYP3A4**." ➢ Dasatinib may affect the heart's electrical activity (QTc prolongation). Use caution when administering dasatinib with other potential QTc-prolonging medications. ➢ Avoid aspirin, antacids, and NSAIDS, ➢ Before prescribing new medicines, your regular prescribers should consult a frequently-updated list or medical reference text such as the Physician's Desk Reference for a list of drugs to avoid, or contact your study doctor. ➢ Your study doctor's name is **Dr. Christine Heske** and can be contacted at **240-760-6197.**

CYP3A4 Inhibitors:

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

CYP3A4 Inducers:

- aminoglutethimide, primidone, rifabutin, rifampin, St. John's wort
- carbamazepine, nevirapine, oxcarbazepine, rifapentine
- fosphenytoin, pentobarbital, phenobarbital, phenytoin

Agents with Proarrhythmic Potential

- quinidine, procainamide, disopyramide, amiodarone, sotalol, ibutilide, dofetilide
- erythromycins, clarithromycin
- chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide
- cisapride, bepridil, droperidol, methadone, arsenic, chloroquine, domperidone, halofantrine, levomethadyl, pentamidine, sparfloxacin, lidoflazine

_____.

18.4 APPENDIX 4: DOSING NOMOGRAM FOR DASATINIB FOR PHASE I/II TRIAL OF RHABDOMYOSARCOMA

Dose level																		
2 (60 mg/m^2/dose BID)	BSA*	0.5-0.54	0.55-0.62	0.63-0.71	0.72-0.79	0.8-0.87	0.88-0.96	0.97-1.04	1.05-1.12	≥1.13								
	Dose†	30	35	40	45	50	55	60	65	70								
1 (60 mg/m^2/dose once daily)	BSA*	0.5-0.54	0.55-0.62	0.63-0.71	0.72-0.79	0.8-0.87	0.88-0.96	0.97-1.04	1.05-1.12	1.13-1.21	1.22-1.29	1.3-1.37	1.38-1.46	1.47-1.54	1.55-1.62	≥1.63		
	Dose†	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100		
-1 (40 mg/m^2/dose once daily)	BSA*	0.5-0.56	0.57-0.69	0.70-0.81	0.8-0.94	0.95-1.06	1.07-1.19	1.2-1.31	1.3-1.44	1.45-1.56	1.57-1.69	1.7-1.81	1.82-1.94	1.95-2.06	2.07-2.18	2.19-2.31	2.32-2.44	≥2.45
	Dose†	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100

- *BSA, body surface area in m^2.
- †Actual dose in mg (tablet sizes 5 mg, 20 mg, and 50 mg).

The dosing nomogram will not be used to make dose reductions for toxicity due to overlap in dose levels for certain BSA. Section **6** describes dose reductions for toxicity.

18.5 APPENDIX 5: PATIENT'S MEDICATION DIARY – DASATINIB- CYCLE 1

(For once per day dosing)

Today's date _____ **Agent** _____**Dasatinib**__

Patient Name_____(*initials acceptable)* **Patient Study ID**_____

INSTRUCTIONS TO THE PATIENT: **CYCLE 1**

1. Complete one form for each 5 week-period while you take **dasatinib**.
2. You will take your dose of **dasatinib** daily (unless instructed otherwise due to dose reduction). You will take ____5 mg tablets, ____20 mg tablets, and ____ 50 mg tablets. You may take the tablets with or without food as you wish.
3. Record the date, the number of tablets of each size you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please return this form to your physician when you go for your next appointment.

Day	Date	Time of dose	# of tablets taken			Comments
			5 mg	20 mg	50 mg	
-7						
-6						
-5						
-4						
-3						
-2						
-1						
0						
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						

Day	Date	Time of dose	# of tablets taken			Comments
			5 mg	20 mg	50 mg	
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						

POB will complete this section:

1. Date patient started protocol treatment_____
2. Date patient was removed from study_____
3. Patient's planned total daily dose_____
4. Total number of tablets taken this month (each size)_____
5. Reviewing Physician/Nurse's Signature_____

Patient / Parent Signature: _____ Date:_____

Number of Tablets Returned: ___5 mg tablets, ____20 mg tablets, ____ 50 mg tablets.

RN / MD Signature: _____ Date:_____

18.6 APPENDIX 6: PATIENT'S MEDICATION DIARY – DASATINIB- SUBSEQUENT CYCLES

(For once per day dosing) for Cycle # _____

Today's date _____ **Agent** _____**Dasatinib**_

Patient Name_____(*initials acceptable)* **Patient Study ID**_____

INSTRUCTIONS TO THE PATIENT: **CYCLE ____**

1. Complete one form for each 4 week-period while you take **dasatinib**.
2. You will take your dose of **dasatinib** daily (unless instructed otherwise due to dose reduction). You will take ____5 mg tablets, ____20 mg tablets, and ____50 mg tablets. You may take the tablets with or without food as you wish.
3. Record the date, the number of tablets of each size you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please return this form to your physician when you go for your next appointment.

Day	Date	Time of dose	# of tablets taken			Comments
			5 mg	20 mg	50 mg	
0						
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						

19						
20						
21						
Day	**Date**	**Time of dose**	**# of tablets taken**			**Comments**
			5 mg	**20 mg**	**50 mg**	
22						
23						
24						
25						
26						
27						

POB will complete this section:

1. Date patient started protocol treatment_____
2. Date patient was removed from study_____
3. Patient's planned total daily dose_____
4. Total number of tablets taken this month (each size)_____
5. Reviewing Physician/Nurse's Signature_____

Patient / Parent Signature: _____ Date:_____

Number of Tablets Returned: ___5 mg tablets, ____20 mg tablets, ____ 50 mg tablets.

RN / MD Signature: _____ Date:_____

18.7 APPENDIX 7: PATIENT'S MEDICATION DIARY – DASATINIB- CYCLE 1

(For twice per day dosing)

Today's date _____ **Agent** _____**Dasatinib**__

Patient Name_____(*initials acceptable)* **Patient Study ID**_____

INSTRUCTIONS TO THE PATIENT: **CYCLE 1**

1. Complete one form for each 5 week-period while you take **dasatinib**.
2. You will take your dose of **dasatinib** twice daily in the morning and evening (unless instructed otherwise due to dose reduction). You will take ____5 mg tablets, ____20 mg tablets, and ____50 mg tablets. You may take the tablets with or without food as you wish.
3. Record the date, the number of tablets of each size you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please return this form to your physician when you go for your next appointment.

Day	Date	Time of AM dose	# of tablets taken			Time of PM dose	# of tablets taken			Comments
			5 mg	20 mg	50 mg		5 mg	20 mg	50 mg	
-7										
-6										
-5										
-4										
-3										
-2										
-1										
0										
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										

Day	Date	Time of AM dose	# of tablets taken			Time of PM dose	# of tablets taken			Comments
			5 mg	20 mg	50 mg		5 mg	20 mg	50 mg	
13										
14										
15										
16										
17										
18										
19										
20										
21										
22										
23										
24										
25										
26										
27										

POB will complete this section:

1. Date patient started protocol treatment_____
2. Date patient was removed from study_____
3. Patient's planned total daily dose_____
4. Total number of tablets taken this month (each size)_____
5. Reviewing Physician/Nurse's Signature_____

Patient / Parent Signature: _____ Date:_____

Number of Tablets Returned: ___5 mg tablets, ____20 mg tablets, ____ 50 mg tablets.

RN / MD Signature: _____ Date:_____

18.8 APPENDIX 8: PATIENT'S MEDICATION DIARY – DASATINIB- SUBSEQUENT CYCLES

(For twice per day dosing) for Cycle # _____

Today's date _____ **Agent** _____**Dasatinib**__

Patient Name_____(*initials acceptable)* **Patient Study ID**_____

INSTRUCTIONS TO THE PATIENT: **CYCLE _____**

1. Complete one form for each 4 week-period while you take **dasatinib**.
2. You will take your dose of **dasatinib** twice daily in the morning and evening (unless instructed otherwise due to dose reduction). You will take ____5 mg tablets, ____20 mg tablets ,and ____50 mg. You may take the tablets with or without food as you wish.
3. Record the date, the number of tablets of each size you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please return this form to your physician when you go for your next appointment.

Day	Date	Time of AM dose	# of tablets taken			Time of PM dose	# of tablets taken			Comments
			5 mg	20 mg	50 mg		5 mg	20 mg	50 mg	
0										
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
15										
16										
17										
18										
19										

20										
21										
Day	**Date**	**Time of AM dose**	**# of tablets taken**			**Time of PM dose**	**# of tablets taken**			**Comments**
			5 mg	**20 mg**	**50 mg**		**5 mg**	**20 mg**	**50 mg**	
22										
23										
24										
25										
26										
27										

POB will complete this section:

1. Date patient started protocol treatment_____
2. Date patient was removed from study_____
3. Patient's planned total daily dose_____
4. Total number of tablets taken this month (each size)_____
5. Reviewing Physician/Nurse's Signature_____

Patient / Parent Signature: _____ Date:_____

Number of Tablets Returned: ___5 mg tablets, ____20 mg tablets, ____ 50 mg tablets.

RN / MD Signature: _____ Date:_____

18.9 APPENDIX 9: PROCESSING AND SHIPPING SAMPLES TO NIH

At least one week in advance, please obtain study kits from:

Donna Bernstein, RN
Research Nurse Specialist
NIH/NCI/POB
10 Center Drive
Building 10/Room 1-3750
Bethesda, MD 20892

18.9.1 Collection and Shipping Instructions Pathology

Samples should only be drawn Sunday through Thursday and sent via overnight courier.

Refer to NantOmics Sample Collection manual pages 20-23 for sample requirements and collection instructions.

Page 9 of the NantOmics Sample Collection manual MUST be filled out and returned with the pathology.

Please also include:

- Patient ID: *This should be the protocol specific number given to the patient: site number followed by the patient number enrolled (ie: MD004-004)*
- Specimen ID: *this is the path identifier (ie: SS17-NO041)*
- Container type: *(block or slides)*

In addition please provide a redacted pathology report with specimen ID (that matches the pathology identifier)

Ship at room temperature to:

Donna Bernstein, RN
Research Nurse Specialist
NIH/NCI/POB
10 Center Drive
Building 10/Room 1-3750
Bethesda, MD 20892

18.9.2 Collection and Shipping Instructions for Whole Blood Samples

Samples should only be drawn Sunday through Thursday and sent via overnight courier.

Refer to NantOmics Sample Collection manual pages 19 for sample requirements and collection instructions.

Page 9 of the NantOmics Sample Collection manual MUST be filled out and returned with the pathology.

Please also include:

- Patient ID: *This should be the protocol specific number given to the patient: site number followed by the patient number enrolled (ie: MD004-001)*
- Container type: *blood*

Ship at room temperature to:

Donna Bernstein, RN
Research Nurse Specialist
NIH/NCI/POB
10 Center Drive
Building 10/Room 1-3750
Bethesda, MD 20892

18.9.3 Instructions for Use of the Streck Cell-Free DNA BCT tube

Samples should only be drawn Sunday through Thursday and sent via overnight courier.

For a video demonstration, visit www.streck.com/mixing.

- Collect specimen by venipuncture according to CLSI GP41-A61 . Prevention of Backflow - Since Cell-Free DNA BCT contains chemical additives, it is important to avoid possible backflow from the tube. To guard against backflow, observe the following precautions: a. Keep patient's arm in the downward position during the collection procedure. b. Hold the tube with the stopper in the uppermost position so that the tube contents do not touch the stopper or the end of the needle during sample collection. c. Release tourniquet once blood starts to flow in the tube, or within 2 minutes of application.
- Follow recommendations for order of draw outlined in CLSI GP41-A61 . Cell-Free DNA BCT should be drawn after the EDTA tube and before the fluoride oxalate (glycolytic inhibitor) tube. If a CellFree DNA BCT tube immediately follows a heparin tube in the draw order, Streck recommends collecting a non-additive or EDTA tube as a waste tube prior to collection in the Cell-Free DNA BCT.
- Fill tube completely.
- Remove tube from adapter and immediately mix by gentle inversion 8 to 10 times. Inadequate or delayed mixing may result in incorrect analytical results or poor product performance. One inversion is a complete turn of the wrist, 180 degrees.
- Ship overnight on wet ice to:

  Donna Bernstein, RN
  Research Nurse Specialist
  NIH/NCI/POB
  10 Center Drive
  Building 10/Room 1-3750
  Bethesda, MD 20892