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Dasatinib with Ifosfamide, Carboplatin, Etoposide: A Pediatric Phase I/II Trial

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ABSTRACT

Dasatinib, a kinase inhibitor that has demonstrated activity to inhibit SRC family kinases, BCR-ABL, c-KIT, EPHA2 and the PDGF-∃, has been shown to inhibit cellular proliferation, cell adhesion, migration and invasion, in numerous cancer cell lines that express activated SRC or c-KIT (13, 14). This novel molecular –targeted agent will be administered with a proven cytotoxic chemotherapy regimen, ifosfamide, carboplatin, and etoposide (ICE) in this study, in two phases: the Phase I portion to define the maximally tolerated dose of dasatinib when administered with ICE; the Phase II portion (stratum A & B) to define the overall response rate of the 4 drug combination as well as to estimate the progression free survival for relapsed pediatric malignancies; and the Phase II (stratum C) study for newly diagnosed, high risk patients with sarcoma, to define the overall response rate of D-ICE in previously untreated patients.

Patients aged 1 – 25 years with recurrent childhood solid tumors are eligible for this study. Patients will first be enrolled in the Phase I portion of this study, in a standard Phase I dose escalation manner with a starting dose of Dasatinib at 35 mg/m^2/dose twice a day, given immediately following standard doses of ICE chemotherapy. After two to six courses of D-ICE, patients with stable disease or with response, will undergo local control/consolidation by either surgical resection of metastases and/or radiation. In the Phase I portion, patients will then continue with Dasatinib alone for six months, if tolerable. If the patient does not develop dose limiting toxicity in the first two months after consolidation, he/she may escalate the dose of dasatinib to the next level.

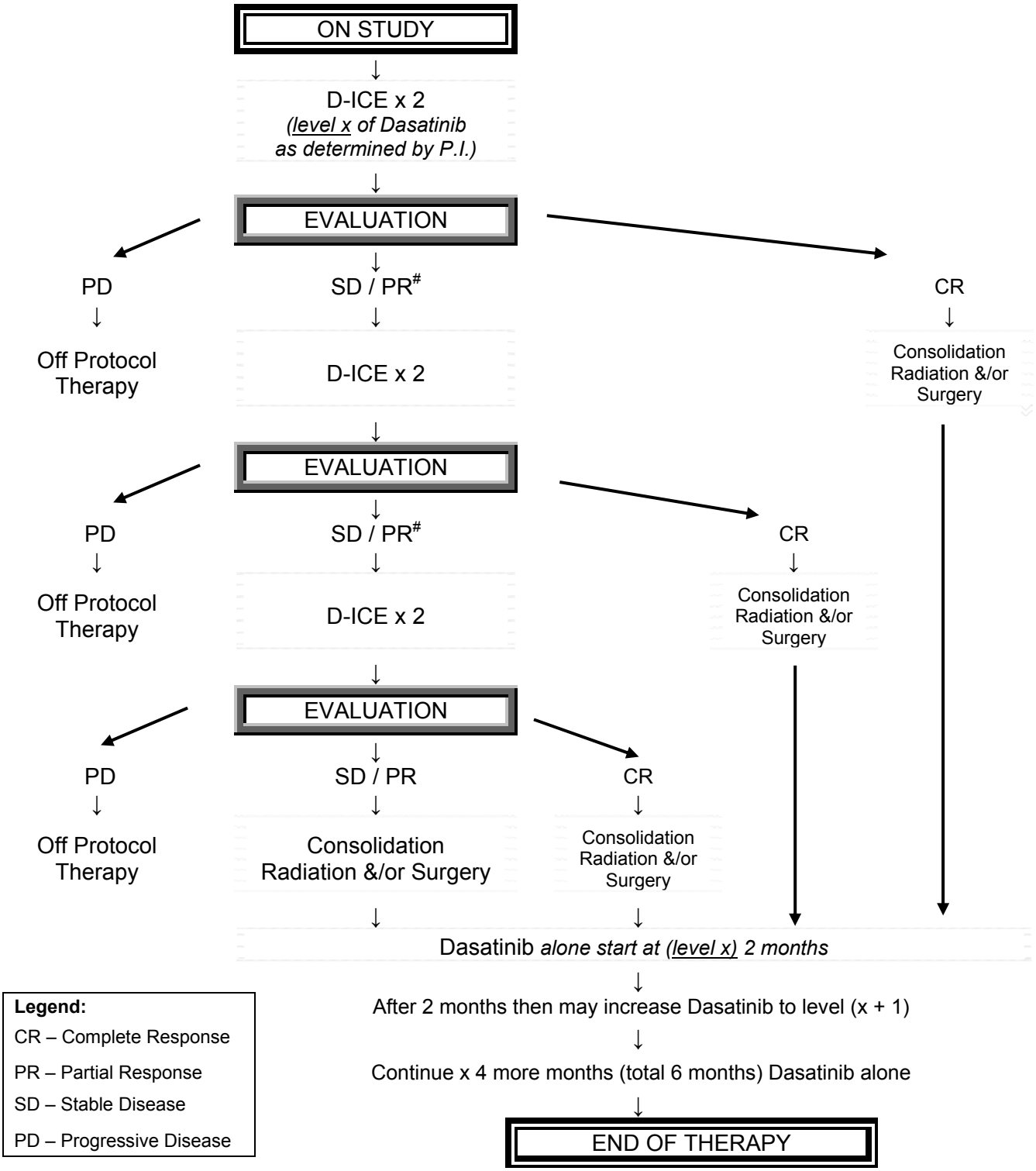
After completion of the Phase I portion of the study, patients with relapsed sarcomas and other solid tumors will be enrolled in the Phase II portion of the study, at the maximally tolerated dose of Dasatinib, as defined in the Phase I portion of this study. All patients will be evaluated for overall response rate and time to progression.

Patients with metastatic sarcoma and very poor chance of response will be allowed to enroll on this study in the Phase II portion of the study, at the defined MTD. The data from these patients will be analyzed for 1-yr overall survival response.

Correlative studies of Dasatinib are a crucial part of this study. Characteristics to be examined by Richard Jove, Ph.D. at the City of Hope Cancer Center include: (1) phosphotyrosine state of the tumor by immunohistochemistry analysis in paraffin-embedded tumor specimens, and in peripheral blood mononuclear cells as a surrogate of the tumor, (2) gene expression profiling by microarray analysis in fresh frozen tissues to identify molecular signatures to predict responsiveness to dasatinib, and (3) correlate the biomarkers and molecular signatures with dasatinib dosage, toxicity, and antitumor activity.

Our hypothesis is that pediatric patients with recurrent solid tumors including recurrent or refractory sarcomas, will tolerate and respond to a novel combination of dasatinib with cytotoxic chemotherapy, ICE (D-ICE). Furthermore, we propose that prolonged treatment with dasatinib alone will be safe and feasible following completion of 2-6 courses of D-ICE.

EXPERIMENTAL DESIGN SCHEMA*:



Legend:

CR – Complete Response

PR – Partial Response

SD – Stable Disease

PD – Progressive Disease

* **Phase I**: Dasatinib **(SPRYCEL®)** dose escalation per Table 3
Phase II: Dasatinib **(SPRYCEL®)** dose will be administered at the maximally tolerated dose, as determined by the Phase I portion of this study.

\# At Investigators discretion subject may proceed to consolidation, radiation and/or surgery

1.0 INTRODUCTION

Rational incorporation of novel molecular targeted anticancer agents into cytotoxic chemotherapy regimens, is an exciting and new challenge sure to increase overall response rates in all forms of cancer. The purpose of this study is to combine dasatinib [SPRYCEL®], a kinase inhibitor with demonstrated activity inhibiting tyrosine kinases including SRC family kinases, BCR-ABL, c-KIT, EPHA2, and PDGFb receptors (1), with cytotoxic chemotherapy, ifosfamide, carboplatin, and etoposide (ICE).

The prognosis for children with recurrent childhood solid tumors including recurrent or refractory sarcomas, such as rhabdomyosarcoma, osteosarcoma, and Ewings sarcoma, is poor with 5 year survival rates between 4% and 31% (2-4). Re-induction chemotherapy regimens including cytotoxic agents such as cyclophosphamide/ topotecan (5), ifosfamide/etoposide (6,7), carboplatin/etoposide (8,9), irinotecan (10, 11) and ifosfamide/carboplatin/etoposide (12) have been used in an attempt to re-induce remissions and thus achieve an improved overall survival. The most effective regimen for relapsed or refractory sarcoma reported to date, is the use of ifosfamide/carboplatin/ etoposide (ICE) with an overall response rate of 51% (12). This combination was in fact, superior to each agent given alone or to regimens given as two drug combinations (12). ICE induced a complete or partial response in 65% of patients with Wilm's Tumor, Ewing's sarcoma, rhabdomyosarcoma, other soft tissue sarcomas and lymphomas (12).

Dasatinib has been shown to inhibit cellular proliferation, cell adhesion, migration and invasion, in numerous cancer cell lines that express activated SRC or c-KIT (13, 14). We have recently shown that dasatinib inhibits the migration and invasion of 12 different human sarcoma cell lines of diverse origins, including osteogenic and soft-tissue sarcomas (15). Furthermore, dasatinib induces apoptosis of bone sarcomas, including osteosarcomas and Ewings sarcoma, but not soft-tissue sarcomas. This is based on the first report on the action of dasatinib in mesenchymally derived tumors. Based on these findings, we predict that dasatinib will complement the cytotoxic activity of ICE by preventing invasion and metastases of sarcomas.

Because of the very different mechanisms of action of dasatinib and ICE, we do not expect that these therapies will synergize with each other, if given simultaneously. In addition, we hypothesize that dasatinib and ICE given simultaneously could mask the anti-tumor benefit of dasatinib or result in antagonistic effects. For these reasons, we propose to give ICE first followed by dasatinib daily, during each course of D-ICE prior to consolidation, and then to continue with dasatinib alone after consolidation. Thus, dasatinib will be given during the re-induction phase of treatment and should theoretically, increase the response rate of the cytotoxic chemotherapy. We hypothesize that dasatinib can be given with cytotoxic therapy without a significant increase in toxicity. Furthermore, we propose that prolonged treatment with dasatinib alone following local control/consolidation will be feasible and ultimately decrease the chance of disease progression/recurrence and metastases.

This phase I/II study is designed to establish the feasibility and safety of dasatinib given immediately following ICE cytotoxic therapy administered every 28 days (D-ICE) and to define the feasibility and safety of prolonged administration of dasatinib alone following completion of 2-6 courses of D-ICE.

Our hypothesis is that pediatric patients with recurrent solid tumors including recurrent or refractory sarcomas, will tolerate and respond to a novel combination of dasatinib with cytotoxic chemotherapy, ICE (D-ICE). Prolonged treatment with dasatinib alone will be safe and feasible following completion of 2-6 courses of D-ICE.

1.1 DASATINIB

Dasatinib [SPRYCEL®] is a potent, broad spectrum ATP-competitive inhibitor of 5 critical oncogenic tyrosine kinase/kinase families: BCR-ABL, SRC, c-KIT, PDGF receptor β (PDGFRβ), and ephrin (EPH) receptor kinases, each of which has been linked to multiple forms of human malignancies (16).

Drug discovery and nonclinical pharmacology studies showed that dasatinib (16):

- Kills BCR-ABL dependent leukemic cell lines, including a number that are resistant to imatinib due to kinase domain mutations or overexpression of SRC family kinases and is effective against all imatinib-resistant kinase domain mutations tested to date, except T315I
- Inhibited proliferation of cancer cell lines that express activated SRC or c-KIT
- Potently inhibits VEGF-stimulated proliferation and migration in HUVECs
- Has potent bone anti-resorptive activity

1.1.1 Preclinical Anti-tumor Activity

1.1.1.1 In Vitro Molecular Studies

Dasatinib potently inhibits: SRC kinases, BCR-ABL, c-KIT, PDGFRβ and EPHA and was less potent against 16 other unrelated protein tyrosine kinases (PTKs) and serine/threonine kinases. Imatinib is less potent against several key enzymes: for example, Dasatinib was 260-, 8-, 60-, and >1000-fold more potent than imatinib versus BCR-ABL, c-KIT, PDGFRβ, and SRC kinases, respectively (17).

In vitro, dasatinib was active in leukemic cell lines representing variants of imatinib mesylate sensitive and resistant disease. dasatinib inhibited the growth of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) cell lines overexpressing BCR-ABL. Under the conditions of the assays, dasatinib was able to overcome imatinib resistance resulting from BCR-ABL kinase domain mutations, activation of alternate signaling pathways involving the SRC family kinases (LYN, HCK), and multi-drug resistance gene overexpression (16).

Dasatinib inhibits the BCR-ABL kinase with an *in vitro* IC_{50} of 3 nM, a potency 260-fold greater than that of imatinib mesylate (IC_{50} = 790 nM). In cellular assays, dasatinib killed or inhibited the proliferation of all BCR-ABL dependent leukemic cell lines tested to date. Dasatinib also demonstrated undiminished anti-tumor activity against several preclinically- and clinically-derived models of imatinib mesylate resistance. Evidence that SRC family kinase over expression may play a role in clinical resistance to imatinib mesylate was demonstrated in three CML cell lines established from patients who failed imatinib mesylate therapy. These cells remained highly sensitive to the cell-killing effects of dasatinib (17).

These results demonstrate that dasatinib is effective in reducing the proliferation or survival of both imatinib mesylate-sensitive and resistant cells, and its inhibitory activity is not solely dependent on BCR-ABL.

Recently, the Jove Laboratory has demonstrated the efficacy of dasatinib against 12 human sarcoma cell lines of diverse origins (15). In these sarcoma cells, dasatinib inhibited SRC kinase activity at low nanomolar concentrations. Furthermore, signaling pathways downstream of SRC, including Focal Adhesion Kinase (FAK), were also inhibited at similar concentrations. These signaling pathways have been shown previously to have important roles in cell migration and invasion. Significantly, inhibition of SRC kinase and downstream signaling through FAK was

accompanied by blockade of cell migration and invasion in all of the sarcoma cell lines. Moreover, apoptosis was induced in the osteosarcoma and Ewings subset of bone sarcomas, but not in the soft-tissue subset of sarcomas. These finding provide the first evidence that dasatinib inhibits migration and invasion of diverse sarcoma cell types, and selectively blocks the survival of bone sarcoma cells. Therefore, dasatinib may provide therapeutic benefit by preventing the growth and metastasis of sarcomas in pediatric patients.

1.1.1.2 In Vivo Studies

The activity of dasatinib against CML cells *in vitro* was reproduced *in vivo* against several human CML xenograft models grown subcutaneously in SCID mice. Against the K562/imatinib mesylate/R CML model, dasatinib was curative in 100% of the treated animals. In contrast, at its optimal dose and schedule, imatinib mesylate was inactive.

1.1.2 Preclinical Toxicology

Single or repeated oral administration of dasatinib principally affected the gastro-intestinal (GI) tract, including the liver, the hematopoietic and lymphoid systems in rats and monkeys. Other prominent effects after single oral administration of dasatinib included renal and cardiac toxicity in rats at lethal doses, and cutaneous hemorrhage in monkeys. Dasatinib can also affect the immune system and bone turnover.

Dasatinib *in vitro* activity in the HERG/IKr and Purkinje-fiber assays indicated a moderate liability for prolongation of cardiac ventricular repolarization (QT interval) in the clinic. However, there were no dasatinib -related changes observed in electrocardiograms, nervous system function, respirations and heart rate, blood pressure, or arterial oxygen saturation in single-dose, 10-day, or 1-month oral toxicity studies in monkeys.

Dasatinib was found to exhibit a profile of broad-spectrum platelet inhibition best typified by anti-platelet agents such as the GPIIb/IIIa antagonists, integrelin and abciximab. Finally, modulation of SRC kinase activity could also affect osteoclast morphology and function and bone remodeling. This effect could potentially result in an increase in bone mineral density and a phenotype analogous to osteopetrosis (17).

1.1.3 Clinical Pharmacokinetics

The pharmacokinetics of dasatinib have been evaluated in 229 healthy subjects and in 137 patients with leukemia.

1.1.3.1 Absorption

Maximum plasma concentrations (C_{max}) of dasatinib are observed between 0.5 and 6 hours (T_{max}) following oral administration. Dasatinib exhibits dose proportional increases in AUC and linear elimination characteristics over the dose range of 15 mg to 240 mg/day. The overall mean terminal half-life of dasatinib is 3–5 hours (16).

Data from a study of 54 healthy subjects administered a single, 100-mg dose of dasatinib 30 minutes following consumption of a high-fat meal resulted in a 14% increase in the mean AUC of dasatinib. The observed food effects were not clinically relevant.

1.1.3.2 Distribution

In patients, dasatinib has an apparent volume of distribution of 2505 L, suggesting that the drug is extensively distributed in the extravascular space. Binding of dasatinib and its active metabolite to

human plasma proteins *in vitro* was approximately 96% and 93%, respectively, with no concentration dependence over the range of 100–500 ng/mL (16).

1.1.3.3 Metabolism

Dasatinib is extensively metabolized in humans, primarily by the cytochrome P450 enzyme 3A4. CYP3A4 was the primary enzyme responsible for the formation of the active metabolite. Flavin-containing monooxygenase 3 (FMO-3) and uridine diphosphate-glucuronosyltransferase (UGT) enzymes are also involved in the formation of dasatinib metabolites. In human liver microsomes, dasatinib was a weak time-dependent inhibitor of CYP3A4.

The exposure of the active metabolite, which is equipotent to dasatinib, represents approximately 5% of the dasatinib AUC. This indicates that the active metabolite of dasatinib is unlikely to play a major role in the observed pharmacology of the drug. Dasatinib also had several other inactive oxidative metabolites.

1.1.3.4 Elimination

Elimination is primarily via the feces. Following a single oral dose of [^{14}C]-labeled dasatinib, approximately 4% and 85% of the administered radioactivity was recovered in the urine and feces, respectively, within 10 days. Unchanged dasatinib accounted for 0.1% and 19% of the administered dose in urine and feces, respectively, with the remainder of the dose being metabolites.

1.2 Safety of Dasatinib in Clinical Studies in CML and Ph+ ALL

The data described below reflect exposure to dasatinib in 911 patients with leukemia from 1 Phase I and 5 Phase II clinical studies. The median duration of therapy was 6 months (range 0–19 months).

The majority of dasatinib -treated patients experienced adverse drug reactions at some time. Drug was discontinued for adverse drug reactions in 6% of patients in chronic phase CML, 5% in accelerated phase CML, 11% in myeloid blast phase CML, and 6% in lymphoid blast phase CML or Ph+ ALL.

The most frequently reported serious adverse events (SAEs) included pyrexia (9%), pleural effusion (8%), febrile neutropenia (7%), gastrointestinal bleeding (6%), pneumonia (6%), thrombocytopenia (5%), dyspnea (4%), anemia (3%), cardiac failure (3%), and diarrhea (2%).
All treatment-emergent adverse events (excluding laboratory abnormalities), regardless of relationship to study drug, that were reported in at least 20% of the patients in dasatinib clinical studies are shown in Table 1.

Table 1: Adverse Events Reported ≥20% in Clinical Studies in CML and Ph+ ALL

	All Patients (n=911)		Chronic Phase (n=488)	Accelerated Phase (n=186)	Myeloid Blast Phase (n=132)	Lymphoid Blast Phase and Ph+ ALL (n=105)
	All Grades	Grades 3/4	Grades 3/4	Grades 3/4	Grades ¾	Grades ¾
Preferred Term	**Percent (%) of Patients**					
Fluid Retention	50	9	6	6	23	9
Superficial Edema	36	1	0	2	3	2
Pleural Effusion	22	5	3	3	14	8
Diarrhea	49	5	3	10	8	6
Headache	40	2	2	2	4	6
Hemorrhage	40	10	3	18	23	17
Musculoskeletal Pain	39	4	2	3	6	13
Pyrexia	39	5	1	5	13	9
Fatigue	39	3	2	4	4	8
Skin Rash[a]	35	1	1	1	1	4
Nausea	34	1	<1	0	5	2
Dyspnea	32	6	5	7	11	9
Cough	28	<1	<1	1	1	0
Infection (including bacterial, viral, fungal, non-specified)	34	7	4	8	15	13
Infection/Inflammation	26	1	1	1	5	1
Abdominal Pain	25	2	1	2	4	6
Pain	26	2	<1	1	5	4
Vomiting	22	1	1	2	2	2
Febrile Neutropenia	9	8	2	11	17	20

1.2.1 Laboratory Abnormalities

Myelosuppression was commonly reported in all patient populations. The frequency of Grade 3 or 4 neutropenia, thrombocytopenia, and anemia was higher in patients with advanced CML or Ph+ ALL than in chronic phase CML. Myelosuppression was reported in patients with normal baseline laboratory values as well as in patients with pre-existing laboratory abnormalities. (Table 2)

In patients who experienced severe myelosuppression, recovery generally occurred following dose interruption and/or reduction; permanent discontinuation of treatment occurred in 1% of patients.

Grade 3 or 4 elevations of transaminases or bilirubin and Grade 3 or 4 hypocalcemia and hypophosphatemia were reported in patients with all phases of CML but were reported with an increased frequency in patients with myeloid or lymphoid blast CML and Ph+ ALL. Elevations in transaminases or bilirubin were usually managed with dose reduction or interruption. Patients developing Grade 3 or 4 hypocalcemia during the course of dasatinib therapy often had recovery with oral calcium supplementation. (Table 2)

Table 2: CTC Grades 3/4 Laboratory Abnormalities in Clinical Studies in CML and Ph+ ALL

	Chronic Phase (n=488)	Accelerated Phase (n=186)	Myeloid Blast Phase (n=132)	Lymphoid Blast Phase and Ph+ ALL (n=105)
	Percent (%) of Patients			
Hematology Parameters				
Neutropenia	49	74	83	81
Thrombocytopenia	48	83	82	83
Anemia	18	70	70	51
Biochemistry Parameters				
Hypophosphatemia	11	13	23	21
Hypocalcemia	2	9	20	15
Elevated SGPT (ALT)	1	4	7	11
Elevated SGOT (AST)	1	2	5	8
Elevated Bilirubin	<1	1	5	8
Elevated Creatinine	0	2	1	1

CTC grades: neutropenia (Grade 3 ≥0.5–1.0 × 10^9/L, Grade 4 <0.5 × $10^{9/}$L); thrombocytopenia (Grade 3 ≥10–50 × 10^9/L, Grade 4 <10 × 10^9/L); anemia (hemoglobin ≥65–80 g/L, Grade 4 <65 g/L); elevated creatinine (Grade 3 >3–6 × upper limit normal range (ULN), Grade 4 >6 × ULN); elevated bilirubin (Grade 3 >3–10 × ULN, Grade 4 >10 × ULN); elevated SGOT or SGPT (Grade 3 >5–20 × ULN, Grade 4 >20 × ULN); hypocalcemia (Grade 3 <7.0–6.0 mg/dL, Grade 4 <6.0 mg/dL); hypophosphatemia (Grade 3 <2.0–1.0 mg/dL, Grade 4 <1.0 mg/dL).

1.2.2 Anticipated Adverse Events

Myelosuppression

Treatment with dasatinib is associated with severe (NCI CTC Grade 3 or 4) thrombocytopenia, neutropenia, and anemia. Their occurrence is more frequent in patients with advanced CML or Ph+ ALL than in chronic phase CML. Complete blood counts should be performed weekly for the first 2 months and then monthly thereafter, or as clinically indicated. Myelosuppression was generally reversible and usually managed by withholding dasatinib temporarily or dose reduction (16).

Bleeding Related Events

In addition to causing thrombocytopenia in human subjects, dasatinib caused platelet dysfunction *in vitro*. Severe CNS hemorrhages, including fatalities, occurred in 1% of patients receiving dasatinib. Severe gastrointestinal hemorrhage occurred in 7% of patients and generally required treatment interruptions and transfusions. Other cases of severe hemorrhage occurred in 4% of patients. Most bleeding events were associated with severe thrombocytopenia.

Patients were excluded from participation in dasatinib clinical studies if they took medications that inhibit platelet function or anticoagulants. Caution should be exercised if patients are required to take medications that inhibit platelet function or anticoagulants.

Fluid Retention

Dasatinib is associated with fluid retention, which was severe in 9% of patients, including pleural and pericardial effusion reported in 5% and 1% of patients, respectively. Severe ascites and generalized edema were each reported in 1%. Severe pulmonary edema was reported in 1% of patients. Patients who develop symptoms suggestive of pleural effusion such as dyspnea or dry cough should be evaluated by chest X-ray. Severe pleural effusion may require thoracentesis and oxygen therapy. Fluid retention events were typically managed by supportive care measures that include diuretics or short courses of steroids (16).

QT Prolongation

In vitro data suggest that dasatinib has the potential to prolong cardiac ventricular repolarization (QT interval). In single-arm clinical studies in patients with leukemia treated with dasatinib, the mean QTc interval changes from baseline using Fridericia's method (QTcF) were 3–6 msec; the upper 95% confidence intervals for all mean changes from baseline were <8 msec. Nine patients had QTc prolongation reported as an adverse event. Three patients (<1%) experienced a QTcF >500 msec.

Dasatinib should be administered with caution to patients who have or may develop prolongation of QTc. These include patients with hypokalemia or hypomagnesemia, patients with congenital long QT syndrome, patients taking anti-arrhythmic medicines or other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy. Hypokalemia or hypomagnesemia should be corrected prior to dasatinib administration (16).

1.3 Phase I Experience in Solid Tumors

In a Phase I study (CA180003) conducted by Bristol Myers Squibb (BMS), dasatinib was administered on a BID schedule to 42 subjects with refractory solid tumor. To date, doses up to 160 mg BID on a 5-day on/2-day off schedule have been administered. A dose of 120 mg BID continuous daily schedule is currently under investigation.

No severe clinical toxicity has been encountered. Gastrointestinal symptoms were reported in most subjects, fatigue was reported in 17 subjects (40%) and rash in 10 subjects (24%). Edema, lethargy and headache were uncommon, and appear to be dose-related. Grade 3 asymptomatic

hypocalcemia was considered dose-limiting in one subject, Grade 2 rash was considered dose-limiting in two other subjects, and Grade 2 nausea and vomiting (with dysarthria, lightheadedness and lethargy in a 49 kg subject taking concurrent diazepam) was considered dose-limiting in one subject.

In another Phase I study (CA180021), dasatinib was administered on a QD schedule to 24 subjects at doses up to 180 mg. Pleural effusions were observed in three subjects at the 180 mg dose level (one with pneumonia and two with malignant effusion). A dose of 250 mg QD is currently under consideration. Hypocalcemia, GI symptoms and skin rash have been mild and infrequent.

To date, the safety profile in solid tumor subjects has been similar to that in CP CML subjects with the exception of severe myelosuppression, which has not been observed in solid tumor subjects and is considered related to efficacy against the leukemia as noted above, and severe bleeding which is secondary to thrombocytopenia in most instances (18).

1.4 Ifosfamide, Carboplatin, Etoposide

The combination of ifosfamide, carboplatin, and etoposide (ICE) has been successful in the treatment of relapsed/refractory pediatric malignancies (12,30). Preclinical studies demonstrate that the three drug combination may have a higher efficacy as each agent has different mechanisms of action with minimal overlap of non-hematologic toxicities; each drug has a different antitumor profile in tumor cell lines as well as in preclinical models (30-33).

Each agent alone has demonstrated some activity in pediatric solid tumors. Ifosfamide (I) demonstrated an overall response rate (ORR) of 24-33% in children with osteosarcoma (OGS) and soft tissue sarcomas (STS) (19-22). In Wilms Tumor, a response rate of 50% to Ifosfamide was reported (23).

Carboplatin (C) has been studied as a single agent in pediatric recurrent disease with limited success: an ORR of 6-9% was reported in recurrent OGS, STS, Wilms tumor, and pediatric brain tumors (24, 25). For relapsed Wilms tumor, an ORR of 40-53% was reported (24, 26).

Etoposide (E) as a single agent produces limited responses. In refractory Wilms tumor, an ORR of 42% was reported (27), with an ORR in recurrent childhood solid tumors of only 6%. Etoposide however, has been evaluated in combination trials (IE, CE, or ICE) for its possible synergistic or additive effects in pediatric recurrent solid tumors, with improved responses.

The combination of Ifosfamide and Etoposide was studied in a phase II study which demonstrated the effectiveness of this regimen in children with recurrent Ewing's sarcoma, osteosarcoma, rhabdomyosarcoma, primitive neuroectodermal tumor, lymphomas and other solid tumors (6,28). In a separate study, a CR of 10% was reported in children with recurrent solid tumors, including hepatoblastoma, neuroblastoma, and Wilms tumor (7).

The combination of Carboplatin and Etoposide has also been studied in relapsed Wilms tumor (29), resulting in an ORR of 73%.

The Children's Cancer Group (CCG) studied a large number of relapsed patients using ICE as the cytotoxic chemotherapy regimen while investigating multiple cytokines and growth factors, including g-CSF, IL-6, PIXY 321, thrombopoietin. In a recently published report from the CCG, Van Winkle reported a 51% overall response rate in children with recurrent/refractory sarcomas, with overall survival at 1 and 2 years of 49% and 28%, respectively (12). Ninety-seven patients with recurrent sarcomas were evaluable for response, with rhabdomyosarcoma having the highest response rate of 66% (12).

2.0 STUDY RATIONALE

The prognosis for children with recurrent childhood solid tumors including recurrent or refractory sarcomas, such as rhabdomyosarcoma, osteosarcoma, and Ewings sarcoma, is poor with 5 year survival rates between 4% and 31% (2-4). Re-induction chemotherapy regimens including cytotoxic agents such as cyclophosphamide/ topotecan (5), ifosfamide/etoposide (6,7), Carboplatin/etoposide (8,9), irinotecan (10, 11) and ifosfamide/carboplatin/etoposide (12) have been used in an attempt to re-induce remissions and thus achieve an improved overall survival. The most effective regimen for relapsed or refractory sarcoma reported to date, is the use of ifosfamide/carboplatin/ etoposide (ICE) with an overall response rate of 51% (12). This combination was in fact, superior to each agent given alone or to regimens given as two drug combinations (12). ICE induced a complete or partial response in 65% of patients with Wilm's Tumor, Ewing's sarcoma, rhabdomyosarcoma, other soft tissue sarcomas and lymphomas (12).

Dasatinib has been shown to inhibit cellular proliferation, cell adhesion, migration and invasion, in numerous cancer cell lines that express activated SRC or c-KIT (13, 14). Given that ICE is a cytotoxic regimen, and dasatinib is a molecular targeted agent with defined biological activities in terms of preventing invasion and metastases (15), we do not expect that dasatinib will enhance the cytotoxic activity of ICE. Instead, our prediction, based on the molecular and biological mechanism of action of dasatinib, is that dasatinib will complement the cytotoxic activity of ICE by inhibiting invasion and metastases of tumor cells that escape ICE cytotoxic killing. Therefore, we propose to administer dasatinib immediately following each ICE in order to better evaluate the complementary activities of dasatinib and ICE, as well as to avoid potential adverse interactions between these two therapeutic combinations.

In this study, dasatinib will be given after each ICE administration, during the re-induction phase of treatment and should theoretically, increase the response rate of the cytotoxic chemotherapy. We hypothesize that dasatinib can be given with cytotoxic therapy without a significant increase in toxicity. Furthermore, we propose that prolonged treatment with dasatinib alone following local control/consolidation will be feasible and ultimately decrease the chance of disease progression/recurrence.

This phase I/II study is designed to establish the feasibility and safety of dasatinib given immediately following each ICE cytotoxic therapy administered every 28 days (D-ICE) and to define the feasibility and safety of prolonged administration of dasatinib alone following completion of 2-6 courses of D-ICE.

3.0 OVERVIEW OF STUDY DESIGN AND EVALUATION

3.1 Study Design

This novel molecular – targeted agent will be administered with a proven cytotoxic chemotherapy regimen, ifosfamide, carboplatin, and etoposide (ICE) in this study, in two phases: the Phase I portion to define the maximally tolerated dose of dasatinib when administered with ICE; the Phase II portion (stratum A & B) to define the overall survival and response rate of the 4 drug combination as well as to estimate the progression free survival for relapsed pediatric malignancies; and the Phase II (stratum C) study for newly diagnosed, high risk patients with sarcoma, to define the overall survival, response rate and progression-free survival associated with D-ICE in previously untreated patients.

Patients aged 1 – 25 years with recurrent childhood solid tumors are eligible for this study. Patients will first be enrolled in the Phase I portion of this study, in a standard Phase I dose escalation manner with a starting dose of Dasatinib at 35 mg/m^2/dose twice a day, given immediately following standard doses of ICE chemotherapy. After two to six courses of D-ICE,

patients with stable disease or with response, will undergo local control/consolidation by either surgical resection of metastases and/or radiation. In the Phase I portion, patients will then continue with Dasatinib alone for six months, if tolerable. If the patient does not develop dose limiting toxicity in the first two months after consolidation, he/she may escalate the dose of dasatinib to the next level.

After completion of the Phase I portion of the study, patients with relapsed sarcomas and other solid tumors will be enrolled in the Phase II portion of the study, at the maximally tolerated dose of Dasatinib, as defined in the Phase I portion of this study. All patients will be evaluated for overall survival, response rate and time to progression.

Patients with metastatic sarcoma and very poor chance of response will be allowed to enroll on this study in the Phase II portion of the study, at the defined MTD. The data from these patients will be analyzed for 1-year overall survival response. Data analysis at 6 months, an additional 6 months, if beneficial.

Correlative studies of Dasatinib are a crucial part of this study. Characteristics to be examined by Richard Jove, Ph.D. at the City of Hope Cancer Center include: (1) phosphotyrosine state of the tumor by immunohistochemistry analysis in paraffin-embedded tumor specimens, and in peripheral blood mononuclear cells as a surrogate of the tumor, (2) gene expression profiling by microarray analysis in fresh frozen tissues to identify molecular signiatures to predict responsiveness to dasatinib, and (3) correlate the biomarkers and molecular signatures with dasatinib dosage, toxicity, and antitumor activity, (see Experimental Design Schema, page 8).

DASTINIB TREATMENT DURING THE D-ICE PHASE I PORTION OF STUDY:

The dose of dasatinib will be escalated as per Section 6.3.1; Cohorts of 3 subjects will be studied at each dose level, up to 18 patients will be accrued during Phase I and given during the re-induction phase of treatment prior to local control measures. Following completion of 2-6 courses of D-ICE and appropriate local control measures, responding patients and those with stable disease will receive 28 day courses of dasatinb alone. Courses 1 and 2 will be administered at the dose of dasatinib received in the initial phase of D-ICE. If tolerated without significant adverse events, intra-patient dose escalation of dasatinib may occur after the first 2 months of dasatinib alone, using the dose levels outlined in Section 6.3.1, by only 1 dose level to a maximum of the Level 5 dose. In addition, data from other dasatinib trials will be reviewed and the maximum dose and dose levels may be modified based on clinical data available at that time from other trials, as well as target modulation data available from this and other trials.

PHASE II PORTION OF STUDY

Thus, during the Phase II portion of the study, there are three strata:

- Stratum A (75 patients): patients with relapsed Osteosarcoma, Ewings Sarcoma, Rhabdomyosarcoma;
- Stratum B (max of 25 patients): Patients with relapsed solid tumors not listed above;
- Stratum C (max of 25 patients): Patients with newly diagnosed metastatic sarcomas of poor risk

Stratum A & B:

Once the MTD of D-ICE and dasatinib alone are defined, a phase II portion of the study will occur at the MTD. Up to 100 patients (Stratum A: 75 from the sarcoma tumor group and Stratum B: 25 patients from other tumor types) will be accrued during the Phase II portion.

During the phase II study, patients will receive a minimum of 2 and a maximum of 6 courses of D-ICE followed by appropriate local control/consolidation measures (e.g., surgical resection of

metastases or radiation to metastatic sites). Responding patients and those with stable disease will then receive 28-day courses of dasatinib alone. A primary objective of the phase II portion of the study will be to determine the 1-yr overall survival of Stratum A. Secondary endpoints include response rate as defined by RECIST criteria prior to consolidation; progression-free survival; further assessment of toxicity; and evaluation of exploratory correlative studies.

Stratum C:

After completion of the Phase I portion of this study which will have determined the MTD of dasatinib when given with ICE, 25 patients with metastatic disease at initial diagnosis and who have a poor risk for response and survival (e.g., unresectable metastases, pulmonary metastases greater than 6 in number), will be treated at the MTD of D-ICE. These patients will receive D-ICE at the MTD, be evaluated for response after every two courses of D-ICE, undergo local control/consolidation with either surgery and/or radiation, and then will continue with dasatinib alone for a minimum of 6 months of dasatinib.

3.1.1 Duration of Study

Subjects with stable disease or objective tumor response will be allowed to continue treatment as long as clinical benefit is observed. Treatment will be discontinued for disease progression, unacceptable toxicity and/or reasons outlined in Section 6.4.

4.0 STUDY OBJECTIVES

4.1 Primary Objective

4.1.1 Phase I

1) To determine the maximally tolerated dose (MTD) of dasatinib given immediately following ifosfamide, carboplatin and etoposide (D-ICE) as a re-induction regimen to pediatric patients with recurrent solid tumors
2) To describe and define the toxicities of D-ICE
3) To determine the safety and feasibility of prolonged administration of single agent dasatinib following completion of 2-6 courses of D-ICE therapy

4.1.2 Phase II

1) In the phase II portion of the study, to estimate the overall survival, progression free survival and time to progression in patients with recurrent sarcoma and other solid tumors (including primary CNS tumors), to D-ICE given at the MTD, plus dasatinib alone given after consolidative therapy.
2) In the phase II portion of the study, to estimate the response rate to 2 courses of D-ICE, given at the MTD.

4.2 Secondary Objectives

1) To determine the phosphotyrosine state by immunohistochemistry of SRC family kinases and related signaling pathways including FAK, STAT3, VEGFR, AKT, EGFR, KIT, EPHA2 and PDGFR in paraffin-embedded tumor specimens prior to and during treatment with dasatinib.

2) Gene expression profiling by microarray analysis (Affymetrix GeneChips) of fresh frozen tissues prior to treatment to identify molecular signatures that may predict response to dasatinib.
3) To correlate the biomarkers and molecular signatures with dasatinib dosage, toxicity, and anti-tumor activity.
4) To evaluate the effect of dasatinib on phosphorylation of SRC family kinases in peripheral blood mononuclear cells (PBMCs) as a surrogate marker of response prior to treatment with dasatinib, at day 14 - 21 or when WBC $\geq$ 500, during each treatment course, at the time of local control, and at time of progression, if any.

5.0 STUDY POPULATION AND PATIENT ELIGIBILITY

5.1 Inclusion Criteria

5.1.1 Evidence of Disease

Subjects must have histologic proof of malignancy at initial diagnosis. Each subject must have radiographic, nuclear image, or biopsy proof of recurrent disease within 4 weeks prior to study entry. Patients must have failed or relapsed from standard first-line chemotherapy (or other antineoplastic therapy) for their tumor, if a standard treatment for their tumor is generally recognized to be beneficial.

5.1.1.1 Phase I

Patients who have recurrent or metastatic disease completely resected just prior to study entry are eligible for the phase I portion of the study.

Subjects with bone marrow involvement are NOT eligible for the phase I portion of the study.

Relapsed patients on the Phase I study do not have to have measurable disease.

5.1.1.2 Phase II

Enrollment of patients with bone marrow involvement will be allowed on the phase II portion of the study; they will not be evaluable for hematologic toxicity. These patients must not be known to be refractory to red cell or platelet transfusions.

The patient must have measurable disease defined radiographically, to be eligible for this portion of study.

5.1.2 Age

All subjects must be > 1 year old at study entry, and must have initially been diagnosed with their malignancy prior to the age of 25 years old.

5.1.3 Prior Therapy

Subjects must have fully recovered from the toxic effects of any prior therapy. At least 3 weeks should have elapsed since the last dose of chemotherapy (6 weeks in the case of nitrosourea-containing therapy).

Subjects who have received the exact combination and dosage of ifosfamide, carboplatin and etoposide as administered in this study, within the last 3 months are ineligible. Patients may have

received ifosfamide, carboplatin, and/or etoposide singly, in pairs, or in the same combination and doses, prior to study entry, and still be eligible.

Patients who have received cranial-spinal irradiation (>2400 cGy) are ineligible. Patients are also ineligible if they have received radiation therapy (including TBI) to greater than 50% of the bone marrow space.

Patients must have recovered from previous colony-stimulating factor therapy and have been off colony-stimulating factors (G-CSF, GM-CSF, IL-11) for more than 7 days (G-CSF) or 14 days (Neulasta) and off EPO for 30 days.

5.1.4 Organ Function Requirements

ANC and Platelet Count
Subjects must have an ANC > 1000/uL and a platelet count > 75,000/uL to be eligible for therapy.

Renal Function
All subjects must have a creatinine clearance or GFR which is greater than or equal to 70 ml/min/1.73 m^2, or Cr < 1.5 X ULN.

Hepatic function
All subjects must have bilirubin less than 1.5 x NL and an SGOT or SGPT less than 2.5 x NL for age. If there is liver involvement by tumor, the ALT/AST must be less than 5x ULN.

Cardiac function
Patients should have a normal ejection fraction and a fractional shortening of >28% (per institutional limits) or normal MUGA, no evidence of cardiac arrhythmias requiring therapy, and corrected QT (QTc) interval < 450 msecs

5.1.5 Life Expectancy

All patients must have a life expectancy of 8 weeks or more

5.1.6 Diagnostic Categories

5.1.6.1 Phase I

All patients with relapsed/refractory solid tumor malignancies (excluding CNS tumors) will be eligible for enrollment and data will be analyzed in cohorts of 3 patients.

5.1.6.2 Phase II (Stratum A & B)

For the Phase II portion of the study, patients will be stratified by their diagnosis.

Stratum A:

Sarcoma (Rhabdomyosarcoma, Osteosarcoma, Ewings sarcoma)

Stratum B:

a) Other Soft Tissue sarcomas
b) Kidney Tumors
c) Lymphoma
d) CNS Tumors (pending toxicities analysis in any Phase I study, including dasatinib)
e) Other solid tumors (neuroblastoma, gonadal and germ cell tumors, liver tumors, and miscellaneous tumors)

5.1.6.3 Phase II (Stratum C)

Newly diagnosed, poor risk patients with metastatic sarcoma consisting of unresectable pulmonary metastases (six or more nodules) and/or disease involving multiple bones or other organs, will be eligible. Sarcoma includes Rhabdomyosarcoma, Osteosarcoma, Ewings sarcoma and other Soft Tissue Sarcomas.

5.1.7 Performancy Status

Must be > or = 50 from Lansky (age 1 to 16) or Karnofsky (age >16)

5.2 Exclusion Criteria

Patients with any of the following will not be eligible for study:

1) Pregnancy or Breast-Feeding

   Pregnant or breast-feeding women will not be entered on this study due to risks of fetal and teratogenic adverse events seen in animal studies. Pregnancy tests must be obtained in girls who are post-menarchal. Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method.

2) Patients with central nervous system tumors are excluded from the Phase I portion of the study. Patients with recurrent primary CNS tumors will be added to the Phase II portion of the study if there is no significant intratumor bleeding toxicities seen on either the COG Pediatric Phase I studies of Dasatinib or the Phase I portion of this study.

3) Concomitant Medications

   a) Growth factors: Growth factors that support the number or function of platelets or white cells must not have been administered within the past 7 days. Pegfilgrastin (Neulasta) must not have been administered within the past 14 days.

   b) Investigational Agents: Patients who are currently receiving another investigational drug.

   c) Anti-cancer Agents: Patients who are currently receiving other anti-cancer agents.

   d) Enzyme inducing anticonvulsants: phenytoin, phenobarbital, felbamate, primdone, oxcarbazepine and/or carbamazepine.

   e) Anti-thrombotic and anti-platelet agents: warfarin (coumadin), heparin, low molecular weight heparin, aspirin, and/or ibuprofen, or other NSAIDs.

   f) CYP3A4 inhibitors including itraconazole, ketoconazole, and voriconazole.

   g) Infection: Patients who have an uncontrolled infection.

   h) Patients who have swallowing dysfunction that would prevent taking an oral medication and who do not have a functioning gastric or jejunal tube (if a patient is unable to swallow a pill, dasatinib may be administered via a nasogastric tube (NGT) or gastrostomy, see section 9.1.8)

   i) HIV+ patients whose HAART regimen may interact with dasatinib.

   j) Drugs that are generally accepted to have a risk of causing Torsades de Pointes including: (Patients must discontinue drug 7 days prior to starting dasatinib)

      i) procainamide, disopyramide

      ii) amiodarone, sotalol, ibutilide, dofetilide

      iii) erythromycin, clarithromycin

iv) chlorpromazine, haloperidol, mesoridazine, thioridazine

v) bepridil, droperidol, methadone, arsenic, chloroquine, domperidone, halofantrine, levomethadyl, pentamidine, sparfloxacin, lidoflazine.

k) The concomitant use of H2 blockers or proton pump inhibitors with dasatinib is not recommended. The use of antacids should be considered in place of H2 blockers or proton pump inhibitors in patients receiving dasatinib therapy.

l) Patient agrees to discontinue St. Johns Wort while receiving dasatinib therapy

m) Patient agrees that IV bisphosphonates will be withheld for the first 8 weeks of dasatinib therapy due to risk of hypocalcemia.

4) History of significant bleeding disorder unrelated to cancer, including:

a) Diagnosed congenital bleeding disorders (e.g., von Willebrand's disease)

b) Diagnosed acquired bleeding disorder within one year (e.g., acquired anti-factor VIII antibodies)

c) Ongoing or recent (≤ 3 months) significant gastrointestinal bleeding

5) Patients who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study.

6.0 TREATMENT OF SUBJECTS

6.1 Treatment Overview

6.1.1 Phase I Therapy with D-ICE

During the initial phase I portion of the study, dose limiting toxicities (DLT) will be defined based on the agent-specific toxicities of dasatinib including prolongation of blood count recovery significantly beyond that expected with ICE alone (see Section 6.5). Disease re-evaluation will be performed following 2, 4 and 6 courses of D-ICE.

Patients who achieve a complete response to therapy may undergo local control/consolidative therapy as clinically indicated (including surgical resection of metastatic sites of disease, if possible, or radiation to bony metastases) after 2-6 courses of D-ICE. Patients achieving a partial response or stable disease after 2 or 4 courses of D-ICE, may receive an additional 2 courses of D-ICE, up to a maximum of 6 courses of D-ICE.

Following completion of a maximum of 6 courses of D-ICE, patients will receive therapy with dasatinib alone for up to 6 months or until disease progression occurs. Single agent therapy will initially be at the same dose of dasatinib used in D-ICE, but may be escalated by one dose level, after two months of dasatinib alone. Patients treated at Level 4 of D-ICE, who have no dose limiting toxicities, may be escalated to the maximum dasatinib dose level 5.

No patients will be treated at dose level 5 in combination with ICE.

6.1.2 Phase II Therapy with D-ICE: Stratum A & B

In the phase II portion of the study, patients will receive D-ICE at the MTD, be evaluated for response after every two courses of D-ICE, undergo local control/consolidation with either surgery and/or radiation, and then will continue with dasatinib alone for a minimum of 6 months of dasatinib.

6.1.3 Phase II Therapy with D-ICE: Stratum C (Newly Diagnosed, Poor Risk Patients with Metastatic Disease at Diagnosis)

After completion of the Phase I portion of this study which will have determined the MTD of dasatinib when given with ICE, selected patients with metastatic disease at initial diagnosis and who have a poor risk (consisting of unresectable pulmonary metastases (six or more nodules) and/or disease involving multiple bones or other organs).for response and survival, will be treated at the MTD of D-ICE. These patients will receive D-ICE at the MTD, be evaluated for response after every two courses of D-ICE, undergo local control/consolidation with either surgery and/or radiation, and then will continue with dasatinib alone for a minimum of 6 months of dasatinib.

6.2 Study Registration

6.2.1 Subject Registration

6.2.1.1 Contact Requirements

Written consent must be documented on the appropriate consent form designated and approved by the Institutional Review Board at the institution at which the patient is enrolled.

For Phase I portion only: Before enrolling the patient, the Principal Investigator, Judith K. Sato, M.D. at (626) 930-5430 (office) or (626)257-1315 (cell phone) and/or her designee, must be contacted to discuss patient eligibility, assign dose level and review correlative studies.

Then, all patients must be centrally registered by fax to City of Hope National Medical Center at (626) 256-8787

6.2.1.2 Informed Consent/Assent

The investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks and discomforts, and potential alternative therapies will be carefully explained to the patient or the patient's parents or guardian if the patient is a child, and a signed informed consent and assent will be obtained according to the institutional guidelines.

6.2.1.3 Eligibility Checklist

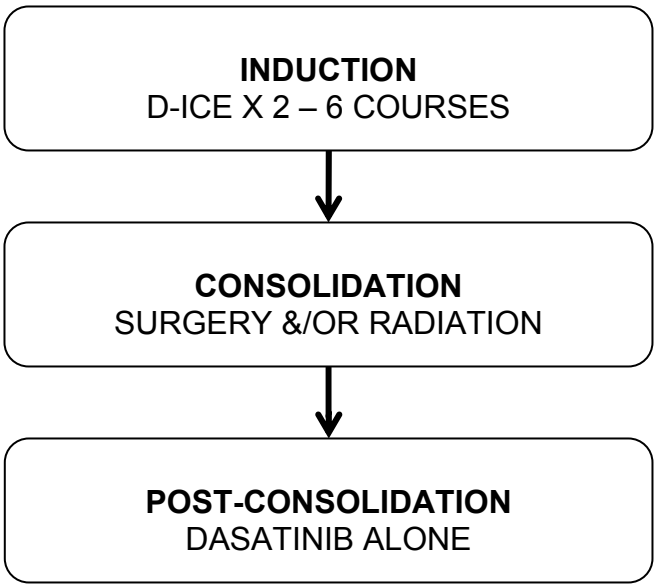
Before the patient can be enrolled, the responsible institutional investigator must sign and date the completed eligibility checklist. A signed copy of the checklist will be FAXed to the Principal Investigator, Judith K. Sato, M.D. at (626) 930-5415 and/or her designee (to facilitate enrollment verification as noted in 6.2.1.1) and City of Hope National Medical Center at (626) 256-8787.

6.2.1.4 Study Enrollment

Patients may be enrolled on the study once all eligibility requirements for the study have been met. Patients must be enrolled before treatment begins. Patients must not receive any protocol therapy prior to enrollment.

6.3 Study Treatment

Overall Study Plan:



Induction:

For the Phase I portion of study, dasatinib will be escalated as per table 3.

Consolidation:

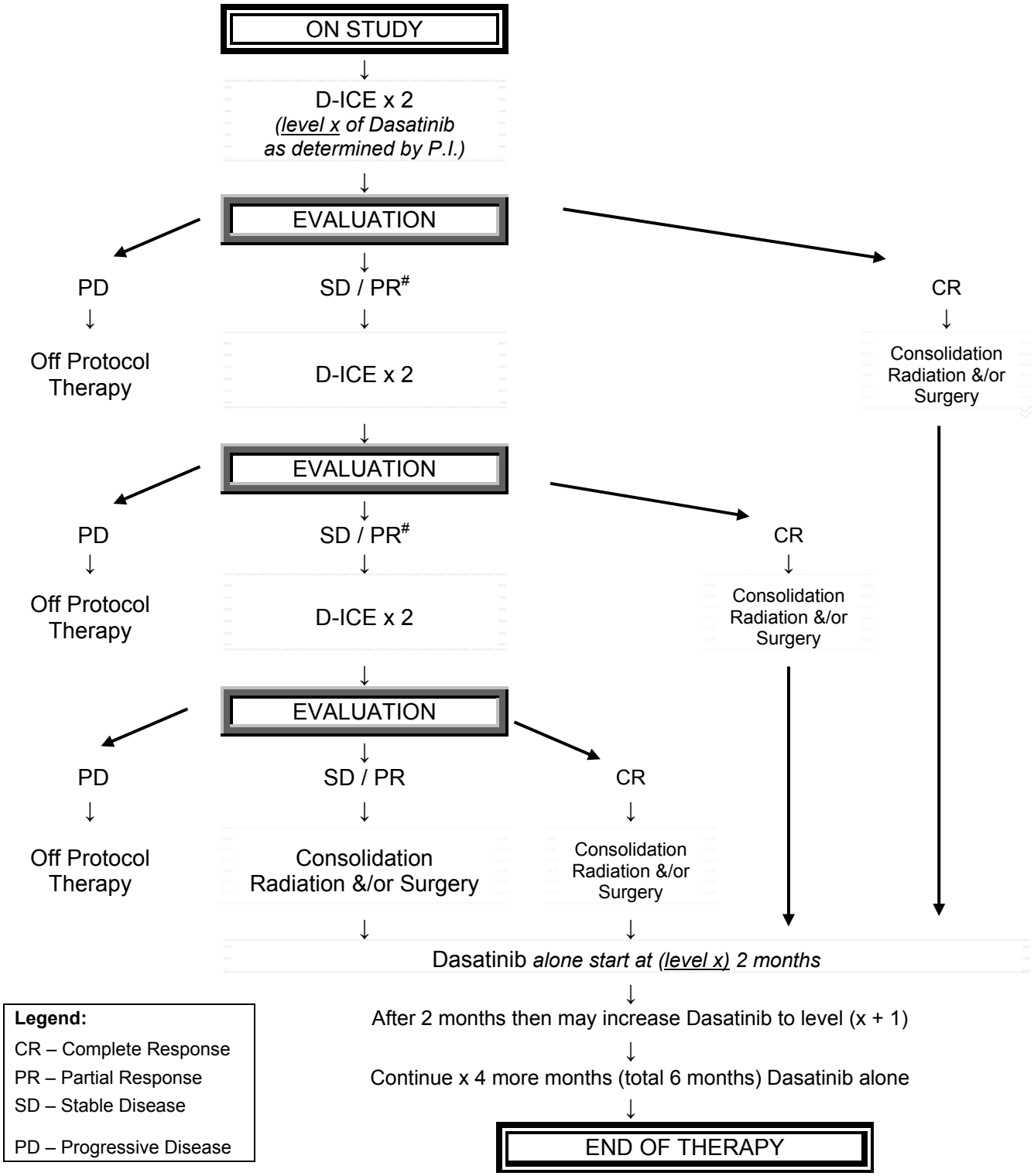
After 2-6 courses of D-ICE, patients will have surgery and/or radiation for residual disease (see Appendix 10 [Surgical Guidelines] and Appendix 11 [Radiation Therapy Guidelines])

Post-Consolidation: Dasatinib administered alone without ICE.

In the Phase I portion of study, dose of dasatinib starts at same level as study entrance.

In the Phase II portion of study, dose of dasatinib is at the M.T.D. as determined by the Phase I portion of study.

EXPERIMENTAL DESIGN SCHEMA*:



Legend:
CR – Complete Response
PR – Partial Response
SD – Stable Disease
PD – Progressive Disease

* **Phase I**: Dasatinib **(SPRYCEL®)** dose escalation per Table 3
Phase II: Dasatinib (**SPRYCEL®)** dose will be administered at the maximally tolerated dose, as determined by the Phase I portion of this study.

At Investigators discretion subject may proceed to consolidation, radiation and/or surgery

6.3.1 Dasatinib

1) Patients will receive dasatinib twice daily for 17 days, starting on Day 5 of each course until Day 21, of each course. One course of therapy will be 28 days. Use of a medication calendar to monitor patient compliance is recommended (See Appendix 2).

2) Drug doses should be adjusted based on the BSA determined at the beginning of each course and rounded to the nearest 5 mg.

3) If necessary to permit administration in young children, tablets may be allowed to dissolve into 1 oz of lemonade; double-strength juice is recommended to obscure the bitter taste (see section 9.1.8.1),

4) If the patient is unable to swallow a pill, dasatinib may be administered via a nasogastric tube or gastrostomy.

Table 3 Inter-patient Dose Escalation Schema (**Phase I portion only**):

Dasatinib Level	Dose, BID PO Daily x 17 days
Level -1	25 mg/m^2/dose
Level 1	35 mg/m^2/dose
Level 2	50 mg/m^2/dose
Level 3	65 mg/m^2/dose
Level 4	85 mg/m^2/dose
Level 5 (Dasatinib alone phase only)	110 mg/m^2/dose

5) In the Post-Consolidation phase of treatment, each patient will receive dasatinib only, and take the same dose as assigned for the Re-Induction phase of treatment. The patient will take the same dose twice a day, every day of each 28 day course of treatment. If there is no DLT from dasatinib alone after the first 2 months of dasatinib alone, the dose will be escalated by one dose level. Chemotherapy should be resumed two weeks after surgery is performed or thereafter when ANC > 750 /uL or platelets > 75,000 /uL.

6.3.2 Ifosfamide, Carboplatin, Etoposide

Ifosfamide, Carboplatin, Etoposide, MESNA doses will not be escalated.

Table 4: Schedule for Chemotherapy Administration

Drug	Route	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5 - 21	Day 22 - 28
Ifosfamide	Intravenous (IV)	X	X	X	X	X		
Carboplatin	Intravenous (IV)	X	X					
Etoposide	Intravenous (IV)	X	X	X	X	X		
Mesna	Intravenous (IV)	X	X	X	X	X		
Dasatinib	By mouth (oral)						X	
Rest								X

Ifosfamide 1800 mg/m^2/day IV over 1 hour per day x 5 days Q 28 days

Carboplatin 400 mg/m^2/day IV over 1 hour per day x 2 days Q 28 days

Etoposide 100 mg/m^2/day IV over 1 hour per day x 5 days Q 28 days

Dasatinib During Phase I (refer to table 3)
During Phase II (as determined in Phase I)

MESNA 360 mg/m^2/dose IV with ifosfamide, then 360mg/m^2 IV over 3 hours after completion of ifosfamide/mesna, then 360mg/m^2 IV over 15min Q3H x 3 more doses/day after completion of 3hr mesna infusion daily x 5 days on days 0-4 Q 28 days

Neupogen 5-10 microgms/kg/day subcutaneously, daily starting on Day 5, until ANC $\geq$ 10,000, every course; Neupogen required first course only. Neulasta may be given for subsequent courses to patient > 50 kg.

See DRUG INFORMATION, section 9, for guidelines for administration, formulation, source and pharmacology.

6.4 Grading Adverse Events

Adverse events (toxicities will be graded according to the NCI Common Terminology Criteria for Adverse Events v3.0 (CTCAE) http://ctep.cancer.gov/reporting/ctc.html, CTEP Simplified Disease Classification v1.0 (MedDRA v10.0) (Effective July 1, 2007) = CTCAE v3.0 (MedDRAv10.0) (Effective July 1, 2007). Any suspected or confirmed dose-limiting toxicity should be reported immediately (i.e. within 24 hours) to the Study Chair, Judith K. Sato, M.D. at (626) 930-5430

(office) or (626) 257-1315 (cell) and/or her designee. Case report forms outlining the DLT must be submitted to City of Hope National Medical Center at (626) 301-8787 by 7 days after the event.

6.5 Definition of Dose-Limiting Toxicity (DLT)

Definition of Dose Limiting Toxicity (DLT): DLT will be determined in the Phase I portion of this study. DLT will be defined as any of the following events that are possibly, probably or definitely attributable to dasatinib. Dose limiting toxicities likely due to ICE will be excluded from the definition of DLT for dasatinib. DLT will be determined in the Phase I portion of the study, as specified below.

6.5.1 Non-Hematological Dose-Limiting Toxicity

- Any Grade 4 non-hematological toxicity
- Any Grade 3 non-hematological toxicity, with the specific exception of:
    - Grade 3 nausea and vomiting of less than 3 days duration with appropriate anti-emetic therapy, and/or
    - Grade 3 transaminase elevation that return to levels that meet initial eligibility criteria within 13 days of study drug interruption and that do not recur upon study re-challenge with study drug
    - Grade 3 fever or infection < 7 days duration, and/or,
    - Grade 3 hypocalcemia responsive to oral calcium supplementation; note that an adequate response to oral calcium supplementation is a return to a $\leq$ grade 1 hypocalcemia.
- Any Grade 2 non-hematologic toxicity that persists for $\geq$ 7 days and is considered either sufficiently medically significant or sufficiently intolerable by patient that it requires treatment interruption;
- Any adverse event requiring interruption of study drug for 7 days or which recurs upon drug rechallenge.

6.5.2 Hematological Dose Limiting Toxicity

Hematologic suppression is an expected toxicity from ICE chemotherapy. Therefore, the definition of hematologic dose limiting toxicity will be modified to include the addition of Dasatinib to ICE. Prolongation of recovery to ANC > 750 /uL or platelets > 50,000 significantly beyond that expected with ICE alone. If these parameters are not attained by day 42 (14 days after the 28 day length of each course), then a DLT has occurred, see Section 6.7.1.1)

6.6 Criteria for Starting Subsequent Courses

A course may be repeated every 28 days if the patient has at least stable disease and has met the following laboratory parameters as defined in the eligibility section, except for hematologic parameters as follows:

- Peripheral absolute neutrophil count (ANC) $\geq$ 750/uL
- Platelet count $\geq$ 50,000 (transfusion independent)
- Hemoglobin $\geq$ 8.0 gm/dL (may receive RBC transfusions)

6.7 Dose Modifications

During the Phase I portion of this study, there will be no dose modification of dasatinib for mylosuppresion.

The Principal Investigator must be notified within 24 hours of any dose limiting toxicity as defined in section 6.5.

6.7.1 Myelosuppression

6.7.1.1 Neutropenia and Thrombocytopenia

Neutropenia and thrombocytopenia are expected toxicities of ICE chemotherapy. Dasatinib will be administered after ICE chemotherapy between days 5 and 21, for 17 days. There is a 7 day "rest" period between day 21 and 28. DLT for this study is defined as inability to start the next course of therapy by day 42. Thus, there is no dose modification for neutropenia or thrombocytopenia in the Phase I portion of the study. Dasatinib should be stopped for sepsis, overwhelming infection with neutropenia, or bleeding not responsive to best therapeutic measures. The Principal Investigator must be notified of any dose modification.

6.7.1.2 Hematological Dose Modifications in the Phase II study

If a patient experiences hematological dose-limiting toxicity, the treatment will be withheld. When the toxicity resolves to meet on study paramenters within 7 days of drug discontinuation, the patient may resume treatment at the next lower dose level in the subsequent course. For patients enrolled at dose Level 1, the dose should be reduced to 25 mg/m^2/dose.

If toxicity does not resolve to meet study parameters for re-treatment by day 42 of the course, the patient must be removed from study

If dose-limiting toxicity recurs in a patient who has resumed treatment at the reduced dose, the patient must be removed from study.

It is up to the discretion of the investigator/participating clinician for a patient to go off study.

6.7.2 Non-Hematological Toxicity

If a patient experiences non-hematological dose-limiting toxicity as defined in Section 6.5, the treatment will be withheld. When the toxicity resolves to meet on study paramenters within 7 days of drug discontinuation, the patient may resume treatment at the next lower dose level. For patients enrolled at dose Level 1, the dose should be reduced to 25 mg/m^2/dose.

If a patient misses a dose due to vomiting that does NOT qualify as a dose limiting toxicity as defined in Section 6.5.1, then the dose will be re-administered if the vomiting occurs within 15 minutes of drug ingestion. Doses will not be re-administered if the vomiting occurs more than 15 minutes after drug ingestion.

If toxicity does not resolve to meet on study parameters within 14 days of drug discontinuation, the patient must be removed from study.

If dose-limiting toxicity recurs in a patient who has resumed treatment at the reduced dose level, the patient must be removed from study.

6.7.3 Dose Escalation

6.7.3.1 Inter-patient Escalation Schema

The starting dose will be 35 mg/m^2/dose BID with dose level for subsequent groups of patients as follows:

Table 3 Inter-patient Dose Escalation Schema:

Dasatinib Level	Dose, BID PO Daily x 17 days
Level -1	25 mg/m^2/dose
Level 1	35 mg/m^2/dose
Level 2	50 mg/m2/dose
Level 3	65 mg/m^2/dose
Level 4	85 mg/m^2/dose
Level 5 (Dasatinib alone phase only)	110 mg/m^2/dose

There will be no dose escalations for dasatinib beyond Level 5 (110 mg/m^2/dose).

If the MTD has been exceeded at the first dose level, then the subsequent cohort of patients will be treated at a dose of 25 mg/m^2/dose.

After the initial re-induction phase of therapy and the local control/consolidative phase of treatment, patient will continue with dasatinib alone at the same assigned dose level at study entry. If after two post-consolidative courses of therapy, there is no dose limiting toxicities, the dose of dasatinib will be escalated by one level (intra-patient dose escalation).

6.8 Discontinuation of Therapy

Study therapy must be discontinued for the following reasons:

1) Progressive disease at any time
2) Any clinical adverse event, laboratory abnormality or intercurrent illness which, in the opinion of the Investigator, indicates that continued treatment with the study therapy is not in the best interest of the subject
3) Excessive toxicity despite dose reduction
4) Withdrawal of informed consent (subject's decision to withdraw for any reason)
5) Pregnancy

- All WOCBP should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period at any time during study participation. Institutional policy and local regulations should determine the frequency of on-study pregnancy tests for WOCBP enrolled in the study
- The Investigator must immediately notify the Principal Investigator and BMS in the event of a confirmed pregnancy in a patient participating in the study

All patients will be assessed for adverse events according to the NCI Common Terminology Criteria for Adverse Events v3.0 (CTCAE).

6.9 Prohibited and Restricted Therapies During Study

6.9.1 Prohibited Therapies

Subjects requiring any of the following prohibited therapies should not be enrolled.

Bisphosphonates

Intravenous bisphosphonates will be withheld for the first 8 weeks of treatment due to the risk of hypocalcemia. After the need for Ca^{2+} supplementation has been assessed and levels documented to be >LLN, subjects on prior bisphosphonate may be restarted with caution at the investigator's discretion.

CYP3A4

Drugs that may increase dasatinib plasma concentrations

Strong CYP3A4 Inhibitors: Dasatinib is primarily metabolized by the CYP3A4 enzyme. Therefore, potent inhibitors of CYP3A4 are prohibited during study; for such medications (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole), a wash-out period of $\geq$7 days is required prior to starting dasatinib. Subjects should be advised not to consume substantial quantities of grapefruit juice.

Drugs that may decrease dasatinib plasma concentrations

Strong CYP3A4 Inducers: Drugs that induce CYP3A4 activity may decrease dasatinib plasma concentrations. In patients in whom CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampicin, rifabutin, phenobarbital) are indicated, alternative agents with less enzyme induction potential should be used.

St. John's wort (*Hypericum perforatum*): May decrease dasatinib plasma concentrations unpredictably. Patients receiving dasatinib should not take St. John's wort.

H_2 Blockers/Proton Pump Inhibitors: Long-term suppression of gastric acid secretion by H_2 blockers or proton pump inhibitors (e.g., famotidine and omeprazole) is likely to reduce dasatinib exposure. The concomitant use of H_2 blockers or proton pump inhibitors with dasatinib is not recommended. The use of antacids should be considered in place of H_2 blockers or proton pump inhibitors in patients receiving dasatinib therapy.

In patients receiving treatment with dasatinib, close monitoring for toxicity and a dasatinib dose reduction should be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided.

Medications that prolong QT Interval

Subjects enrolled in this study should not take or begin to take concomitant medications known to prolong the QT interval. For such medications, a wash-out period of ≥7days is required prior to starting dasatinib. (Agents which may possibly prolong the QT interval are restricted). Medications known to prolong the QT interval (Class I; see http://www.qtdrugs.org/medical-pros/drug-lists/drug-lists.htm) are:

Drugs that are generally accepted to have a risk of causing Torsades de Pointes include:

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

Should the Investigator believe that beginning therapy with a potentially QT prolonging medication (other than the ones explicitly prohibited) is vital to an individual subject's care, the Investigator must check that the subject's prior on-therapy EKG has not shown a QTcF ≥ 450 msec or an increase in QTc ≥ 60 msec over the baseline value.

6.9.2 Restricted Therapies

Drugs that may have their plasma concentration altered by dasatinib

CYP3A4 Substrates: CYP3A4 substrates known to have a narrow therapeutic index such as alfentanil, astemizole, terfenadine, cisapride, cyclosporine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, or ergot alkaloids (ergotamine, dihydroergotamine) should be administered with caution in patients receiving dasatinib.

Less-potent inhibitors, inducers, and substrates of CYP3A4 are restricted.

Antacids: Nonclinical data demonstrate that the solubility of dasatinib is pH dependent. Simultaneous administration of dasatinib with antacids should be avoided. If antacid therapy is needed, the antacid dose should be administered at least 2 hours prior to or 2 hours after the dose of dasatinib.

Medications that inhibit Platelet Function and Anticoagulants

Caution should be exercised if patients are required to take medications that inhibit platelet function or anticoagulants.

Subjects enrolled in this study should not take concomitant medications which durably inhibit platelet function. For such medications, a wash-out period of ≥7days is required prior to starting dasatinib. (Agents which inhibit platelet function transiently or inhibit coagulation by other mechanisms are restricted.)

Medications which directly and durably inhibit platelet function include:

- dipyridamole
- tirofiban, dipyridamole, epoprostenol, eptifibatide, cilostazol, abciximab, ticlopidine, cilostazol

Medications which directly and durably inhibit anticoagulation include:

- Exceptions: low-dose warfarin for prophylaxis to prevent catheter thrombosis, and heparin for flushes of IV lines.

7.0 EVALUATION AND VISIT SCHEDULE

7.1 Required Clinical, Laboratory and disease Evaluation

All entry and eligibility studies must be performed within 2 week prior to treatment, unless otherwise specified. If more than 14 calendar days elapse between the date eligibility studies outlined in Section 5.1 were obtained and the start date of treatment, then the following studies must be repeated prior to treatment: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If any of these repeat laboratory studies are outside the parameters required for eligibility, then the patient is off study. Imaging studies are required within 2 weeks prior to study entry.

STUDIES	Pre-Study	During Phase I Course 1	Subsequent Courses	End of therapy / relapse
History	X	X	Start of each course	X
Physical Exam with vital signs	X	Weekly	Days 1 and 14 of each course	X
Height, weight, BSA	X	X	Start of each course	X
Performance Status	X			X
CBC, differential, platelets	X	Twice Weekly (every 3 to 4 days)[3]	Weekly[4]	X
Peripheral blood for biology studies[1]	X	Day 14 - 21 or when WBC $\geq$ 500	Day 14 - 21 or when WBC $\geq$ 500 of each course	X
Electrolytes including Ca, PO4, Mg	X	Weekly	Days 1 and 14 of each course[5]	X
Creatinine, ALT, bilirubin	X	Weekly	Days 1 and 14 of each course[5]	X
Total protein/albumin	X	Days 1 and 14 of each course	Days 1 and 14 of each course[5]	X
Disease Evaluation	X		Start of every other course[6]	X
Pregnancy Test[2] (must be done wihtin 72 hours prior to 1st dose of treatment)	X			
EKG	X		Start of each course prior to Consolidation; Start of first post-consolidation course & any time dasatinib dose escalated	
Echocardiogram/MUGA	X		As clinically indicated	
Tumor tissue for Correlative Studies[1]	X		From any surgical specimen; At time of progression, if possible	X

1 See Section 7.2 for details and timing of biology studies

2 Patients of child bearing 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.

3 If patients develop Grade 4 neutropenia, then CBCs should be checked every other day until recovery to Grade 3.

4 If patient develop Grade 4 neutropenia, then CBCs should be checked every 3 to 4 days until recovery to Grade 3

5 Day 14 Chemistry tests required for the Phase I portion of study only

6 Disease Evaluation should be obtained every other course after initial documentation of either a PR, CR, or SD, or at time of suspected disease relapse or progression.

7.1.1 Post-therapy Evaluation

7.1.1.1 First year off-therapy (reporting every 6 months)

- Physical and history with pertinent laboratory test examinations every months x 6 months then every 2 months x 6 months
- Imaging studies that were positive at study entry every 3 months

7.1.1.2 Second and subsequent years off-therapy (reporting every year)

- Physical and history with pertinent laboratory test examination every 3 months
- Imaging studies that were positive at study entry every 6 months

7.2 Correlative Laboratory Studies

7.2.1 Overview of Laboratory Studies

Our primary emphasis for correlative laboratory studies will be peripheral blood mononuclear cells from the majority of patients for pre-treatment and on-treatment surrogate molecular marker analysis. In all cases, we will use standard protocols that we have optimized for the biomarkers indicated below. Whenever possible, tissue biopsies will also be collected for biomarker immunohistochemistry, with any remaining tissue specimens to be used for future microarray gene-expression profiling. Funding for the collection and processing of clinical specimens at all study sites is being requested from BMS and from the Pediatric Cancer Foundation. The Jove Laboratories will provide their own funding for the correlative laboratory biomarker and microarray analyses performed at the City of Hope.

7.2.2 Peripheral Blood Mononuclear Cells

Based upon prior experience, we expect that only a minority of patients will consent to have pre-treatment and on-treatment tissue biopsies performed. Peripheral blood mononuclear cells are easily isolated and express many relevant tyrosine kinases, including SRC and FAK. Consequently, we will assess phosphorylation levels of these proteins in circulating mononuclear cells as a surrogate marker for dasatinib drug activity in all patients who consent to have blood drawn. **Ten ml of peripheral blood** will be collected from study participants **at the time of study initiation (baseline), and on day 14- 21 or when WBC $\geq$ 500 of dasatinib treatment during all subsequent courses (total of 13 specimens).** Blood specimens should be collected in an EDTA (purple top) tube, labeled properly and kept in an ice-bath at 0ºC until delivered to the local institutional laboratory for centrifugation. The blood must promptly undergo Ficoll-Hypaque gradient separation by gradient centrifugation at 1200 rpm and at 4ºC in a clinical centrifuge; the mononuclear cells will be collected from the interface. Mononuclear cells will be immediately frozen and stored frozen at -70 º C until shipped on dry ice to Translational Research Laboratory (see Sections 7.2.4 and 7.2.5).

For biomarkers analysis, the frozen cell pellets of mononuclear cells will be thawed in cell lysis buffer, which preserves the phosphorylation state of cellular proteins. After brief centrifugation, the insoluble components will be removed, and protein lysates will be analyzed by Western blotting for total and phospho-SRC, phospho-FAK and other relevant biomarkers described below.

7.2.3 Tumor Specimens

Due to the labile nature of protein phosphorylation, only freshly acquired tissue will be used for these studies. Tissue specimens will be collected from patients in accordance with the standard of care required for each individual case, primarily either core biopsies and in some cases surgical biopsies. The most important issues are the tissue processing time and methods. It is extremely critical to either fix or snap freeze the specimens within 15 min of procurement, in order to preserve the phosphorylation state of SRC and other signaling proteins (34). Formalin fixation and paraffin embedding will be done according to standard protocols, and snap freezing will be in liquid nitrogen. Since only a minority of patients are expected to provide tissue specimens, we will also perform surrogate marker analysis using mononuclear white blood cells for the majority of patients (see section 7.2.2)

If core biopsies are indicated, multiple passages will be performed to obtain several cores of the tumor tissues prior, during, and/or relapse/progression to dasatinib treatment. Cores will be processed as follows: 1) one core for formalin fixation to be used for immunohistochemistry (e.g., phospho-SRC; see below for additional biomarkers) of paraffin-embedded specimens; 2) another core will be used for snap frozen sections to determine quality (e.g., absence of necrosis or fibrosis, and % tumor cells); 3) extra core to be placed in RNAlater 4) any remaining cores will be snap frozen for future studies (e.g., microarray gene-expression profiling, see below).

In cases where tumor is resected prior to initiating dasatinib therapy and/or during relapse/progression, both tumor and adjacent non-tumor tissues will be collected whenever possible. The non-tumor tissues will be collected as far away from the tumor tissue as possible. A piece of tissue at least 1.5 cm x 1 cm x 1 cm will be excised from each of the selected areas. This piece will be divided into three fragments and processed for formalin fixation, snap freezing and RNAlater, as described above for the core biopsies.

We have extensive experience with all of the correlative laboratory methods described below (34, 35) Pre-treatment and on-treatment (if possible on day 14 - 21 or when WBC $\geq$ 500 of dasatinib treatment), formalin-fixed, paraffin-embedded sections will be subjected to immunohistochemistry analysis for total SRC and phospho-SRC, phospho-FAK, phospho-STAT3, as previously described by us in primary breast tumors from high-risk breast cancer patients treated with neoadjuvant chemotherapy with docetaxel and doxorubicin (34, 35). In these prior studies, we performed computer-assisted quantitative image analysis on digitized microscopy images, and similar analyses will be carried out in the present study to quantify biomarkers. Other relevant biomarkers associated with SRC signal transduction and/or dasatinib response that will be examined in a similar fashion include phospho-KIT, phospho-PDGFR, EPHA2, and VEGF. All paraffin-embedded, formalin-fixed specimens may be kept at room temperature.

A second priority will be to perform microarray gene-expression profiling, preferably using frozen tissue specimens obtained from pre-treatment biopsies, based on the Affymetrix GeneChip platform. Laboratory data will be analyzed by appropriate biostatistics and bioinformatics methods in order to reveal correlations of biomarkers and gene expression profiles with response to dasatininb treatment. We have extensive experience with all of the above microarray procedures and data analysis methods (35). The goal of these microarrays studies will be to define a potential molecular signature or gene expression pattern that may predict response to dasatinib.

7.2.4 Blood Sample Labeling

Each specimen must be labeled with the patient's identifying number. Labels are patient and sampling time point specific and are not to be interchanged between patients. Each tube must be labeled with the patient's study registration number, the study I.D., the date and time the sample was drawn, specimen type and timepoint. Once affixed on tubes, the labels should be wrapped completely by applying protective transparent tape for protection during handling, storage and shipment. Data are to be recorded on the COH Specimen Transmittal Form (Appendix 3), which must accompany each specimen.

Label Sample:	Study Registration number: Study ID number: RPN number: Date: Time: Specimen type: Timepoint:

7.2.5 Blood Sample Shipping Instructions

Please send frozen peripheral blood mononuclear cells on dry ice by Federal Express to:

Translational Research Laboratory
City of Hope Cancer Center
1500 E. Duarte Road
KCRB 1026
Duarte, CA 91010
Fax: 626 471 7204

Attention: Yafan Wang, M.S., M.P.H., Lab Coordinator
Tel: 626 256 4673 x65544
Email: yawang@coh.org

Linling Chen, M.S.
Tel: 626 256 4673 x64784
Email: lchen2@coh.org

Ship specimens by Federal Express Priority Overnight using the COH Federal Express account number _____ (TBD). Arrange for Federal Express pickup per your usual institutional procedure or by calling 1-800-238-5355. Please include email notification to the COH at jsato@coh.org **and yawang@coh.org** on the billing slip. When requesting pick-up, be sure to give the account number on the preprinted air-bill, but stress that pick-up is at your institutional address. Specimens should only be sent to the COH Monday-Thursday for Tuesday-Friday delivery. If a specimen is obtained on a Friday, please hold it under appropriate conditions until the following Monday.

7.2.6 Tumor Specimen Labeling

Labels are patient and sampling time point specific and are not to be interchanged between patients. Each specimen container must be labeled with the patient's study registration number, the study I.D., and the date and time the sample was procured. Once affixed on the specimen container, the labels should be wrapped completely by applying protective transparent tape for protection during handling, storage and shipment. Data are to be recorded on the COH Specimen Transmittal Form (Appendix 3), which must accompany the sample(s).

7.2.7 Tumor Specimen Shipping Instructions

The COH provides specimen procurement kits upon request. To obtain a specimen procurement kit, call the COH at (626) 930-5430 during regular business hours, between 8 AM and 4 PM (Pacific time) Monday through Friday. The specimen procurement kit is constructed to allow shipment of frozen (on dry ice) and ambient temperature tissues in the same container. Dry ice may be placed in either compartment of the kit, but should not be put in both.

Ship specimens by Federal Express Priority Overnight using the COH Federal Express account number _____ (TBD). Arrange for Federal Express pickup per your usual institutional procedure or by calling 1-800-238-5355. Please include email notification to the COH at jsato@coh.org **and yawang@coh.org** on the billing slip. When requesting pick-up, be sure to give the account number on the preprinted air-bill, but stress that pick-up is at your institutional address. Specimens should only be sent to the COH Monday-Thursday for Tuesday-Friday delivery. If a specimen is obtained on a Friday, please hold it under appropriate conditions until the following Monday.

Using a waterproof marker, clearly label specimens with the COH number, patient I.D. number, Study number, and date and time specimen was obtained. Before placing the specimens in the appropriate compartments of the Specimen procurement Kit, please place the individual specimen bags (keeping ambient and frozen specimens separated) first into the watertight biohazard diagnostic envelope with absorbent material. Next place the biohazard diagnostic envelope into the pressure-proof Tyvek diagnostic envelope and seal the envelope securely.

Frozen tissue must be sent on dry ice in one compartment of the Specimen Procurement Kit. The blocks, slides or formalin fixed tissue should be shipped in the other compartment of the kit. Be sure to include the specimen transmittal form with the shipment. If available, also include the institutional pathology report.

Ship all specimens to:

Translational Research Laboratory
City of Hope Cancer Center
1500 E. Duarte Road
KCRB 1026
Duarte, CA 91010
Fax: 626 471 7204

Attention: Yafan Wang, M.S., M.P.H., Lab Coordinator
Tel: 626 256 4673 x65544
Email: yawang@coh.org

Linling Chen, M.S.
Tel: 626 256 4673 x64784
Email: lchen2@coh.org

7.2.8 Summary: Submission of Biological Specimens

Please see Appendix 4 for an Overview summarizing specimen types and procurement, for all correlative biological specimens requested for this study.

8.0 EFFICACY ASSESSMENTS

8.1 Response Criteria for Patients with Solid Tumors (RECIST)

Although patients will be enrolled on the portion of the Phase I study, response data will be collected and analyzed. All Phase II patients response will be required for study.

This study will use the Response Evaluation Criteria in Solid Tumors (RECIST) from the NCI for assessment of radiographic response.

8.1.1 Measurable Disease

The presence of at least one lesion that can be accurately measured in at least one dimension, with the longest diameter (LD) at least 20 mm. With spiral CT scan, lesions must be at least 10 mm. The investigator will identify up to 10 measurable lesions to be followed for response.

Serial measurements of lesions are to be done with appropriate imaging modalities (bone scans cannot be used to measure lesions). The same method of assessment will be used to characterize each identified and reported lesion at baseline and during followup.

8.1.1.1 Quantification of Disease Burden

The sum of the longest diameter (LD) for all target lesions will be calculated and reported as the disease measurement.

8.1.1.2 End of Course Response

a) Complete Response (CR)

Disappearance of all target and non-target lesions.

b) Partial Response (PR)

At least a 30% decrease in the disease measurement, taking as reference the disease measurement done to confirm measurable disease at study entry

c) Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest disease measurement since the treatment started.

d) Progressive Disease (PD)

At least a 20% increase in the disease measurement, taking as reference the smallest disease measurement recorded since the start of treatment, or the appearance of one or more new lesions, or evidence of laboratory or clinical progression.

8.1.2 Evaluable Disease

The presence of at least one lesion that cannot be accurately measured in at least one dimension. Such lesions may be evaluable by nuclear medicine techniques, immunocytochemistry techniques, tumor markers or other reliable measures.

8.1.2.1 Response Criteria for Patients with Solid Tumors and Evaluable Disease

a) Complete Response (CR)

Disappearance of all evaluable disease

b) Partial Response (PR)

Partial responses cannot be determined in patients with evaluable disease

c) Stable Disease (SD)

That which does not qualify as Comprete Response (CR), Partial Response (PR), or Progressive Disease (PD).

d) Progressive Disease (PD)

The appearance of one or more new lesions, or evidence of laboratory, clinical or radiographic progression.

8.1.2.2 Overall Response Assessment

Each patient will be classified according to their “best response” for the purposes of analysis of treatment effect. Best response is determined from the sequence of the objective criteria described below (see Section 8.2).

8.2 Best Response

Two objective status determinations of disease status, by CT or MRI, obtained on two consecutive determinations, separated by at least four weeks, are required to determine the

patient's overall best response. Two objective status determinations of CR before progression are required for best response of CR. Two determinations of PR or better before progression, but not qualifying for a CR, are required for a best response of PR. Two determinations of stable/no response or better before progression, but not qualifying as CR or PR, are required for a best response of stable/no response; if the first objective status is unknown, only one such determination is required. Patients with an objective status of progression on or before the second evaluations (the first evaluation is the first radiographic evaluation after treatment has been adminstered) will have a best response of progressive disease. Best response is unknown if the patient does not qualify for a best response of progressive disease and if all objective statuses after the first determination and before progression are unknown.

8.3 Definitions of PFS, OS, and PFS rate and OS rate are defined in section 11.0

9.0 STUDY DRUGS INFORMATION

9.1 Dasatinib [SPRYCEL®]

9.1.1 Physical/Chemical:

N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl] amino]-5-thiazolecarboxamide, monohydrate (NSC# 732517)

9.1.2 Mechanism of Action:

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

9.1.3 Molecular Formula:

C22H26CIN7O2S. H2O

9.1.4 Formula Weight:

BMS-354825 monohydrate: 506.02 daltons and anhydrous free base is 488.01

9.1.5 Potential Drug Interactions:

Dasatinib [SPRYCEL®/ BMS-354825] is primarily metabolized by the human CYP3A4 enzyme, is a significant inhibitor of CYP3A4, and is a weak inhibitor of CYP1A2, CYP2D6, CYP2C9, and CYP2C19. It may decrease the metabolic clearance of drugs that are significantly metabolized by the CYP3A4 enzyme. Due to the potential of Dasatinib to prolong the QT/QTc, use caution when administering Dasatinib with other potential QTc-prolonging medications.

Due to the possibility of gastrointestinal, cardiac, and cutaneous hemorrhage, avoid using using medications that inhibit platelet function or anticoagulants with Dasatinib.

Dasatinib is not a p-glycoprotein inhibitor.

9.1.6 Source and Pharmacology

The investigational new drug substance (an aminothiazole analogue), Dasatinib, is a SRC kinase inhibitor that is currently under development for treatment of chronic myelogenous leukemia (CML) and as a broad-spectrum antitumor agent against solid tumors. [SPRYCEL®] is a potent, broad spectrum ATP-competitive inhibitor of 5 critical oncogenic tyrosine kinase families: BCRABL, SRC family kinases, c-KIT, ephrin (EP) receptor kinases, and PDGFβ receptor.

Each of these protein kinases has been strongly linked to multiple forms of human malignancies. Animal studies have shown that Dasatinib is likely to have >50% oral absorption in humans, is highly bound to serum proteins (>91%), has extensive extravascular distribution and has a moderate rate of blood clearance in the animal species studied. Preclinical studies in humans with Dasatinib have demonstrated a mean terminal half-life of around 4 hours (range:2.5-11.1 hours) and rapid oral absorption with peak levels at 0.5-3 hours on average. Urinary excretion plays only a minor role in the elimination of Dasatinib. Dasatinib is primarily metabolized in the liver by the human CYP3A4 enzyme, is a significant inhibitor of CYP3A4, and is a weak inhibitor of CYP1A2, CYP2D6, CYP2C9, and CYP2C19. Dasatinib may decrease the metabolic clearance of drugs that are significantly metabolized by the CYP3A4 enzyme. Due to the potential of Dasatinib to prolong the QT/QTc, caution must be used when administering Dasatinib with other potential Qtcprolonging medications. Due to the possibility of gastrointestinal, cardiac, and cutaneous hemorrhage, avoid using medications that inhibit platelet function or anticoagulants in conjunction with Dasatinib. (Dasatinib is not a p-glycoprotein inhibitor.)

9.1.7 Formulation and Stability

Dasatinib is available in the following tablet and bottle sizes:

Strength	Description
5 mg	round, plain white film-coated tablets containing 30 tablets per bottle.
20 mg	biconvex round, white to off-white film-coated tablets containing 30 tablets per bottle. The tablet is debossed with “20” on one side and “527” on the other side.
50 mg	biconvex oval, white to off-white film-coated tablets containing 30 tablets per bottle. The tablet is debossed with “50” on one side and “528” on the other side.
70 mg	biconvex round, white to off-white film-coated tablets containing 30 tablets per bottle. The table is debossed with “BMS” on one side and either “468” or “524” on the other side.

Each bottle will be labeled with the following information at a minimum: product name, table strength, batch number, directions for use, storage conditions, and appropriate caution statements.

Storage:

The intact bottles should be stored at controlled room temperature 15°-25°C (59°-77°F)

9.1.8 Guidelines for Administration

See the Treatment and Dose Modifications Sections of the protocol (Sections 6.3 and 6.7)

While the risk from dermal exposure is considered minimal, it is advised that protective gloves be worn when handling the study medication. A mask is not required when handling the study medication. Pregnant women or breastfeeding mothers should not handle Dasatinib.

9.1.8.1 Dosing Solution Procedure

Dasatinib tablets can be allowed to dissolve in solution and mixed with lemonade. The following is the procedure for preparation of the lemonade dosing solution:

1. Mix the contents of one 12 ounce can of Minute Maid Premium Frozen Concentrate with 2 cans (i.e. the emptied lemonade container) of water. This will produce a lemonade that is a little

more than twice as concentrated as the instructions on the can with a sweeter taste. Please keep the lemonade solution refrigerated when not in use.

2. Place 1 ounce (30 mL) of this lemonade solution into a drinking glass.

3. Place the proper dose of intact tablets into the lemonade. Please be sure to always wear protective gloves when handling the medication. A mask is not required when handling the medication. Always use the 1 oz of lemonade. Do not increase the lemonade volume.

4. Start timing for 20 minutes. At approximately the 5 minute mark, swirl the contents of the glass well for about 3 seconds.

5. At approximately the 15 minute mark, swirl the contents of the glass a second time. At the 20 minute mark, swirl the contents of the glass one last time. Immediately administer the entire contents of the glass.

6. In order to ensure administration of the entire medication dose, a rinsing step is necessary. Add 0.5 ounce (15 mL) of lemonade into the same glass that has just been emptied. Swirl the contents to remove any remaining signs of tablets from the sides or bottom of the glass.

7. Administer the washing lemonade to the patient.

If a young child is unable to swallow a pill, Dasatinib may be administered via a naso-gastric tube (NGT) or gastrostomy.

9.1.9 Dispensing

It is the responsibility of the Investigator to ensure that dasatinib is only dispensed to study subjects. Dasatinib must be dispensed only from official study sites by authorized personnel according to local regulations.

The Investigator (or assigned designee, i.e., study pharmacist) will dispense the proper number of each strength tablet to the the subject to satisfy dosing requirements for the study. The containers provided to the subject should be labeled with proper instructions for use. The lot numbers, dosing start dates and the number of tablets for each dosage strength must be recorded on the drug accountability pages of record for the site. The subject must be instructed to return all unused dasatinib in the provided packaging at each subsequent visit.

9.1.9.1 Supplier

Dasatinib [SPRYCEL®] is supplied by Bristol-Myers Squibb.

9.1.10 Obtaining the Agent

Initial orders of dasatinib will be requested by the assigned BMS protocol manager. Initial drug supply is provided for a 12 week treatment period per subject.

Re-suppply requests can be obtained by completing the SRC re-supply request form and submitting the request form electronically via e-mail to srcsupply@bms.com. Re-supply requests should be submitted at least 5 – 7 business days before the expected delivery date. Deliveries will be made Tuesday through Friday.

9.1.11 Dasatinib Accountability

It is the responsibility of the Investigator to ensure that a current record of dasatinib disposition is maintained at each study site where dasatinib is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area
- Amount currently in storage area
- Label ID number or batch number and use date or expiring date

- Dates and initials of person responsible for each dasatinib inventory entry/movement
- Amount dispensed to and returned by each subject, including unique subject identifiers
- Amount transferred to another area/site for dispensing or storage
- Non-study disposition (e.g., lost, wasted, broken)
- Amount returned to BMS, if applicable
- Retain samples sent to third party for bioavailability/bioequivalence, if applicable.

Dasatinib dispensing record/inventory logs and copies of signed packing lists must be maintained at the investigational site. Batch numbers for dasatinib must be recorded in the drug accountability records.

9.1.12 Destruction of Dasatinib

It is the Investigator/s responsibility to ensure that arrangements have been made for disposal and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures. Appropriate records of the disposal must be maintained.

9.1.13 Dasatinib Toxicity (revised per IB version IX, dated 11/03/2009)

System Organ Class	Adverse Reaction Very Common (≥ 1/10)	Adverse Reaction Common (≥ 1/100 to < 1/10)	Adverse Reaction Uncommon (≥ 1/1,000 to < 1/100)	Adverse Reaction Rare (≥ 1/10,000 to < 1/1,000)
Infections and infestations	• Infection (including bacterial, viral, fungal, non-specified)	• Pneumonia (including bacterial, viral, and fungal) • Upper respiratory tract infection/inflammation • Herpes virus infection • Enterocolitis infection • Sepsis (including fatal outcomes)		
Neoplasms benign, malignant and unspecified (including cysts and polyps)			• Tumor lysis syndrome	
Blood and lymphatic system disorders		• Febrile neutropenia • Thrombocytopenia • Anemia • Leukopenia • Pancytopenia		• Aplasia pure red cell
Immune system disorders			• Hypersensitivity (including erythema nodosum)	

System Organ Class	Adverse Reaction Very Common (≥ 1/10)	Adverse Reaction Common (≥ 1/100 to < 1/10)	Adverse Reaction Uncommon (≥ 1/1,000 to < 1/100)	Adverse Reaction Rare (≥ 1/10,000 to < 1/1,000)
Metabolism and nutrition disorders		• Appetite disturbances • Anorexia • Hyperuricemia		
Psychiatric disorders		• Depression • Insomnia	• Anxiety • Confusional State • Affect lability • Libido decreased	
Nervous system disorders	• Headache • Lightheadedness	• Dizziness • Neuropathy (including peripheral neuropathy) • Dysgeusia • Somnolence	• Reversible posterior leukoencephalopathy syndrome • Amnesia • Tremor • Syncope • Central nervous system hemorrhage[a]	• Transient ischemic attack • Convulsion • Cerebrovascular accident
Eye disorders		• Dry eye • Visual disorder (including visual disturbance, vision blurred, and visual acuity reduced	• Conjunctivitis	
Ear and labyrinth disorders		• Tinnitus	• Vertigo	
Cardiac disorders		• Congestive heart failure/ Cardiac dysfunction • Pericardial effusion • Arrhythmia (including tachycardia) • Palpitations	• Cardiomegaly • Angina pectoris • Myocardial infarction • Pericarditis • Ventricular tachycardia • Electrocardiogram QT prolonged	• Acute coronary syndrome • Myocarditis • Cor pulmonale
Vascular disorders	• Hemorrhage	• Hypertension • Flushing	• Hypotension • Thrombophlebitis	• Livedo reticulares
Respiratory, thoracic and mediastinal disorders	• Pleural effusion • Dyspnea • Cough	• Pulmonary edema • Lung infiltration • Pneumonitis • Pulmonary Hypertension	• Asthma • Bronchospasm	• Acute respiratory distress syndrome

System Organ Class	Adverse Reaction Very Common (≥ 1/10)	Adverse Reaction Common (≥ 1/100 to < 1/10)	Adverse Reaction Uncommon (≥ 1/1,000 to < 1/100)	Adverse Reaction Rare (≥ 1/10,000 to < 1/1,000)
Gastrointestinal disorders	• Diarrhea • Nausea • Vomiting • Abdominal pain • Gastrointestinal hemorrhage	• Abdominal pain • Abdominal distension • Mucosal inflammation (including • Mucositis / stomatitis) • Colitis (including neutropenic colitis) • Gastritis • Oral soft tissue disorder • Dyspepsia • Constipation • Dehydration	• Pancreatitis • Upper gastrointestinal ulcer • Ascites • Dysphagia • Anal fissure • Esophagitis	
Hepatobiliary disorders			• Hepatitis, • Cholestasis	• Cholecystitis
Skin and subcutaneous tissue disorders	• Skin rash[a]	• Pruritus • Alopecia • Acne • Dry skin • Urticaria • Hyperhydrosis • Dermatitis (including eczema)	• Acute febrile neutrophilic dermatosis • Photosensitivity reaction • Pigmentation disorder • Skin ulcer • Bullous conditions (including • Erythema multiforme) • Nail disorder • Palmar-plantar • Erythrodysesthesia syndrome • Panniculitis	
Musculoskeletal and connective tissue disorders	• Musculoskeletal pain	• Arthralgia • Myalgia • Muscle inflammation • Muscular weakness • Musculoskeletal stiffness	• Rhabdomyolysis	• Tendonitis
Renal and urinary disorders			• Renal failure • Urinary frequency proteinuria	
Reproductive system and breast disorders			• Gynecomastia • Menstruation irregular	

System Organ Class	Adverse Reaction Very Common (≥ 1/10)	Adverse Reaction Common (≥ 1/100 to < 1/10)	Adverse Reaction Uncommon (≥ 1/1,000 to < 1/100)	Adverse Reaction Rare (≥ 1/10,000 to < 1/1,000)
General disorders and administration site conditions	• Superficial edema[b] • Fatigue • Pyrexia	• Pain • Chest pain • Chills • Asthenia	• Malaise • Temperature intolerance • Lethargy	
Investigations		• Weight decreased • Weight increased	• Blood creatinine phosphokinase increased	
Injury, poisoning, and procedural complications		• Contusion		
Metabolic/laboratory	• Hypocalcemia		• Hypoalbuminemia	

[a] Includes erythema, exfoliative rash, generalized erythema, milia, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, skin exfoliation, systemic lupus erythematosus rash, urticaria vesiculosa, drug eruption, and rash vesicular.
[b] Includes eye edema, eye swelling, eyelid edema, orbital edema, face edema, periorbital edema, swelling face, gravitational edema, localized edema, edema peripheral, pitting edema, edema genital, scrotal edema.

9.2 Ifosfamide (IFX, IFOS) NSC #109724

9.2.1 Source and Pharmacology:

Ifosfamide (IFOS) is a structural analogue of cyclophosphamide. Ifosfamide requires hepatic microsomal activation for the production of the reactive 4-hydroxyoxazaphorine intermediate which serves as a carrier molecule for the ultimate intracellular liberation of phosphoramide mustard, an alkylating agent. The occurrence of another reactive metabolite, acrolein, is thought to be the cause of the hemorrhagic cystitis, identical to that seen with cyclophosphamide. The metabolism of ifosfamide is dose-dependent, with the terminal halflife varying between 7 and 16 hours at doses of 1.6-2.4g/m² and 3.8-5 g/m², respectively. At 1.6- 2.4g/m²/d, 12 to 18% of the dose was excreted in the urine, whereas at 5g/m² single-dose, 61% was excreted in the urine. Evidence also exists to suggest that metabolism is inducible, with more rapid clearance occurring in the second and later doses of fractionated courses of 3-5 times daily.

Unlike cyclophosphamide, as much as 50% of a large dose of ifosfamide may be subject to alternative metabolic degradation, with the production of reactive but non-cytotoxic species.

Some of these products (chloracetaldehyde) are suggested as being the cause of ifosfamide neurotoxicity.

9.2.2 Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to<5 children out of every 100
Immediate Within 1-2 days of receiving drug	Nausea (L), vomiting (L), anorexia (L)	Somnolence, confusion, weakness, seizure, inappropriate ADH1	Encephalopathy (L)
Prompt Within 2-3 weeks, prior to next course	Myelosuppression, arrhythmia, EKG changes	Hemorrhagic cystitis, cardiac toxicities with arrythmias2, myocardial necrosis2	

Delayed Any time later during therapy, excluding the above conditions	Alopecia	Fanconi's renal syndrome	Peripheral neuropathy, acute renal failure, pulmonary fibrosis (L)
Late Any time after completion of treatment			Secondary malignancy, bladder fibrosis

1 Less common with lower doses

2 Extremely rare at doses of < 10 g/m2/course

(L) Toxicity may also occur later

9.2.3 Formulation and Stability:

Available in 1 g and 3 g vials of lyophilized white powder without preservatives. Intact vials should be stored at room temperature and bear a stamped 5-year expiration date from the manufacturer. Reconstitute with sterile water, 20ml/g, to produce a final solution of 50mg/ml ifosfamide. Although the reconstituted product is stable for several days at room temperature, the absence of preservatives mandates that all drug be used or discarded within 8 hours.

9.2.4 Guidelines for Administration:

Ifosfamide will be infused intravenously over 1 hour daily for 5 days every 28 day course.

9.2.5 Supplier:

The 1 g and 3g vials are commercially available. See package inserts for further information.

9.3 Etoposide (VP-16, VePesid) NSC #141540

ETOPOSIDE (VP-16, VePesid) NSC #141540 Revised: Oct 01.

Approved roadmap abbreviation: ETOP.

9.3.1 Source and Pharmacology:

A semisynthetic derivative of podophyllotoxin that forms a complex with topoisomerase II and DNA which results in a single and double strand DNA breaks. Its main effect appears to be in the S and G2 phase of the cell course. The initial t1/2 is 1.5 hours and the mean terminal half-life is 4 to 11 hours. It is primarily excreted in the urine. There is poor diffusion into the CSF. The maximum plasma concentration and area under the concentration time curve (AUC) exhibit a high degree of patient variability. Etoposide is highly bound to plasma proteins (~94%), primarily serum albumin. Pharmacodynamic studies have shown that etoposide systemic exposure is related to toxicity. Preliminary data suggests that systemic exposure for unbound etoposide correlates better than total (bound and unbound) etoposide. Etoposide is well absorbed after oral administration, but a high degree of interpatient variability has been reported (25 - 75% bioavailability).

9.3.2 Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to<5 children out of every 100
Immediate Within 1-2 days of receiving drug	Nausea, vomiting		
Prompt	Myelosuppression	Alopecia (L), enhanced damage due to radiation,	Peripheral neuropathy,

Within 2-3 weeks, prior to next course		diarrhea	stomatitis
Delayed Any time later during therapy, excluding the above conditions			
Late Any time after completion of treatment			Secondary malignancy

(L) Toxicity may also occur later

9.3.3 Formulation and Stability:

Supplied as solution in 100 mg ampules (20 mg/ml) containing 5 ml. May be diluted in either 5% dextrose (DSW) or 0.9% sodium chloride injection (normal saline) to a final concentration of 0.4. mg/ml. When diluted as above, the drug is stable for 48 hourse at room temperature.

9.3.4 Supplier:

Commercially available. See package insert for further information.

9.4 Carboplatin (Paraplatin, CBDCA) NSC #241240

9.4.1 Source and Pharmacology:

The mechanism of action of carboplatin would appear to be similar to that of cisplatin, i.e., it binds to replicating DNA causing single strand breaks and cross-links with DNA. Data suggests that other factors also contribute to cytotoxicity. The μ t½ is 1.1 to 2 hours and the gamma t½ is 2.6 to 5.9 hours. Carboplatin is not protein bound. Elimination is dependent on the glomerular filtration rate; the dose may require adjustment depending on GFR.

9.4.2 Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to<5 children out of every 100
Immediate Within 1-2 days of receiving drug	Nausea (L), vomiting (L)		Metallic taste
Prompt Within 2-3 weeks, prior to next course	Myelosuppression1	Electrolyte disturbances (L)	Peripheral neuropathy, hepatotoxicity (L), renal toxicity (L), ototoxicity (L)
Delayed Any time later during therapy, excluding the above conditions			
Late Any time after completion of treatment			Secondary leukemia

1 Thrombocytopenia is more severe or dose limiting

(L) Toxicity may also occur later

9.4.3 Formulation and Stability:

Supplied in amber vials containing 50, 150, and 450 mg of carboplatin, prepared as a white lyophilized powder. Store at room temperature (15°-30°C) and away from light. Reconstitute with 5, 15, or 45ml of sterile water, respectively, each ml containing 10mg carboplatin. Carboplatin may be further diluted to 0.5-2 mg/mL with 5% dextrose or 0.9% sodium chloride with a 24 hour stability at room temperature. Lower chloride concentrations enhance stability. Sodium bicarbonate reduces stability.

9.4.4 Guidelines for Administration:

IV infusion over 15 minutes or longer. Pre-hydration and posthydration with IV fluids (D5W in 0.45 NaCl) are less important than with cisplatin. Aluminum reacts with carboplatin, causing loss of potency; therefore, needles and intravenous sets containing aluminum parts must not be used for the preparation or administration of carboplatin.

9.4.5 Supplier:

Commercially available. See package insert for further information.

9.5 Mesna (sodium 2-mercaptoethane sulfonate, MESNA) NSC #113891

9.5.1 Source and Pharmacology:

MESNA is a thiol compound with the capacity of inhibiting the urotoxicity of the oxazaphosphorines, ifosfamide and cyclophosphamide. Within 1 hour of administration, MESNA is completely oxidized to DiMESNA, a totally inert compound. After an 800mg dose the t½ for MESNA and DiMESNA is 0.36 hours and 1.17 hours, respectively. There is little or no tissue penetration. Following glomerular filtration DiMESNA is rapidly reduced in the renal tubules back to MESNA which inactivates acrolein and the oxazaphosphamides, thus preventing bladder toxicity. After 3 hours, negligible amounts of MESNA were present in the urine of rats given 100mg/kg by IV push.

9.5.2 Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to<5 children out of every 100
Immediate Within 1-2 days of receiving drug	Bad taste with oral use	Nausea, vomiting, stomach pain	Headache, pain in arms, legs, and joints; fatigue, rash, transient hypotension, allergy
Prompt Within 2-3 weeks, prior to next course			Diarrhea
Delayed Any time later during therapy, excluding the above conditions			
Late Any time after completion of treatment			

Young children receiving high doses of benzyl alcohol (> 99 mg/kg/day) may develop the gasping syndrome manifested by gasping, metabolic acidosis and multiple organ system failure. Benzyl alcohol is the preservative in multidose vials of MESNA.

9.5.3 Formulation and Stability:

Available in 1000 mg/10mL multidose vials which contain 10.4 mg/mL of benzyl alcohol* as a preservative, or in 200 mg/2 mL ampules without preservatives for neonates and infants or patients with hypersensitivity to benzyl alcohol. In Canada, only the non-preserved ampules are available. Store either product at controlled room temperature (15- 30°C). MESNA is not light-sensitive, but is oxidized to DIMESNA when exposed to oxygen. Non-preserved ampules should be used immediately after opening, while benzyl alcohol-preserved vials may be stored and used for 8 days. After further dilution for administration, either product is chemically stable for at least 24 hours. Lack of an antimicrobial preservative suggests that the non-preserved product should be used within 6-8 hours after diluted for administration. For IV administration, dilute to 20 mg/mL with any of the following fluids: 5% dextrose, 5% dextrose in 0.45% sodium chloride, 0.9% sodium chloride or Lactated Ringer's. MESNA may be mixed with ifosfamide or cyclophosphamide.

*The package insert for MESNA states that multidose vials contain benzyl alcohol 10.4 mg/mL (1%) as a preservative, should not be used in neonates or infants, and should be used with caution in older pediatric patients. A 200 mg/2 mL ampule remains available free of charge for pediatric patients less than 2 years old and for patients with hypersensitivity to benzyl alcohol. It may be obtained in the U.S. by calling Bristol-Myers Squibb Oncology at 1-800-437-0994.

The medical literature includes reports of gasping syndrome in premature infants receiving saline flushes with benzyl alcohol at **benzyl alcohol** doses greater than 99 mg/kg/day. (Gershanik J, et al. N Engl J Med 1982;307:1384) There is also a report of metabolic acidosis occurring in a 5 year old girl receiving continuous infusion diazepam which contained 180 mg/kg/day of benzyl alcohol. (Lopez-Herce, et al. Ann Pharmacother 1995;29:632) The syndrome includes gasping respiration, severe metabolic acidosis, and multiple organ system failure. It results from inability to adequately conjugate benzoic acid with glycine, a metabolic pathway poorly developed under 8 weeks of age.

Even if the amount of **benzyl alcohol** in MESNA is not enough to cause problems in a patient, a number of other drug products contain benzyl alcohol and therefore could add to the dose a patient is receiving. Your pharmacist can check product contents and calculate the dose of benzyl alcohol any patient is receiving.

9.5.4 Guidelines for Administration:

IV 5 does of MESNA per day per dose of ifosfamide, will be given each day of ifosfamide treatment.. Can be given orally but has a foul taste. Total dose is usually 60% of the oxazaphosphorine dose given in divided doses. Higher doses or continuous infusions are used with high dose ifosfamide or cyclophosphamide, or in patients with a history of hemorrhagic cystitis.

9.5.5 Supplier:

Commercially available. See package insert for further information.

9.6 Granulocyte Colony-Stimulating Factor (R-MetHuG-CSF, G-CSF, Filgastim, Neupogen) NSC #614629

9.6.1 Source and Pharmacology:

r-metHuG-CSF (produced in E. coli by recombinant DNA technology) stimulates the production of neutrophils in the bone marrow and selected end-cell activation. The 175 amino acid protein (M.W. of 18,800 daltons) differs from the natural protein in that the N-terminal amino acid is a methionine and it is not o-glycosylated. 3.45 ug to 11.5 ug of G-CSF administered

subcutaneously resulted in a maximum serum concentration of 4 ng/ml to 49 ng/ml within 2 to 8 hours. The elimination half-life is similar for SQ and IV, approximately 3.5 hours.

9.6.2 Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to<5 children out of every 100
Immediate Within 1-2 days of receiving drug		Local irritation at the injection site	Allergic reaction, low grade fever
Prompt Within 2-3 weeks, prior to next course		Medullary bone pain, increased alkaline phosphatiase, increased lactate dehydrogenase, increased urice acid, thrombocytopenia	Subclinical splenomegaly, exacerbation of pre-existing skin rashes, alopecia
Delayed Any time later during therapy, excluding the above conditions			Cutaneous vasculitis
Late Any time after completion of treatment			

9.6.3 Formulation and Stability:

Supplied as a clear solution in 300 ug/ml (1 ± 0.6 x 108 U/mg) (1 ml or 1.6 ml) vials. Vials are preservative free and are intended to be single-use vials; do not reuse opened vials. Filgrastim must be stored between 2° and 8°C. Stability has been demonstrated for at least 24 months when stored under these conditions. Do not use if discolored or if there is particulate matter. For IV use, dilute in D5W to concentrations > 15 ug/ml; G-CSF is incompatible with normal saline. At dilutions from 5 ug/ml to 14 ug/ml, add human serum albumin to a final albumin concentration of 2 mg/ml to protect against absorption of the G-CSF to container walls (glass or plastic). Filgrastim, when diluted as described above, is compatible with a number of plastics commonly used in the manufacture of syringes, IV bags, infusion sets, and IV pump cassettes. These include polyvinyl chloride, polyolefin, and polypropylene. Diluted filgrastim should be stored at 2° to 8° C and used within 24 hours. **Do not shake or freeze.**

9.6.4 Guidelines for Administration:

Administer once daily, subcutaneously without dilution or if necessary dilute with 5% dextrose in water, preferably to concentrations of 15 ug/ml or greater for IV administration. Dilutions should be prepared as close to the time of administration as possible (up to 24 hours), since the product is preservative-free. When diluting Filgrastim to 5-14 ug/ml in D5W, it is necessary at all times to add human serum albumin, to reach a final albumin concentration of 2 mg/ml. The suggested starting dose is 5 ug/kg.

Recommended continue G-CSF until ANC >10,000 after the nadir is reached (usually 10-14 days)

9.6.5 Supplier:

Commercially available. See package insert for further information.

10.0 ADVERSE EVENTS

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of dasatinib whether or not considered related to dasatinib.

During clinical trials, adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more adverse events.)

A ***serious AE*** is any untoward medical occurrence that at <u>any dose</u>:

- results in death,
- is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe),
- requires inpatient hospitalization or causes prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- results in the development of drug dependency or drug abuse,
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) **For reporting purposes, also consider the occurrences of pregnancy or overdose (regardless of adverse outcome) as events which must be reported as important medical events.**

10.1 Reporting of SAEs

Following the subject's written consent to participate in the study, all SAEs should be collected and reported, including those thought to be associated with clinical trial procedures. Following study completion, any SAE thought to be related to study drug or clinical trial procedures should also be reported to BMS.
SAE terminology and severity grading will be based on (*i.e., CTCAEv3*).

The following categories and definitions of causal relationship to study drug should be considered for use for all clinical studies supported by BMS:

- Certain: There is a known causal relationship between the study drug and the SAE. The event responds to withdrawal of study drug (dechallenge), and recurs with rechallenge when clinically feasible. (>95% certainty)
- Probable: There is reasonable causal relationship between the study drug and the SAE. The event responds to dechallenge. Rechallenge is not required. (65%-95% probability)
- Possible: There is reasonable causal relationship between the study drug and the SAE. Dechallenge information is lacking or unclear. (35%-65% probability of relatedness)
- Not likely: There is temporal relationship to study drug administration, but there is not a reasonable causal relationship between the study drug and the SAE. (5-35% probability of relatedness)

- Not related: There is not a temporal relationship to study drug administration (too early, or late, or study drug not taken), or there is known causal relationship between the SAE and another drug, concurrent disease, or other circumstance. (<5% chance of relatedness)
- Adverse events classified as "serious" require expeditious handling and reporting to BMS to comply with regulatory requirements.
- All SAEs whether related or unrelated to dasatinib, must be immediately reported to BMS (by the investigator or designee) within 24 hours of becoming aware of the event. If only limited information is initially available, follow-up reports are required. The original SAE form must be kept on file at the study site.

  All SAEs should be faxed or emailed to BMS at:

  Global Pharmacovigilance & Epidemiology
  Bristol-Myers Squibb Company
  Fax Number: 609-818-3804
  Email: Worldwide.safety@bms.com

- For studies conducted under an Investigator IND, any event that is both serious and unexpected must be reported to the FDA as soon as possible and, in no event, later than 7 days (death or life-threatening event) or 15 days (all other SAEs) after the investigator's or institution's initial receipt of the information. BMS will be provided with a simultaneous copy of all adverse events filed with the FDA. SAEs should be reported on the MedWatch Form 3500A, which can be accessed at: http://www.accessdata.fda.gov/scripts/medwatch/

  MedWatch SAE forms should be sent to the FDA at:

  MEDWATCH
  City of Hope National Medical Center
  1500 East Duarte Road, MOB 4th Floor
  Duarte, California 91010
  Fax (626) 256-8787

  All SAEs should simultaneously be faxed or e-mailed to BMS at:

  Global Pharmacovigilance & Epidemiology
  Bristol-Myers Squibb Company
  Fax Number: 609-818-3804
  Email: Worldwide.safety@bms.com

- Collection of complete information concerning SAEs is extremely important. Full descriptions of each event will be followed by BMS. Thus, follow-up information which becomes available as the SAE evolves, as well as supporting documentation (e.g., hospital discharge summaries and autopsy reports), should be collected subsequently, if not available at the time of the initial report, and immediately sent using the same procedure as the initial SAE report.
- An overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important. For reporting purposes, BMS considers an overdose, regardless of adverse outcome, as an important medical event.
- AEs should be followed to resolution or stabilization, and reported as SAEs if they become serious. This also applies to subjects experiencing AEs that cause interruption or discontinuation of dasatinib, or those experiencing AEs that are present at the end of their participation in the study; such subjects should receive post-treatment follow-up as appropriate.

- In BMS supported trials, all SAEs must be collected which occur within 30 days of discontinuation of dosing or completion of the patient's participation in the study if the last scheduled visit occurs at a later time. In addition, the Investigator should notify BMS of any SAE that may occur after this time period which they believe to be certainly, probably, or possibly related to dasatinib.

11.0 STATISTICAL METHODOLOGY

11.1 Phase I Portion of Study:

11.1.1 Sample Size and Study Duration

This trial will seek to determine the toxicity profile and the maximum tolerated dose (MTD) of dasatinib in relapsed pediatric solid tumor patients, treated in combination with ICE, excluding patients with active brain/CNS involvement. The DLT will be based on the first course and the delay to second course and is defined earlier. Toxicity will be graded according to the NCI CTCAE version 3.0. To be evaluable for toxicity, a patient must receive at least 1 complete course of treatment and be observed for at least 28 days (or until re-treatment) after the start of the first course or have experienced a DLT. All patients enrolled are to be fully followed for DLT and any patient who is not evaluable for toxicity will be replaced. The MTD will be defined as the highest dose tested in which fewer than 33% of patients experienced DLT attributable to the study drug(s), when at least six patients were treated at that dose and are evaluable for toxicity. Dose escalation will proceed according to a standard 3+3 design. There will be no intra-patient dose escalation prior to consolidation, but one intra-patient dose escalation is permitted during the post-consolidation treatment with dasatinib. Three patients will be treated at each new dose level. If 0/3 patients experience a DLT, 3 patients will be treated at the next new dose level (in the case of dose level 4, 3 more patients will be added to the same dose level). If DLT attributable to the study drugs is experienced in exactly 1/3 patients, 3 more patients (for a total of 6) will be treated at that dose level. If no additional DLT is observed at the expanded dose level (i.e., 1/6 with DLT), the dose will be escalated. Escalation will be terminated as soon as two or more patients experience any DLT attributable to the study drugs at a given dose level, or dose level five has enrolled 6 patients with <2 DLTs. The dose finding portion of the Phase I trial will be terminated when the MTD has been determined.

Tables will be created to summarize these toxicities and side effects by dose, course, organ and severity, along with additional tables documenting the patient characteristics treated in this Phase I study. All responses will be reported. Note that dose level 5 required patients to be treated at 85 mg/m2/dose of dasatinib prior to consolidation, start the post-consolidation treatment with 85 mg/m2/dose and tolerate treatment to permit intrapatient escalation to 110 mg/m2/dose during the post-consolidation single agent therapy. Patients treated at or above the MTD and are evaluable for the Phase II portion of this trial, will be counted toward the Phase II portion for the appropriate strata.

The POETIC member institutions see a total of approximately 1000 newly diagnosed and 500 relapsed pediatric cancer patients annually. In 2006, there were 50 patients enrolled to POETIC phase I trials. This study will be open to an additional four sites: City of Hope Cancer Center, Nemours Children Clinic Jacksonville, Moffitt Cancer Center, and All Children's Hospital. Based on the available patient numbers, an adequate patient base is available to complete this trial in a timely manner. POETIC member institutions will not be participating in the Phase I portion of the study. During the Phase II portion of the study, POETIC member institutions may participate.

11.2 Phase II Portion of Study:

11.2.1 Sample Size and Study Duration

During the phase II portion of the study, there are three strata:

- Stratum A (75 patients): patients with relapsed Osteosarcoma, Ewings Sarcoma, Rhabdomyosarcoma;
- Stratum B (max of 25 patients): Patients with relapsed solid tumors not listed above;
- Stratum C (max of 25 patients): Patients with newly diagnosed metastatic sarcomas of poor risk

The primary endpoint of the Phase II study targets only Stratum A, whereas Stratum B and C will be evaluated only in an exploratory manner, and be limited to a maximum of 25 patients each.

The primary endpoint for this analysis is 1-yr overall survival (OS). Based on Van Winkle (12), 1-yr OS was 56%, 41% and 43% for rhabdomyosarcoma, osteosarcoma and Ewing sarcoma, respectively. Based on the percentage of patients in each category accrued, the historical 1-yr OS based on their work will be calculated. For example, in their study there were 28 patients with rhabdomyosarcoma, 25 with osteosarcoma, and 22 with Ewings sarcoma, leading to a weighted 1-yr OS of 46%.

Based on this expected 1-yr OS, this study seeks to detect an 11% improvement in OS at 1-yr. Based on an exponential survival model, with 1-yr accrual and 1-yr follow-up, there is greater than 81% power (regardless of the patient profiles) to detect an 11% improvement in 1-yr OS with a 1-sided type I error of 10% with 75 total patients in this stratum. There is greater than 90% power to detect an improvement of 13% in 1-yr OS.

Secondary endpoints include response rate as defined by RECIST criteria prior to consolidation; progression-free survival; further assessment of toxicity; and evaluation of exploratory correlative studies.

Review of patient accrual onto recent phase II solid tumor studies suggest that there is an adequate patient base to complete this portion of the study in a timely manner.

This portion of the study is expected to take 2 to 3 years to enroll sufficient patients to evaluate response in the stated disease groups. If activity is detected in any category, further trials in subcategories of categories may be conducted at the discretion of the Principal Investigator.

11.2.2 Phase II Study Design: Progression Free Survival

The prognosis for children with recurrent / refractory sarcomas including rhabdomyosarcoma, osteosarcoma, and Ewings sarcoma is poor with a 5- year survival rate between 4% and 31% (2-4). As previously stated in this document, ifosfamide/carboplatin/etoposide (ICE) is the most effective regimen for relapsed or refractory sarcoma with an overall response rate of 51% (12). By disease category: for Rhabdomyosarcoma, the ORR (CR + PR) was 66%, osteosarcoma 36%, Ewings sarcoma 48%, other sarcomas 60% (12). The one-year overall survival was 49% and the 2-year OS was 28%.

In the Phase II portion of this study, patients with relapsed sarcomas will be treated at the MTD as defined by the Phase I portion of the study. After consolidative therapy (surgery or radiation), all patients will receive 6 months of dasatinib alone. Time to progression and the median progression-free survival rate will be estimated at 12 months and 18 months. Twenty-five patients with osteosarcoma, twenty-five patients with Ewings sarcoma, and twenty-five patients

with rhabdomyosarcoma will be evaluated at the MTD. Other pediatric patients with relapsed solid tumors will be enrolled on the study and every attempt will be made to fully accrue enough patients into each group. However, due to the rarity of these other tumors, there is a possibility that we will be unable to fulfill accrual goals and complete the evaluations.

A minimum of 75 patients with relapsed sarcoma will be entered on the phase II portion of this study. This portion of the study is expected to take 2 to 3 years to enroll sufficient patients to evaluate response in the stated disease groups.

11.2.3 Methods of Analysis

Patients who are considered evaluable for response will be included in an analysis of time to progression. Time to progression will be estimated using the product-limit method of Kaplan and Meier (36). The probability of progression free survival at 12 months and 18 months will be summarized. Response rates will be calculated as the percent of patients whose best response is a CR or PR, and the fraction of responses obtained will have a 90% confidence interval. Toxicity information will include the type, severity, time of onset, time of resolution, and the probable association with the study drugs.

Time to progression will be taken as the number of days from start of treatment until: (1) disease progression; (2) death because of treatment complications; or (3) last patient follow-up whichever is first. Patients will be considered to have experience a progression event if (1) or (2) occurs. Otherwise, the patient will be considered censored for time to progression.

12.0 RECORDS, REPORTING, AND DATA SAFETY MONITORING PLAN

12.1 Research Records

Research records for this study can be divided into two categories:

12.1.1 Eligibility Verification

Pathology Reports, Surgical Reports, Radiation Reports to support eligibility verification. These forms are faxed to City of Hope National Medical Center at (626) 256-8787.

12.1.2 Case Report Forms

See separate Data Form Packet, which includes submission schedule. All other data will be faxed over with the aid of schedules and worksheets provided in the data form packet.

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

All sites within this study will use the CRFs, provided in the accompanying data packet. Subjects will be identified by an assigned subject number. All requested information must be entered on the CRF in the space provided. If an item is not available or is not applicable, it must be documented as such; do not leave a space blank. Spaces may be left blank only in those circumstances permitted by the study-specific CRF completion guidelines provided by the sponsor.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

For paper CRFs, a correction must be made by striking through the incorrect entry with a single line and entering the correct information adjacent to the incorrect entry. The correct must be dated, initialed and explained (if necessary) by the person making the correction and must not obscure the original entry.

The completed CRF, including any paper SAE CRFs must be promptly reviewed, signed and dated by the qualified physician who is an investigator or subinvestigator. The investigator must retain a copy of the CRFs including records of the changes and corrections.

12.2 Compliance

12.2.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with and be prepared by, the Study Chair and BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects. Any significant deviation must be documented in the CRF.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion;
- Study Chair, Judith K. Sato, M.D.;
- Bristol-Myers Squibb;
- Regulatory Authority(ies) if required by local regulations.

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to Study Chair, Judith K. Sato, M.D..

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subject prior to enrollment.

If the revision is an administrative letter, investigators must inform their IRB(s)/IEC(s).

12.3 Monitoring

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documentation, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

12.4 Records Retention

The investigator must retain investigational product disposition records, copies of CRFs and source documents for the maximum period required by applicable regulation and guidelines, or institution procedures, or for the period specified by the sponsor, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (e.g. relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g. another investigator, IRB). Notice of such transfer will be given in writing to BMS.

12.5 CRADA/CTA

Standard Language to Be Incorporated into All Protocols Involving Agent Covered by a Clinical Trials Agreement (CTA) or a Cooperative Research and Development Agreement.

The agent supplied by Bristol-Myers Squibb (BMS), used in this protocol is provided to the Individual institutions under a Collaborative Agreement (CRADA, CTA) between the Pharmaceutical Company (hereinafter referred to as Collaborator(s)_). Therefore, the following obligations/guidelines, in addition to the provisions in the _ Intellectual Property Option to Collaborator_contained within the terms of award, apply to the use of the Agent(s) in this study:

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

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

a. BMS must provide all Collaborators with prior written notice regarding the

existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

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

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

3. Clinical Trial Data and Results and Raw Data developed under a collaborative agreement will be made available exclusively to Collaborator(s), BMS, and the FDA, as appropriate. All data made available will comply with HIPAA regulations.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the Study Chair, Judith K. Sato, M.D., who will then notify BMS 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 BMS 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 BMS 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 BMS prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

City of Hope National Medical Center, Judith K. Sato, MD
1500 E. Duarte Road, Duarte, CA 91010
Tel: 626 930 5430 Fax: 626 930 5415

BMS

Insert address

The BMS 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.

12.6 Data and Safety Monitoring Plan

Data and safety is ensured by several integrated components including the Data and Safety Monitoring Committee.

12.6.1 Data and Safety Monitoring Committee

This study will be monitored in accordance with the COH/ BMS policy for data and safety monitoring of Phase 1 and 2 studies. In brief, the role of the Data and Safety Monitoring Committee is to protect the interests of patients and the scientific integrity for all Phase 1 and 2 studies. The DSMC consists of a chair; a statistician; one external member; one consumer representative; the lead statistician of the developmental therapy scientific committee; and a member from the NCI. The DSMC meets at least every 6 months to review current study results, as well as data available to the DSMC from other related studies. Approximately 6 weeks before each meeting of the Phase 1 and 2 DSMC, study chairs will be responsible for working with the study statistician to prepare study reports for review by the DSMC. The DSMC will provide recommendations to the Study Chair and BMS for each study reviewed to change the study or to continue the study unchanged. Data and Safety Committee reports for institutional review boards can be prepared using the public data monitoring report.

12.6.2 Monitoring by the Study Chair and Coordinating Center

The study chair will monitor the study regularly and enter evaluations of patients' eligibility, evaluability, and dose limiting toxicities into the study database. In addition, study data including the study chair's evaluations will be reviewed by the study chair and Statistician on a weekly conference call.

12.7 Investigational Product Records

It is the responsibility of the investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines and should include:

- Amount received and placed in storage area;
- Amount currently in storage area;
- Label ID number of batch number and use date or expiration date;
- Dates and initials of person responsible for each investigational product inventory entry/movements;
- Amount dispensed to and returned by each subject, including unique subject identifiers;
- Amount transferred to another area/site for dispensing or storage;
- Non-study dispositions (e.g. lost, wasted, broken);
- Amount returned to the sponsor;
- Amount destroyed at study site, if applicable;
- Retain samples sent to third party for bioavailability/bioequivalence, if applicable.

The sponsor will provide forms to facilitate inventory control if the staff at the investigational site does not have an established system that meets these requirements.

12.8 Return and Destruction of Investigational Product

12.8.1 Return of Investigational Product

Upon completion or termination of the study, all unused and/or partially used investigational product must be returned to BMS, if not authorized by BMS to be destroyed at the site.

All investigational product returned to BMS must be accompanied by the appropriate documentation and be clearly identified by protocol number and study site number on the outermost shipping container. Returned supplies should be in the original container (e.g. patient kits that have clinical labels attached). Empty containers should not be returned to BMS. It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The return of unused investigational product(s) should be arranged by the responsible Study Monitor.

12.8.2 Destruction of Investigational Product

If investigational products are to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for the disposal, written authorization has been granted by BMS, procedures for proper disposal have been established according to applicable regulations and guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused investigational products can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor.

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APPENDIX 1: List of Abbreviations

Abbreviation	Term
ANC	Absolute Neutrophil Count
BID	Twice a Day
BMS	Bristol-Myers Squibb Company
CAT (or CT scan)	Computed Axial Tomography
CBC	Complete Blood Count
CR	Complete Response
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
EKG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IRB	Institutional Review Board
MRI	Magnetic Resonance Imaging
PD	Progressive Disease
PFS	Progression Free Survival
PO	By Mouth
PR	Partial Response
QD	Once Daily
QoL	Quality Of Life
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
TNM Staging	Tumor, Node and Metastasis Staging
ULN	Upper Limit of Normal
WBC	White Blood Count
WOCPB	Women of Child-Bearing Potential

APPENDIX 2: Dasatinib Subject Diary for Study

City of Hope

Dasatinib Subject Diary for Study

Protocol ID: | Research Participant #: | Participant Initials: | Evaluation Code: | Form #:

19413

Because this is a computer read form, please use **BLACK ink** only.

Dasatinib dose (insert # of pills for each specific dose tablet taken)

○ Induction Phase: Dasatinib begins on Day 5 of course (by mouth 2 times a day for 17 days) **OR** ○ Post-Consolidation Phase: Dasatinib begins on Day 1 of course (by mouth 2 times a day for 28 days)

Day / Date	AM			PM			Dose change?	Changed in the:	Describe
	5 mg	20 mg	50 mg	5 mg	20 mg	50 mg			
Day ☐☐ of Dasatinib Date: mm / dd / yyyy	☐	☐	☐	☐	☐	☐	○ Yes ○ No	○ AM ○ PM	Describe any change(s): Describe any side effect(s):
Day ☐☐ of Dasatinib Date: mm / dd / yyyy	☐	☐	☐	☐	☐	☐	○ Yes ○ No	○ AM ○ PM	Describe any change(s): Describe any side effect(s):
Day ☐☐ of Dasatinib Date: mm / dd / yyyy	☐	☐	☐	☐	☐	☐	○ Yes ○ No	○ AM ○ PM	Describe any change(s): Describe any side effect(s):
Day ☐☐ of Dasatinib Date: mm / dd / yyyy	☐	☐	☐	☐	☐	☐	○ Yes ○ No	○ AM ○ PM	Describe any change(s): Describe any side effect(s):
Day ☐☐ of Dasatinib Date: mm / dd / yyyy	☐	☐	☐	☐	☐	☐	○ Yes ○ No	○ AM ○ PM	Describe any change(s): Describe any side effect(s):
Day ☐☐ of Dasatinib Date: mm / dd / yyyy	☐	☐	☐	☐	☐	☐	○ Yes ○ No	○ AM ○ PM	Describe any change(s): Describe any side effect(s):

Subject's/Parent's Signature: ____________________ Date: mm / dd / yyyy

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APPENDIX 3: COH Specimen Transmittal Form

1) A Specimen Transmittal Form should accompany every specimen shipped to the COH Laboratory. Please complete:

a.) Include one form per specimen per patient
b.) Document the number and type(s) of specimen(s) sent in shipment (see below)

2) The patient must have a Patient ID number. The registration number (and a study number if the patient has been enrolled on a study) must be recorded on each Specimen Transmittal Form for identification purposes.

3) Biology Specimens must be labeled with a COH Registration Number. Each patient is assigned a Registration Number at the time of registration (see Section 6.2). If you have any questions about a patient's Registration Number, please contact the PI, Judith K. Sato, MD at 626 930 5430.

PATIENT/SPECIMEN INFORMATION

Patient Initials (L,F):_____ Date of Birth: _____ (mm/dd/yyyy) IRB Study #:_____

Consent Date:_____ (mm/dd/yyyy) COH Registration Study #:_____ Diagnosis:_____

_____

Institution of Treatment:_____

Primary Site:_____

Inst. # _____ Contact Person: _____

Stage (if applicable):_____

Telephone #:_____

Fed Ex (or other) Tracking Number:_____

Permission Questions:

Patient agreed to the use of specimen blood samples to do research to learn about how Dasatinib may prevent or treat cancer. ____Yes ____No ___ N/A

Patient agreed to the use of specimen tumor samples to do research about medical characteristics of tumor cells and to evaluate the effect of Dasatinib on the tumor cells. ____Yes ____No ___ N/A

Patient agreed to have specimens stored and used for future research purposes that have not yet been determined. ____Yes ____No ___N/A

Research Patient Number								(Specimens will NOT be banked without a Lab #)

Specimen Obtained at (check all that apply)
____Pretreatment/Diagnosis
____Relapse
____During Follow-up
___During Therapy (designate time period)
Course:_____
Week #:_____
Transplant Day #:_____
___End of Therapy

Type of Specimen (check one):
_____ Surgical Resection
_____Core Biopsy

Time Specimen Obtained: (if applicable):_____

Record Number of each type/ of specimen present in shipment. (include # of specimens)	FRESH	FROZEN	PARAFFIN	SLIDES	FORMALIN	Surgical Path ID (SPID)	Date Obtained
Primary Tissue							
Metastatic Tissue specify site:							
Normal Tissue							
Blood and/or WBC aliquots							
Other (specify):							

SPECIMEN SHIPPED TO:	FORM:
	Send original form with specimen Retain a copy in patient file at institution
	LABORATORY CODE (Office use):

APPENDIX 4: Submission Of Biological Samples

COLLECTION TIME	SPECIMEN	WHERE TO SHIP *	STUDIES TO BE DONE
Diagnosis (pre-treatment)	10 ml PB in EDTA tube	City of Hope National Medical Center Attn: Dr. Jove's Laboratory* 1500 E. Duarte Road, Shapiro/Rm1031 Duarte, CA 91010 Phone: (626) 256-7643 x62357 Fax: (626) 256-8708	Biomarker analysis
	Core biopsy and/or surgical biopsy - 1.5 cm x 1 cm x 1 cm snap forzen tumor - Parrafin-embedded tumor specimens	Dr. Jove's Laboratory*	Microarray gene-expression profiling Immunohistochemistry Quality (absence of necrosis or fibrosis, and % tumor cells)
Pre-Consolidation Course 1: Day 14-21 or when WBC ≥ 500 / Date:	10 ml PB in EDTA tube	Dr. Jove's Laboratory*	Biomarker analysis
Pre-Consolidation Course 2: Day 14-21 or when WBC ≥ 500 / Date:	10 ml PB in EDTA tube	Dr. Jove's Laboratory*	Biomarker analysis
Pre-Consolidation Course 3: Day 14-21 or when WBC ≥ 500 / Date:	10 ml PB in EDTA tube	Dr. Jove's Laboratory*	Biomarker analysis
Pre-Consolidation Course 4: Day 14-21 or when WBC ≥ 500 / Date:	10 ml PB in EDTA tube	Dr. Jove's Laboratory*	Biomarker analysis
Pre-Consolidation Course 5: Day 14-21 or when WBC ≥ 500 / Date:	10 ml PB in EDTA tube	Dr. Jove's Laboratory*	Biomarker analysis
Pre-Consolidation Course 6: Day 14-21 or when WBC ≥ 500 / Date:	10 ml PB in EDTA tube	Dr. Jove's Laboratory*	Biomarker analysis
Consolidation	Surgical resection - Parrafin-embedded tumor specimens	Dr. Jove's Laboratory*	Microarray gene-expression profiling Immunohistochemistry Quality (absence of necrosis or fibrosis, and % tumor cells)
Post-Consolidation Course 7: Day 14-21 or when WBC ≥ 500 / Date:	10 ml PB in EDTA tube	Dr. Jove's Laboratory*	Biomarker analysis
Post-Consolidation Course 8: Day 14-21 or when WBC ≥ 500 / Date:	10 ml PB in EDTA tube	Dr. Jove's Laboratory*	Biomarker analysis
Post-Consolidation Course 9: Day 14-21 or when WBC ≥ 500 / Date:	10 ml PB in EDTA tube	Dr. Jove's Laboratory*	Biomarker analysis
Post-Consolidation Course 10: Day 14-21 or when WBC ≥ 500 / Date:	10 ml PB in EDTA tube	Dr. Jove's Laboratory*	Biomarker analysis
Post-Consolidation Course 11: Day 14-21 or when WBC ≥ 500 / Date:	10 ml PB in EDTA tube	Dr. Jove's Laboratory*	Biomarker analysis
Post-Consolidation Course 12: Day 14-21 or when WBC ≥ 500 / Date:	10 ml PB in EDTA tube	Dr. Jove's Laboratory*	Biomarker analysis
Relapse / Progression	10 ml Peripheral Blood in tube	Dr. Jove's Laboratory*	Biomarker analysis
	Surgical resection - 1.5 cm x 1 cm x 1 cm snap forzen tumor - Parrafin-embedded tumor specimens	Dr. Jove's Laboratory*	Microarray gene-expression profiling Immunohistochemistry Quality (absence of necrosis or fibrosis, and % tumor cells)

APPENDIX 5: POETIC Consortium Responsible Investigators

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APPENDIX 6: Performance Status Scales/Scores

PERFORMANCE STATUS CRITERIA
Karnofsky and Lansky performance scores are intended to be multiples of 10

Karnofsky for patients ≥ 16 years of age		**Lansky** for patients ≤ 16 years of age	
Score	Description	Score	Description
100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
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
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.
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.
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.
10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

APPENDIX 7: Study Calendar

Study Assessment	Pre-Study#	Course 1 (total course = 28 days)								Subsequent course (total course = 28 days)						End of therapy / relapse	Post Treatment Follow-Up
			Day 0	Day 1	Day 3	Day 8	Day 14	Day 22	Day 28		Day 0	Day 1	Day 8	Day 14	Day 22		
Informed Consent	X																
History	X		X							Start of each course	X					X	X
Physical Exam with vital signs (BP, HR, and Temp)	X	Weekly	X			X	X	X	X	Days 1 and 14 of each course		X		X		X	X
Height, weight, BSA	X		X							Start of each course	X					X	X
Performance Status	X		X							Start of each course	X					X	X
CBC, differential, platelets	X	Twice Weekly (every 3 to 4 days)[3]	X		X					Weekly[4]	X		X	X	X	X	
Peripheral blood for biology studies[1]	X	Day 14-21 or when WBC ≥ 500					X			Day 14 - 21 or when WBC ≥ 500 of each course				X		X	
Electrolytes including Ca, PO4, Mg	X	Weekly	X			X	X	X	X	Days 1 and 14 of each course[5]		X		X		X	
Creatinine, ALT, bilirubin	X	Weekly	X			X	X	X	X	Days 1 and 14 of each course[5]		X		X		X	
Total protein/albumin	X	Days 1 and 14 of each course		X			X			Days 1 and 14 of each course[5]		X		X		X	
Disease Evaluation	X$	End of course 1								Start of every other course[6]	X					X	X
Pregnancy Test[2] (must be done within 72 hours prior to 1st dose of treatment)	X																
EKG	X									Start of each course prior to Consolidation; Start of first post-consolidation course & any time dasatinib dose escalated	X						
Echocardiogram or MUGA	X									As clinically indicated							
Tumor tissue for Correlative Studies[1]	X									From any surgical specimen; At time of progression, if possible						X	

1 See Section 7.2 for details and timing of biology studies
2 Patients of child bearing 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.
3 If patients develop Grade 4 neutropenia, then CBCs should be checked every other day until recovery to Grade 3.
4 If patient develop Grade 4 neutropenia, then CBCs should be checked every 3 to 4 days until recovery to Grade 3
5 Day 14 Chemistry tests required for the Phase I portion of study only
6 Disease Evaluation should be obtained every other course after initial documentation of either a PR, CR, or SD, or at time of suspected disease relapse or progression.

All entry and eligibility studies must be performed within 2 weeks prior to treatment, unless otherwise specified.
$ Imaging studies are required within 2 weeks prior to study entry

APPENDIX 8: Data and Submission Schedule

Data Management Time Frames		At Screening	Baseline	Course 1	Course 2 and all subsequent courses	F/UP
CRF Title:	Form Number:					
ELIGIBILITY SCREENING CHECKLIST		X				
ACCESSION/DIAGNOSIS RECORD[1]	COH2574		X			
ON STUDY	COH2689		X			
PRIOR THERAPY SUMMARY	COH1987		X			
PRIOR DRUG TREATMENT - SINGLE AGENT	COH2007		X			
PRIOR DRUG TREATMENT - COMBINATION	COH2008		X			
PRIOR TREATMENT - SURGERY	COH1991		X			
PRIOR TREATMENT - RADIATION	COH2009		X			
PRIOR TREATMENT – OTHER THERAPIES	COH1992		X			
PRE-EXISTING CONDITIONS	COH1993		X			
PEDIATRIC TREATMENT AND ADVERSE EVENTS FORM	COHxxxx PEDIATRIC			X	X	
PHASE I TRACKING LOG	COH1033			X		
TUMOR MEASUREMENT[2]	COH2690		X		X[2]	
ADVERSE EVENTS COLLECTION FORM	COH2000			X	X	
RESPONSE/OFF-STUDY/FOLLOW-UP FORM	COH1059 v07			X	X	X
PEDIATRIC CHEMISTRY FORM	COH2737		X	X	X	
CONCOMITANT THERAPIES	COH2691		X	X	X	
PATIENT PILL DIARY FORM	COH2736			X	X	

1 - Accession/Diagnosis record will be completed by Consortium office for the patients outside of COH.

2 - Tumor measurement form to be completed at baseline and every 2 courses -please always confirm with protocol study calendar.

APPENDIX 8: Data and Submission Schedule

BEST RESPONSE CODES FOR PRIOR THERAPY

Response	Codes
NED	**ND**
Complete response	**CR**
Partial response	**PR**
Stable Disease	**SD**
Progression	**PD**
Not Assessed/ Not Available	**NA**

The following codes should be used only for best response on the following forms:

PRIOR THERAPY SUMMARY	COH1987
PRIOR DRUG TREATMENT - SINGLE AGENT	COH2007
PRIOR DRUG TREATMENT - COMBINATION	COH2008
PRIOR TREATMENT - SURGERY	COH1991
PRIOR TREATMENT - RADIATION	COH2009

APPENDIX 9: Surgical Guidelines

The number of patients eligible for limb salvage will be limited and dependent upon the status of other sites of disease. It may be feasible for patients with pulmonary mets who have had a response to undergo limb-sparing procedures in addition to aggressive resection of pulmonary mets.

Resection of the residual tumor is a standard of care to be sought in all patients with relapsed sarcoma. Some metastases tend to arise in well defined anatomic compartments (Enneking) and may be amenable to limb salvage rather than amputative surgery. The general considerations for limb salvage versus amputation have to do with the age of the patient, the resectability of the tumor locally, the neurogenic and vascular status of the limb post resection, and the risks that the patient and patient's family are willing to take in terms of limb sparing. It is recognized that techniques and availability of limb salvage may vary from institution to institution, but in general, the precepts of the Musculoskeletal Tumor Society's guidelines for wide or radical margin resectability should be followed. In general, wide margins rather than radical margins should be adequate unless skip lesions have been identified. Some judgment will have to be used as to the quality of a salvaged limb versus the risk of local recurrence. In general, only patients who experience a good local response to systemic chemotherapy are suitable candidates for resection of the primary and limb-sparing surgery. Limb sparing is also to be encouraged for patients seeking palliation of metastatic disease (pain control, better function, fracture care). Where there has been an excellent response of metastatic foci, allowing successful metastasectomy, local control should be achieved in a curative fashion.

1.0 Margins of Resection

1.1 Radical
Radical margins of resection involve the entire osseous or soft tissue structure. In soft tissues, this should run from the tendon of origin to the tendon of insertion, taking the entire fascial casement of the muscle. Whether this is done by compartment resection or myectomy is up to the surgeon based on the preoperative studies. The bone should be taken out from joint above to joint below to truly get a radical margin.

1.11 Wide Margin
A wide margin of resection as defined by Enneking, removes normal tissue all the way around the lesion. The thickness or depth of this tissue is irrelevant. The wide margin does not eliminate the risk of skip metastases, however. At least 3 cms. of normal bone should be resected around the most extensive area of bony abnormality (defined by x-ray, bone scan, MRI, or CT). Narrower margins are to be discouraged but may be considered in order to preserve joint function. Unusual cases of diaphyseal tumors may allow preservation of the epiphysis, or even the growth plate, while excising the tumor widely. Older guidelines for resection of more bony tissue predated accurate imaging studies. Furthermore, it makes little sense to resect 7 cms. of a bony margin when the soft tissue margin is only 1 mm at times in the popliteal space.

1.12 Marginal or Intralesional
In tumors arising in a non-resectable area, such as vertebral body, a surgical debulking of as much tumor as possible should be undertaken. Wherever possible, if a margin can be obtained that is at least marginal, the risk of local recurrence will be decreased. In those patients where only intralesional surgery can be undertaken, this may still preclude mechanical problems and help in decreasing the tumor load. Additional therapy beside surgery and chemotherapy should be undertaken in these patients.

1.2 Guidelines for Resection of Metastases
Resection of pulmonary metastases will be performed, if considered resectable, after a period the pre-consolidation phase of chemotherapy. Decisions should be made based on repeat chest CT obtained and exploration may be performed if results are equivocal. Thoracoscopy may be performed. In all patients surgical specimens will be analyzed to determine viability and the effects of chemotherapy.

1.3
Questions regarding surgical aspects of this protocol should be directed to:
Dominic Femino, M.D.
City of Hope National Medical Center; Division of Orthopedic Surgery
1500 E. Duarte Road, MOB 4th Floor, Room 4015; Duarte, California 91010
Phone: (626) 256-4673 x 65437; Fax: (626) 930-5415
E-mail: dFemino@coh.org

APPENDIX 10: Radiation Therapy Guidelines

Radiotherapy may be administered during the consolidation (local control) phase of treatment as determined by the type of disease. Radiotherapy is reserved for situations where complete surgery cannot be achieved. Radiotherapy is, however, recommended for inoperable sites or those that could only be operated with inadequate margins. It is strongly suggested that participating institutions use the information and consulting systems set up by their respective groups before assuming inoperability, because some lesions which at first seem inoperable may turn out to be operable for specialized tumor surgeons. Further recommendations about how to proceed in specific situations may vary between groups. Non-target, painful lesions may be given palliative radiation.

1.1 **Timing of Radiation Therapy**

1.1.1 Local Control Variations:
The timing of radiotherapy will differ according to the local control variation. It is essential that the management team including the radiation oncologist and surgeon meet to discuss optimal management of specific patients prior to choosing the favored local control variation.

1.1.2 Planned Rests
Low blood counts during radiotherapy are most commonly due to chemotherapy. Radiation therapy should be interrupted for low blood counts **only** if:

a. There is a significant amount of marrow within the radiation portal (for example, a large pelvic field) **and**
b. ANC < 750 and platelets < 75,000 **and**
c. There is uncontrolled infection, or significant (Grade 3 or more) stomatitis or mucositis in the radiation field.

Radiation therapy should be restarted when the blood counts rise above the levels cited and the mucositis has healed. Recurrent problems with low blood counts may indicate modification of chemotherapy (See Section 6.7). The hemoglobin should be obtained, and the hemoglobin or hematocrit levels recorded on the daily treatment record.

1.1.3 Emergency Radiation Therapy:
Patients requiring emergency radiotherapy, such as patients with spinal cord compression may be treated immediately as deemed necessary by the treating radiation oncologist. The entire course of the emergency radiotherapy should be administered consecutively, if possible.

1.2 **Radiotherapy Dose and Volume**
Type of radiotherapy is to be determined by responsible investigator and institutional treating team. Any modality i.e. photon, proton, intensity modulated radiation therapy, brachytherapy may be used in the best interest of the patient.

1.2.1 Dose:
The daily dose to the prescription points shall be 1.8 Gy with the exception of patients with chest wall tumor and ipsilateral cytology positive pleural fluid, and patients with pulmonary metastases, who will receive 1.5 Gy per fraction.

1.2.2 Bony and soft tissue lesions:
Soft tissue and bony lesions with the exception of vertebral body tumors shall be treated as follows.

For bony and soft tissue tumor sites harboring gross residual disease, dose will be 55.8 Gy in 31 fractions.

A field reduction will be allowed after 45 Gy for soft tissue response to chemotherapy, but is not required. No field reduction is allowed for bony disease however sites with both bony and soft tissue components may qualify for field reduction.

For sites harboring microscopic residual disease, 50.4 Gy in 28 fractions will be delivered. There will be no field reduction for patients with microscopic residual disease.

1.2.3 Regional Lymph Nodes:
The dose to biopsy proven regional lymph nodes will be 50.4 Gy in 28 fractions if they have been excised and 55.8 Gy if biopsied but not excised.

1.2.4 Bone Marrow Metastases:

The bone marrow will not be treated.

1.2.5 Vertebral Body Metastases:
Vertebral body metastases shall receive 45 Gy in 25 daily fractions of 1.8 Gy each.

1.2.6 Chest Wall Tumors and Ipsilateral Cytology Positive Pleural Fluid:
For patients having chest wall tumors and ipsilateral cytology positive pleural fluid, and who are ≥ 6 years of age, ipsilateral lung radiation will be given with 15 Gy in 10 daily fractions of 1.5 Gy each.

For patients < 6 years of age the dose shall be 12 Gy in 8 fractions of 1.5 Gy each. Chest wall tumors without positive pleural fluid shall be treated as bony/soft tissue lesions.

1.2.7 Pulmonary Metastases and Pleural Effusions:
For patients having pulmonary metastases and pleural effusion who are ≥ 6 years of age, bilateral lung radiation will be given with 15 Gy in 10 daily fractions of 1.5 Gy each. For patients < 6 years of age the dose shall be 12 Gy in 8 fractions of 1.5 Gy each.

Surgical management of residual pulmonary tumors after induction chemotherapy is encouraged. Field reduction boost to treat individual lesions is allowed. The dose for field reductions will be 27 Gy in 15 daily fractions of 1.8 Gy for all patients regardless of age. The total dose will therefore be 15 Gy + 27 Gy = 43 Gy for ≥ 6 years of age, and 12 Gy + 27 Gy = 39 Gy for < 6 years of age. Strict volume requirements must be met for field reduction boost of pulmonary metastases (see below).

1.3 **Brachytherapy Dose**:

1.3.1
The dose to the prescription point for low dose-rate brachytherapy will be 5000 cGy if brachytherapy is used alone or 1200 cGy if brachytherapy is combined with external beam radiation. The prescription point dose-rate is expected to be between 40 cGy and 100 cGy per hour.

1.3.2
The dose to the prescription point for high dose-rate brachytherapy will be 3600 cGy delivered in 12 fractions of 300 cGy twice a day with a six hour separation between fractions if brachytherapy is used alone. If high dose-rate brachytherapy is used in combination with external beam radiation, the dose to the prescription point will be 900 cGy in 3 fractions of 300 cGY over 2 days with a minimum of six hours separation between fractions.

1.3.3
The dose for external beam radiation when combined with brachytherapy will be 45 Gy in 25 daily fractions of 1.8 Gy each.

1.4 **Absorbed dose specification**
All doses shall be specified as cGy to muscle.

1.4.1 Fractionation:
All radiation fields should be treated once each day and treatments should be given 5 days per week.

1.4.2 Tissue inhomogeneity consideration:
No inhomogeneity corrections should be made.

1.4.3 Prescription Points:

Spine fields:
The dose to the spine shall be prescribed to the isocenter, or along the central axis at a depth representing the mean depth to the posterior aspect of the vertebral bodies as determined by cross-table lateral x-rays, by CT scan, or by MRI scan.

Conformal Therapy:
The dose shall be prescribed to the isocenter. The isocenter should be within the target volume.

1.4.4 Volume:
Conformal Radiation Therapy:

Volume based 3-D conformal radiotherapy technique is encouraged for all sites treated on the current protocol. In specific instances simple or intermediate complexity methodology may be appropriate however. ICRU definitions for gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV) will be used as appropriate. In the ICRU terminology GTV and CTV are anatomically defined and are intended to direct treatment to gross and microscopic disease respectively.

The PTV is geometric and not anatomically defined. A margin is added to the CTV in 3-dimensions to create the PTV as the purpose of the PTV is to account for uncertainty in immobilization and daily variability in patient positioning.
Conformal radiation therapy will use 3 dimensional treatment planning techniques. This means that three dimensional imaging data (CT and/or MRI) are acquired with the patient in the treatment position and that image data are used to delineate and reconstruct a gross target volume, clinical target volume, planning target volume, and specific normal or critical structures in 3-dimensions. True conformal therapy further requires that the dose distribution is computable on a point-by-point basis in 3-dimensional space.

1.5 **Protocol Specific Definition of Target Volumes**:
Site: A site consists of a discrete body area thought to harbor gross residual or microscopic residual disease. Various non-contiguous sites within the same patient may differ in status regarding residual disease and therefore be treated with different radiotherapy dose and fractionation.

1.5.1
GTV: The radiologically apparent and palpable bony and soft-tissue disease prior to surgical debulking and/or chemotherapy. GTV may be defined based on physical examination, X-ray, computed tomography, bone scan, positron emission tomography, or magnetic resonance imaging. Magnetic resonance imaging is most often the optimal treatment planning modality. **The initial GTV shall specifically, be based on the initial pre-operative, pre-chemotherapy, and pre-irradiation imaging examinations.** The GTV should include adjacent areas of bone destruction and soft tissue extension. The GTV should, when possible, be based on T1 signal changes with and without Gadolinium contrast enhancement as well as T2 signal changes. The GTV may be modified to account for tumors which exhibit an initial "pushing margin" into body cavity if the normal tissues have returned to their natural positions.

Biopsy proven regional disease such as positive lymph nodes draining the primary site will be defined as GTV however regional lymph nodes will not be included within GTV unless proven by biopsy to be involved with tumor.

1.5.2
GTV-P: **For sites in which significant tumor response to initial chemotherapy is demonstrated, the GTV-P (for "post-chemotherapy GTV") may be defined**. The GTV-P terminology will be used for field reduction after 45 Gy for soft tissue tumors, and after 12 or 15 Gy for pulmonary metastases.

1.5.3
For multiple non-contiguous sites, multiple GTVs (i.e. GTV1, GTV2, GTV3, etc.) will be treated.
Similarly for field reductions after 45 Gy multiple GTV-Ps may be treated (GTV-P1, GTV-P2, GTV-P3, etc.) Where sites are considered as separate target volumes, care must be taken to avoid overlap of entrance and exit beams so that normal tissue does not exceed the prescription dose.

1.5.4
CTV: The clinical tumor volume (CTV) is the GTV together with regions of potential occult tumor involvement. For bony or soft tissue tumors, the clinical target volume (CTV) will be an anatomically defined margin of 1.0 cm surrounding the GTV. The CTV may be extended when adjacent to a bony interface, for example at the skull. For multiple GTVs, (i.e. GTV1, GTV2, GTV3, etc.), multiple CTVs will be created. For ipsilateral or bilateral lung irradiation, the involved lung will be arbitrarily defined as the CTV. For field reductions the terminology CTV-P will be used.

1.5.5
PTV: The planning target volume (PTV) is the CTV together with margin added for daily setup
variability and organ motion. For conformal radiation therapy on this protocol the PTV will be the CTV plus 0.5 cm. For field reductions, the terminology PTV-P will be used.

1.5.5.1 Special PTV Considerations:
When the PTV includes the epiphysis of an adjacent bone and there is no extension across the joint space, a smaller PTV may arbitrarily be chosen, so that the adjacent epiphysis is included. Similarly, with a diaphyseal lesion, every attempt should be made to exclude at least one epiphysis of the affected bone. Similarly, every attempt should be made that the PTV does not encompass an extremity circumferentially. An adequate strip of tissue should be spared on extremity tumors, to avoid lymphatic obstruction.

1.6 **Non-conformal Radiation**:
It is recognized that specific clinical situations will arise in which true conformal radiation is not practical and this will not be required for all treatment sites in this study. In specific instances, simple or intermediate complexity methodology may be allowed. Such situations may include irradiation of the long bones of the extremity, and vertebral body radiation, for example. Nevertheless, the use of ICRU definitions (and conformal treatment) is encouraged for all sites.

1.7 **Normal Tissue Tolerance Limitations**:
Normal tissue tolerance limits of liver (50% of volume limited to 30 Gy), heart (50% of volume limited to 30 Gy), small bowel (limited to 45 Gy) and bilateral kidneys (limited to 15 Gy) will be respected. Regarding tolerance of lung, it is recommended that the total lung volume receiving greater than 20 Gy be limited to 35% or less.

1.8 **Special Rule Regarding Volume Limitation for Bone Marrow**:
For patients with widespread metastatic disease, care shall be taken not to allow more than 50% of the active marrow to be irradiated. An estimate of the percentage of active marrow within the radiation field can be made by using established methodology. If, in order to otherwise comply with the protocol requirements, more than 50% of marrow would be included in radiotherapy fields, this situation should be discussed with a pediatric radiotherapist. In cases where all initial presenting lesions cannot be treated, the priority for treatment will be those persistent lesions which have not improved on follow-up imaging after chemotherapy.

APPENDIX 11: Informed Consent Template – Phase I

SAMPLE INFORMED CONSENT / PARENTAL PERMISSION
FOR PARTICIPATION IN RESEARCH

Dasatinib (SPRYCEL®) with Ifosfamide, Carboplatin, Etoposide: A Pediatric Phase I Trial

This study is a clinical trial (a research study involving patients, or protocol) of an experimental new drug Dasatinib (SPRYCEL®) for cancer. We are asking if you want to participate in this study because there is not a standard treatment for your cancer at this point. Clinical trials only include patients who choose to take part in them and your participation is entirely voluntary. Your participation in this study is entirely voluntary. Please read the consent form carefully. You will be given a copy of it to keep if you decide to participate in this study. You may discuss your decision with your friends and family if you would like.

Bristol-Myers Squibb (BMS) and the Pediatric Cancer Foundation (PCF) are collaborators on this clinical trial. These investigators promote the early clinical development of promising therapies for the treatment of children, adolescents and young adults with cancer. There are fourteen large academic medical institutions participating in this study. Bristol-Myers Squibb is the manufacturer of dasatinib **(SPRYCEL®)** and supporter of this research study and the Pediatric Cancer Foundation is a non-profit, charity organization, dedicated to funding research to eliminate childhood cancer worldwide.

This is a Phase I study of the experimental drug called Dasatinib **(SPRYCEL®)**. Dasatinib **(SPRYCEL®)** is considered experimental because it has not been approved by the Food and Drug Administration (FDA) for use in pediatric solid tumors. This is called a Phase I study because the goal is to find the highest dose of Dasatinib **(SPRYCEL®)** that we can give safely when given with chemotherapy of Ifosfamide, Carboplatin and Etoposide (ICE). We are using Dasatinib **(SPRYCEL®)** because it seems to work against cancer in test tubes and animals. Dasatinib **(SPRYCEL®)** has been used in several hundred adults. Some adults with chronic myelogenous leukemia have been helped by Dasatinib **(SPRYCEL®)**. However, there is a lot that we do not know about Dasatinib **(SPRYCEL®)**.

You are being asked to participate in this study because you have a recurrent cancer (cancer that has returned) or metastatic solid tumor including recurrent or refractory sarcomas, such as rhabdomyosarcoma, osteosarcoma, and Ewing sarcoma, or other solid tumors.

Why is this study being done?

We are testing the safety of Dasatinib **(SPRYCEL®)**at different dose levels with cytotoxic chemotherapy, Ifosfamide, Carboplatin, and Etoposide (D-ICE). We want to find out what effects, good and/or bad, it has on you and your recurrent or progressive solid tumor cancer.

The goals of this study are:

- **To determine the maximally tolerated dose (MTD) of dasatinib (SPRYCEL®)given immediately following ifosfamide, carboplatin and etoposide (D-ICE) as a re-induction regimen to pediatric patients with recurrent solid tumors**
- **To describe and define the toxicities of D-ICE**
- **To determine the safety and feasibility of prolonged administration of single agent dasatinib (SPRYCEL®) following completion of 2-6 courses of D-ICE therapy**
- **To examine the effect of Dasatinb (SPRYCEL®) on the biology of cancer cells including**
  - **To determine the phosphotyrosine state by immunohistochemistry of SRC family kinases and related signaling pathways including FAK, STAT3, VEGFR, AKT, EGFR, KIT, EPHA2 and PDGFR in paraffin-embedded tumor specimens prior to and during treatment with dasatinib.**
  - **To identify molecular signatures in tumor cells that may predict response to dasatinib by microarray analyis examined by gene expression.**
  - **To correlate the biomarkers and molecular signatures with dasatinib dosage, toxicity, and anti-tumor activity.**
  - **To evaluate the effect of dasatinib on phosphorylation of SRC family kinases in peripheral blood mononuclear cells (PBMCs) as a surrogate marker of response prior to treatment with dasatinib, at day 14 - 21 or when WBC $\geq$ 500 during each treatment course, at the time of local control, and at time of progression, if any.**

How many people will take part in the study?

There will be approximately of 18 patients participating in this study overall. About ___ patients will be treated at this hospital.

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

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This decision will be up to your study doctor.

Your doctor will also review your current medications with you. Since Dasatinib **(SPRYCEL®)** interacts with some medications, your doctor may stop or change some of your medications. You should talk to your doctor before taking any prescription or over the counter medications while on this study.

- **A medical history**
- **Physical exam**
- **Vital signs (blood pressure, pulse, temperature)**
- **Blood tests**
- **Pregnancy test (if you are female and of childbearing age)**
- **Tests to evaluate heart function**
- **CT scans, MRI, X-rays and/or bone scans of disease sites, will be done to measure tumor, or other tests are needed to check your tumor.**

During the study …

If the exams, tests and procedures show that you can be in the study, and you choose to take part

Study Plan…

You will receive Ifosfamide, Carboplatin, Etoposide and Dasatinib (SPRYCEL®) (D-ICE) every 28 days in this study. The whole tablet of dasatinib (SPRYCEL®) may be placed (and allowed to dissolve) in lemonade, preservative free orange juice, or preservative free apple juice before swallowing. This 28 day time period is called a course. The course will be repeated up to 6 times prior to consolidation. Each course is numbered in order.

The chart below shows what will happen to you during Course 1 and future treatment courses as explained previously.

Course may be repeated up to 6 times, each course will last for 28 days

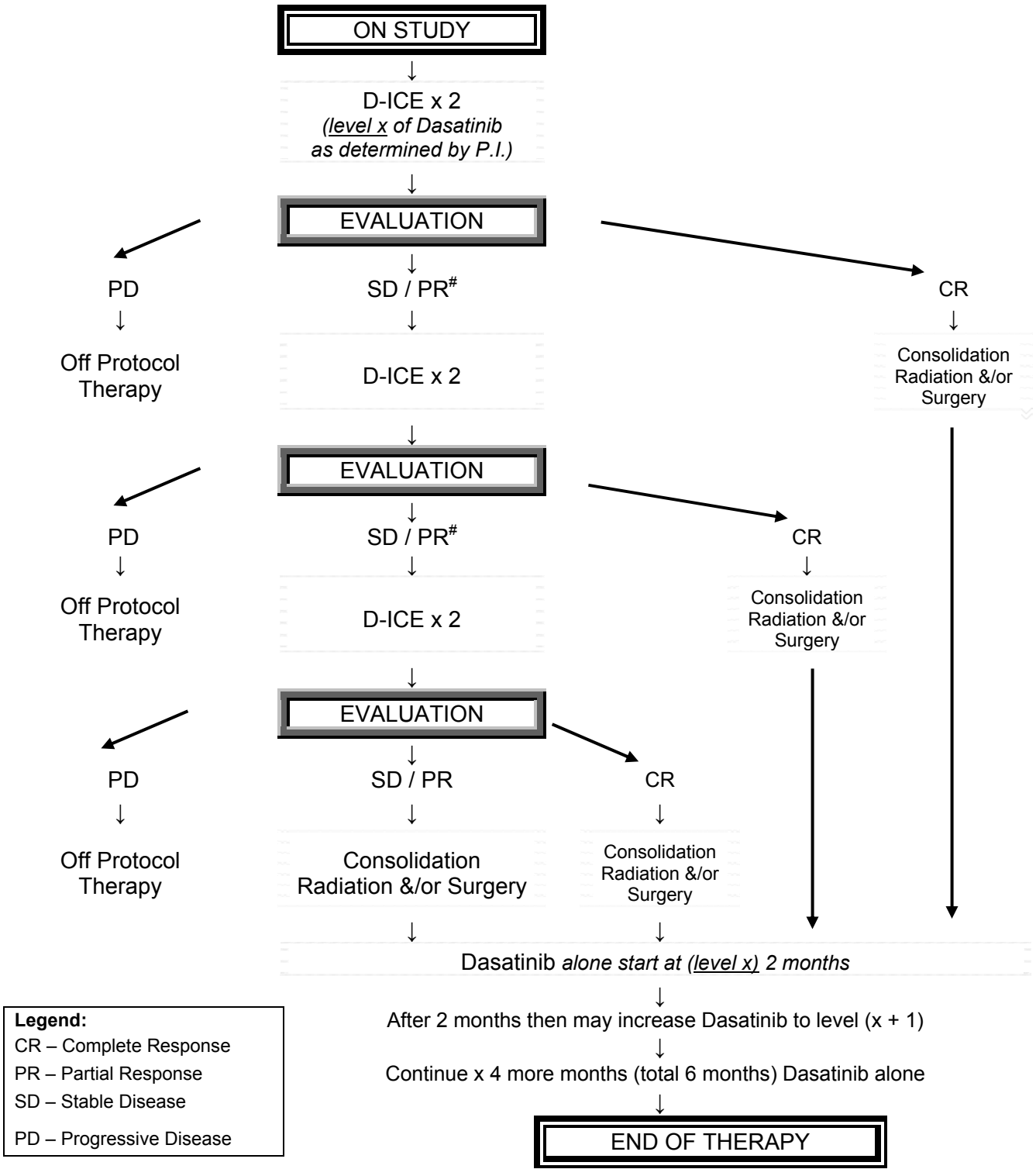
Drug	Route	Schedule	Method of Administration
Ifosfamide (IFOS)	**Intravenous (IV)**	**Day 0 - 4**	**IV infusion over 60 minutes daily for 5 days**
Carboplatin (CBDCA)	**Intravenous (IV)**	**Day 0 - 1**	**IV infusion over 60 minutes daily for 2 days**
Etoposide (VP-16)	**Intravenous (IV)**	**Day 0 - 4**	**IV infusion over 60 minutes (every day) daily for 5 days**
Dasatinib (SPRYCEL®)	**By mouth (oral)**	**Day 5 - 21**	**Oral BID (twice a day) for 17 days**
Mesna	**Intravenous (IV)**	**Day 0 - 4**	**IV infusion over 15 minutes**
MESNA and fluids will be used with Ifosfamide as a bladder protectant			
REST		**Day 22 - 28**	
G-CSF	**Subcutaneously (Subq)**	**Day 5**	**Daily starting day 5, until ANC ≥10,000, first course only. Neulasta may be given for subsequent courses to subjects > 50 kg.**

The dose for the first 3 children enrolled on the study will be based on the side effects seen in adults. Between 3 and 6 children will receive Dasatinib at each dose. If the side effects are not too severe, the next group of children will receive a higher dose. Up to four different doses may be studied. Your dose will not be increased. If you have bad side effects, your drug will be stopped. If you are a patient enrolled early in this study you may receive a lower dose than those who are enrolled later. It is therefore possible that you may receive a dose that is less likely to have any effect on your tumor. If you are a patient enrolled in this study at a high dose level it is possible that you will receive a dose that is more likely to cause side effects. Dosing is done this way because we do not yet know the best dose to use in children.

You may be required to stay in the hospital if the treatment makes you sick, or you are sick because of your tumor.

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.

EXPERIMENTAL DESIGN SCHEMA*:



* **Phase I**: Dasatinib **(SPRYCEL®)** dose escalation per Table 3

\# At Investigators discretion subject may proceed to consolidation, radiation and/or surgery

You will need the following tests and procedures during the study. These exams, tests or procedures are part of regular cancer care.

- **A medical history**
- **Physical exam**
- **Vital signs (blood pressure, pulse, temperature)**
- **Blood tests**
- **Test to evaluate the heart function**

We will also do whatever x-rays, CT scans, or other tests as needed to check your tumor.

You will also be asked to keep a diary of when you take Dasatinib (SPRYCEL®). This diary will help document study compliance.

You will be asked to tell your doctor about other medications and nutritional supplements that you take.

When I am finished taking D-ICE

After you are finished taking Dasatinib, the study doctor will ask you to visit the office for follow-up exams and tests. These exams, tests or procedures are all part of regular cancer care:

First year off-therapy (reporting every 6 months)
- Physical examination every month x 6 months then every 2 months x 6 months
- Imaging studies that were positive at study entry every 3 months

Second and subsequent years off-therapy (reporting every year)
- Physical examination every 3 months
- Imaging studies that were positive at study entry every 6 months until progressive disease

Biology Studies: Blood and Tumor

We would also like to do some extra tests called biology studies and tumor studies. These tests will help us learn more about Dasatinib and may help children who receive this drug in the future. The information learned will not change the way you are treated, and the results of these tests will not be returned to you. Although these tests are a very important part of how we will better learn to use this drug, it is your decision as to whether or not you agree to participate in these tests.

During the study blood samples will be collected to evaluate the biological effects of Dasatinib on your blood cells. The amount of blood for each sample is about 10 mL (which is the about the same as 2 teaspoons) and will be collected on Day 14 - 21 or when WBC $\geq$ 500 of each course during pre-consolidation treatment, and on Day 14 - 21 or when WBC $\geq$ 500 of each course during post-consolidation treatment for all patients.

The tests will help us to better learn how Dasatinib **(SPRYCEL®)** may work.

Please indicate by checking and initialing below whether you choose to participate in the biology studies.

☐/_____ Yes, I agree to participate in the biology studies.

☐/_____ No, I do not agree to participate in the biology studies.

Tumor biology studies:
If a biopsy is done for clinical reasons at any time before or during the study, we would like to have a piece of tumor tissue for research. The tumor samples will be sent to a research laboratory to measure the characteristics of the tumor cell and to evaluate the effect of Dasatinib **(SPRYCEL®)** on the tumor cells.

Please indicate by checking and initialing below whether you choose to participate in the tumor biology studies.

☐/____ Yes, I agree to participate in the tumor biology studies if a tumor biopsy is done for clinical reasons.

☐/____ No, I do not agree to participate in the tumor biology studies if a tumor biopsy is done for clinical reasons.

How long will I be in the study?

You may be in the study for up to 12 courses (about 12 months), if your tumor responds to this therapy and the treatment does not cause bad side effects. You may receive an additional 6 months of Dasatinib (SPRYCEL®) alone if you successfully complete the pre-consolidation phase of treatment.

Your doctor may decide to take you off study if any of the following occur:

- **The side effects of Dasatinib (SPRYCEL®) and ICE are too harmful for you**
- **You need a treatment that is not allowed on this study**
- **Your tumor does not improve or worsens**
- **You are not able to follow study-related treatment instructions**
- **New information becomes available**
- **The study is not in your best interest**
- **The study is stopped**

Can I stop being in the study?

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

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

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

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you

stop taking the Dasatinib. In some cases, side effects can be serious, long lasting, or may never go away.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the DASATINIB (SPRYCEL®) include:

Likely

- **Headache**
- **Hemorrhage**
- **Thrombocytopenia (Low platelet count which may lead to bleeding or bruising)**
- **Pleural effusion**
- **Dyspnea**
- **Diarrhea**
- **Nausea**
- **Vomiting**
- **Abdominal pain**
- **Gastrointestinal hemorrhage**
- **Skin rash**
- **Musculoskeletal pain**
- **Superficial edema**
- **Fatigue**
- **Pyrexia**
- **Hypocalcemia**
- **Infection (including bacterial, viral, fungal, non-specified)**
- **Cough**

Less Likely

- **Pneumonia (including bacterial, viral, and fungal)**
- **Upper respiratory tract infection/inflammation**
- **Herpes virus infection**
- **Enterocolitis infection**
- **Febrile neutropenia**
- **Anemia**
- **Leukopenia**
- **Depression**
- **Insomnia**
- **Dizziness**
- **Neuropathy (including peripheral neuropathy)**
- **Dysgeusia**
- **Dry eye**
- **Congestive heart failure/ Cardiac dysfunction**
- **Pericardial effusion**
- **Arrhythmia (including tachycardia)**
- **Palpitations**
- **Hypertension**
- **Flushing**
- **Pulmonary edema**
- **Lung infiltration**
- **Pneumonitis**
- **Abdominal distension**
- **Mucosal inflammation (including Mucositis/stomatitis)**
- **Colitis (including neutropenic colitis)**

- **Gastritis**
- **Oral soft tissue disorder dyspepsia**
- **Constipation**
- **Dehydration**
- **Pruritus**
- **Alopecia**
- **Acne**
- **Dry skin**
- **Urticaria**
- **Hyperhydrosis**
- **Arthralgia**
- **Myalgia**
- **Muscle inflammation**
- **Muscular weakness**
- **Pain**
- **Chest pain**
- **Chills**
- **Weight decreased**
- **Weight increased**
- **Contusion**
- **Thrombophlebitis**
- **Anorexia**
- **Asthenia**
- **Sepsis (including fatal outcome)**
- **Pancytopenia**
- **Hyperuricemia**
- **Somnolence**
- **Pulmonary hypertension**
- **Dermatitis (including eczema)**
- **Musculoskeletal stiffness**

Rare but serious

- **Tumor lysis syndrome**
- **Aplasia pure red cell**
- **Hypersensitivity (including erythema nodosum, a type of skin inflammation)**
- **Transient ischemic attack**
- **Reversible posterior leukoencephalopathy syndrome**
- **Convulsion**
- **Amnesia**
- **Tremor**
- **Syncope**
- **Central nervous system hemorrhage**
- **Cardiomegaly**
- **Angina pectoris**
- **Myocardial infarction**
- **Pericarditis**
- **Acute coronary syndrome**
- **Myocarditis**
- **Ventricular tachycardia**
- **Hypotension**
- **Livedo reticulares**
- **Asthma**
- **Acute respiratory distress syndrome**
- **Pancreatitis**

- **Upper gastrointestinal ulcer**
- **Ascites**
- **Dysphagia**
- **Hepatitis**
- **Cholestasis**
- **Cholecystitis**
- **Acute febrile neutrophilic dermatosis**
- **Photosensitivity reaction**
- **Pigmentation disorder**
- **Skin ulcer**
- **Bullous conditions (including Erythema multiforme)**
- **Nail disorder**
- **Palmar-plantar erythrodysesthesia syndrome**
- **Rhabdomyolysis**
- **Tendonitis**
- **Blood creatine phosphokinase increased**
- **Renal failure**
- **Urinary frequency proteinuria**
- **Gynecomastia**
- **Menstruation irregular**
- **Malaise**
- **Temperature intolerance**
- **Lethargy**
- **Lightheadedness**
- **Tinnitus**
- **Tendonitis**
- **Cor pulmonale**
- **Cerebrovascular accident**
- **Tendonitis**
- **Hypoalbuminemia**
- **Conjunctivitis**
- **Vertigo**
- **Bronchospasm**
- **Anal fissure**
- **Anxiety**
- **Confusional State**
- **Affect lability**
- **Libido decreased**
- **Electrocardiogram QT prolonged**
- **Esophagitis**
- **Panniculitis**

Risks and side effects related to the IFOSFAMIDE include:

Likely

- **Nausea**
- **Vomiting**
- **Hair loss**
- **Fewer red and white blood cells and platelets in the blood**
    - **A low number of red blood cells can make you feel tired and weak**
    - **A low number of white blood cells can make it easier to get infections**
    - **A low number of platelets causes you to bruise and bleed more easily**
- **Decreased ability of the body to fight infection**

- **Absence or decrease in the number of sperm which may be temporary or permanent which may decrease the ability to have children**
- **Slight decrease in kidney function**

Less Likely

- **Drowsiness**
- **Confusion**
- **Depression**
- **Loss of appetite**
- **Diarrhea or constipation**
- **Seizures**
- **Abnormal hormone function affecting levels of salt in the blood and urine**
- **Abnormal heartbeat or rhythm. This side effect may require frequent evaluations of the hearts function and a heart specialist consult**
- **Blood in the urine that is only seen under the microscope**
- **Body loss of certain important salts and minerals**
- **Failure of the ovaries to function normally which may be permanent and which may decrease the ability to have children**
- **Inflammation and burning along the vein where the medicine is given**
- **Temporary elevation in the blood of certain enzymes found in the liver**

Rare but Serious

- **Damage to brain tissue with very high doses that may lead to coma**
- **Kidney failure or damage**
- **Damage to the bladder, which can lead to large amounts of blood in the urine, pain and the urge to urinate frequently and also permanent scarring of the bladder**
- **A new cancer or leukemia resulting from this treatment**
- **Damage to heart muscle which may make you tired, weak, feel short of breath, and retain fluid**
- **Abnormal bone growth and development**

Risks and side effects related to the ETOPOSIDE include:

Likely

- **Nausea**
- **Hair loss**
- **A feeling of weakness or tiredness**
- **Fewer red and white blood cells and platelets in the blood**
    - **A low number of red blood cells can make you feel tired and weak**
    - **A low number of white blood cells can make it easier to get infections**
    - **A low number of platelets causes you to bruise and bleed more easily**

Less Likely

- **Loss of appetite**
- **Decreased blood pressure during the infusion which may require treatment**
- **Rashes**
- **Diarrhea or constipation**
- **Pain in the abdomen**
- **Mouth sores**
- **Tingling sensation or loss of sensation in fingers or toes**
- **A feeling of extreme tiredness or weakness**
- **The finger or toe nails may loosen from their nail beds**
- **Inflammation and burning along the vein through which the medication was given**
- **Chest pain**

Rare but Serious

- **Damage to the liver**
- **Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate chills and fever**
- **A new cancer or leukemia resulting from this treatment**
- **Temporary severe rashes which can result in loss of skin and damage to mucous membranes**
- **Absence or decrease monthly periods**
- **Damage to heart muscle which may make you tired, weak, feel short of breath, and retain fluid**

Risks and side effects related to the CARBOPLATIN include:

Likely

- **Bone Marrow Suppression (as described for Ifosfamide) - Fewer red and white blood cells and platelets in the blood**
  - **A low number of red blood cells can make you feel tired and weak**
  - **A low number of white blood cells can make it easier to get infections**
  - **A low number of platelets causes you to bruise and bleed more easily**
- **Nausea and vomiting**

Less Likely

- **Kidney and liver damage**

Rare but Serious

- **Tingling and discomfort in arms and legs and weakness may occur rarely**
- **Local allergic reactions at the IV site. Itching, a skin rash, lightheadedness, facial flushing or trouble breathing**
- **Hearing loss**
- **A new cancer or leukemia resulting from this treatment**

Risks and side effects related to the MESNA include:

Likely

- **Bad taste when taken by mouth.**

Less Likely

- **Nausea.**
- **Vomiting**
- **Stomach pain**
- **Headache**
- **Pain in arms, legs and joints**
- **Tired feeling**
- **Rash**
- **Temporary low blood pressure**
- **Diarrhea**
- **Fever**
- **Facial flushing with red cheeks**
- **Nervousness**
- **Dizziness**
- **Confusion**
- **Swelling around the eyes**

- **Coughing**
- **Rapid heart rate**

Rare but Serious

- **Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate chills and fever**

Risks and side effects related to the G-CSF (Growth factor, Filgrastim, Neupogen) include:

Most patients who receive G-CSF have little or no side effects. However, some patients may experience the following:

Likely

- **Mild to moderate aching or pain inside the bones**

Less Likely

- **Local irritation at the site of the injection**
- **Mild headache**
- **Higher than normal levels of liver enzymes**
- **Lower number of platelets in the blood**
- **Low fever**
- **Enlargement of the spleen**
- **Worsening of skin rashes**
- **Inflammation of a blood vessel in the skin leading to a raised purple rash and bruising**
- **Higher than normal white blood count**

Rare but Serious

- **Allergic reactions which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, hives and facial swelling**
- **If you are known to have sickle cell disease, filgrastim may cause a sickle cell crisis.**
- **A blood disorder or leukemia that has only been seen in patients with certain immune disorders who are treated for a very long time**
- **Severe damage to the spleen**
- **Difficulty breathing and lung damage that may be due to the white blood cells that are stimulated by filgrastim traveling to the lungs when they are inflamed or infected**

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. The long-term effects of Dasatinib on fertility are unknown. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. Pregnancy tests will be obtained in women interested in participating in this study.

Risks of blood drawing or placing an intravenous catheter for blood drawing:

Risks associated with drawing blood are slight, but some risks include: pain, excessive bleeding, fainting or feeling lightheaded, bruising, infection (a slight risk any time the skin is broken), and multiple punctures to locate veins.

Risk of Surgery

Some patients on this study will undergo surgery before starting therapy or during this study. You will be asked to sign a separate consent form for the surgical procedure. The planned surgery will be explained to you and your questions about it answered by your surgeon when you sign the consent for the surgical procedure.

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

Are there benefits to taking part in the study?

Taking part in this study may or may not make your cancer to stop growing or shrink for a period of time. While doctors hope the treatment proposed in this study will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about Dasatinib when given with ICE chemotherapy, as a treatment for cancer. This information could help future cancer patients

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

Your other choices may include:

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

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

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- **Pediatric Cancer Foundation**
- **Bristol-Myers Squibb (sponsor/supplier of Dasatinib)**
- **Representatives of the National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people**

What are the costs of taking part in this study?

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

Bristol-Myers Squibb (BMS) is supplying Dasatinib at no cost to you. However, you or your health plan may need to pay for costs of the supplies and personnel who give you the Dasatinib.

The study agent, Dasatinib, will be provided free of charge while you are participating in this study. However, if you should need to take the study agent much longer than is usual, it is possible that the supply of free study agent that has been supplied to could run

out. If this happens, your study doctor will discuss with you how to obtain additional drug from the manufacturer and you may be asked to pay for it.

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

There will be no cost to you for any tissue collected and banked. You will not be paid for allowing your leftover tissue to be used in research, even though it is possible that new cancer tests or treatments may be developed as a result of the research.

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

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

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

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

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

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

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

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

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

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

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

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

Whether you participate or not, you will continue to get the best medical care this hospital can provide.

Who can answer my questions about the study?

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

For questions about your rights while taking part in this study, call the _____

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

Where can I get more information?

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

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

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

- **For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/**
- **For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/**

You will get a copy of this form. You will be given a copy of the protocol (full study plan) upon request.

If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all # pages of this form.
I have read it or it has been read to me.

I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Parent (or Guardian) _____

Date _____

Signature of Physician or Responsible Investigator

_____

Date _____

FOR SUBJECTS/PARTICIPANTS 7-17 YEARS OF AGE

The undersigned physician, _____, M.D., hereby certifies that he/she has discussed the research project with the subject/participant and has explained all the information contained in the informed consent form to the subject/participant, including any risks that may reasonably be expected to occur. The undersigned further certifies that the subject/participant was encouraged to ask questions and that all questions were answered.

_____ _____

Date **Physician's Signature**

APPENDIX 12: Informed Consent Template – Phase II

SAMPLE INFORMED CONSENT / PARENTAL PERMISSION
FOR PARTICIPATION IN RESEARCH

Dasatinib (SPRYCEL®) with Ifosfamide, Carboplatin, Etoposide: A Pediatric Phase II Trial

This study is a clinical trial (a research study involving patients, or protocol) of an experimental new drug Dasatinib (SPRYCEL®) for cancer. We are asking if you want to participate in this study because there is not a standard treatment for your cancer at this point. Clinical trials only include patients who choose to take part in them and your participation is entirely voluntary. Your participation in this study is entirely voluntary. Please read the consent form carefully. You will be given a copy of it to keep if you decide to participate in this study. You may discuss your decision with your friends and family if you would like

Bristol-Myers Squibb (BMS) and the Pediatric Cancer Foundation (PCF) are collaborators on this clinical trial. These investigators promote the early clinical development of promising therapies for the treatment of children, adolescents and young adults with cancer. There are fourteen large academic medical institutions participating in this study. Bristol-Myers Squibb is the manufacturer of dasatinib and supporter of this research study and the Pediatric Cancer Foundation is a non-profit, charity organization, dedicated to funding research to eliminate childhood cancer worldwide.

This is a Phase II study of the experimental drug called Dasatinib **(SPRYCEL®) when given with chemotherapy including Ifosfamide, Carboplatin and Etoposide (ICE)**. A Phase II study is done to measure the response of a disease to an experimental drug. A tolerable dose (the highest dose without bad side effects) for children with recurrent solid tumors was found in a phase I clinical trial that has been completed. Dasatinib **(SPRYCEL®)** is considered experimental because it has not been approved by the Food and Drug Administration (FDA) for use in pediatric solid tumors. This is called a Phase II study because the goal is to find out what effects, good and/or bad. Dasatinib **(SPRYCEL®) with ICE** has on you and your recurrent and/or progressive solid tumor cancer. We are using Dasatinib **(SPRYCEL®)** because it seems to work against cancer in test tubes and animals. Dasatinib **(SPRYCEL®)** has been used in several hundred adults. Some adults with chronic myelogenous leukemia have been helped by Dasatinib **(SPRYCEL®)**. However, there is a lot that we do not know about Dasatinib **(SPRYCEL®)**. Although Dasatinib **(SPRYCEL®)** has been given to a small number of children, we do not know if it will work against the type of tumor you have.

You are being asked to participate in this study because you have a recurrent cancer (cancer that has returned) or relapsed childhood solid tumor including Sarcomas (Rhabdomyosarcoma, Osteosarcoma, Ewing sarcoma and other Soft Tissue sarcomas), Kidney Tumors, Lymphoma, CNS Tumors (pending toxicity analysis in any Phase I study, including Dasatinib), and other solid tumors (neuroblastoma, gonadal, germ cell tumors, liver tumors, and miscellaneous tumors).

Why is this study being done?

We are testing a new experimental drug such as Dasatinib, and combination chemotherapy of Ifosfamide, Carboplatin and Etoposide in the hopes of finding a drug that may be effective against recurrent or refractory solid tumors. The combination of Dasatinib, Ifosfamide, Carboplatin and Etoposide is referred throughout this protocol as D-ICE

The purpose of this study is to….

We are testing the safety of Dasatinib at different dose levels with cytotoxic chemotherapy, Ifosfamide, Carboplatin, and Etoposide (D-ICE). We want to find out what effects, good and/or bad, it has on you and your recurrent or progressive solid tumor cancer.

The goals of this study are:

- **In the phase II portion of the study, to estimate the overall progression free survival and time to progression in patients with recurrent sarcoma and other solid tumors (including primary CNS tumors), to D-ICE given at the MTD, plus dasatinib alone given after consolidative therapy.**
- **In the phase II portion of the study, to estimate the response rate to 2 courses of D-ICE, given at the MTD.**
- **To examine the effect of Dasatinb (SPRYCEL®) on the biology of cancer cells including**
  - **To determine the phosphotyrosine state by immunohistochemistry of SRC family kinases and related signaling pathways including FAK, STAT3, VEGFR, AKT, EGFR, KIT, EPHA2 and PDGFR in paraffin-embedded tumor specimens prior to and during treatment with dasatinib (SPRYCEL®).**
  - **To identify molecular signatures in tumor cells that may predict response to dasatinib by microarray analyis examined by gene expression.**
  - **To correlate the biomarkers and molecular signatures with dasatinib dosage, toxicity, and anti-tumor activity.**
  - **To evaluate the effect of dasatinib on phosphorylation of SRC family kinases in peripheral blood mononuclear cells (PBMCs) as a surrogate marker of response prior to treatment with dasatinib, at day 14 - 21 or when WBC $\geq$ 500 during each treatment course, at the time of local control, and at time of progression, if any.**

How many people will take part in the study?

There will be approximately 125 subjects participating in this study overall. Subjects will be stratified (grouped) by their diagnosis: Stratum A (75 patients with Osteosarcoma, Ewing Sarcoma and Rhabdomyosarcoma tumors); Stratum B (25 other solid tumors); and Stratum C (25 patients with newly diagnosed metastatic sarcomas of poor risk).

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

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

Your doctor will also review your current medications with you. Since Dasatinib interacts with some medications, your doctor may stop or change some of your medications. You should talk to your doctor before taking any prescription or over the counter medications while on this study.

- **A medical history**
- **Physical exam**
- **Vital signs (blood pressure, pulse, temperature)**

- **Blood tests**
- **Pregnancy test (if you are female and of childbearing age)**
- **Tests to evaluate heart function**
- **CT scans, MRI, X-rays and/or bone scans of disease sites, will be done to measure tumor, or other tests are needed to check your tumor.**

During the study …

If the exams, tests and procedures show that you can be in the study, and you choose to take part

Study Plan…

You will receive Ifosfamide, Carboplatin, Etoposide and Dasatinib (D-ICE) every 28 days in this study. The whole tablet of dasatinib may be placed (and allowed to dissolve) in lemonade, preservative free orange juice, or preservative free apple juice before swallowing. This 28 day time period is called a course. The course will be repeated up to 6 times prior to consolidation. Each course is numbered in order.

The chart below shows what will happen to you during Course 1 and future treatment courses as explained previously.

Course may be repeated up to 6 times, each course will last for 28 days

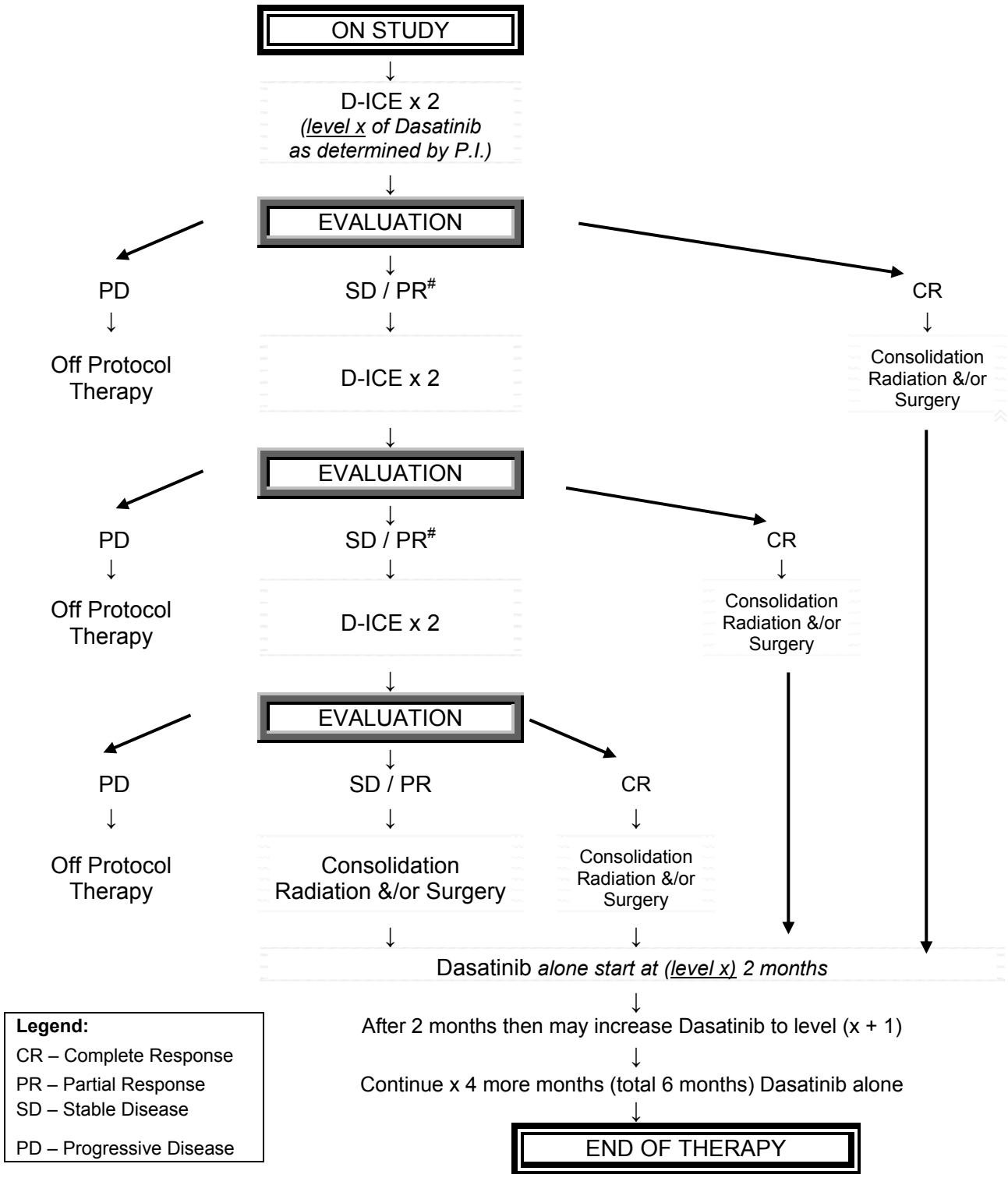
Drug	Route	Schedule	Method of Administration
Ifosfamide (IFOS)	**Intravenous (IV)**	**Day 0 - 4**	**IV infusion over 60 minutes daily for 5 days**
Carboplatin (CBDCA)	**Intravenous (IV)**	**Day 0 - 1**	**IV infusion over 60 minutes daily for 2 days**
Etoposide (VP-16)	**Intravenous (IV)**	**Day 0 - 4**	**IV infusion over 60 minutes (every day) daily for 5 days**
Dasatinib	**By mouth (oral)**	**Day 5 - 21**	**Oral BID (twice a day) for 17 days**
Mesna	**Intravenous (IV)**	**Day 0 - 4**	**IV infusion over 15 minutes**
MESNA and fluids will be used with Ifosfamide as a bladder protectant			
REST		**Day 22 - 28**	
G-CSF	**Subcutaneously (Subq)**	**Day 5**	**Daily starting day 5, until ANC ≥10,000, first course only. Neulasta may be given for subsequent courses to subjects > 50 kg.**

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.

The dose for the first 3 children enrolled on the study will be based on the side effects seen in adults. Between 3 and 6 children will receive Dasatinib at each dose. If the side effects are not too severe, the next group of children will receive a higher dose. Up to four different doses may be studied. Your dose will not be increased. If you have bad side effects, your dose will be stopped. If you are a patient enrolled early in this study you may receive a lower dose than those who are enrolled later. It is therefore possible that you may receive a dose that is less likely to have any effect on your tumor. If you are a patient enrolled in this study at a high dose level it is possible that you will receive a dose that is more likely to cause side effects. Dosing is done this way because we do not yet know the best dose to use in children.

You may be required to stay in the hospital if the treatment makes you sick, or you are sick because of your tumor.

EXPERIMENTAL DESIGN SCHEMA*:



* **Phase II**: Dasatinib **(SPRYCEL®)** dose will be administered at the maximally tolerated dose, as determined by the Phase I portion of this study.

At Investigators discretion subject may proceed to consolidation, radiation and/or surgery

You will need the following tests and procedures during the study. These exams, tests or procedures are part of regular cancer care.

- **A medical history**
- **Physical exam**
- **Vital signs (blood pressure, pulse, temperature)**
- **Blood tests**
- **Tests to evaluate heart function**

We will also do whatever x-rays, CT scans, or other tests as needed to check your tumor.

You will also be asked to keep a diary of when you take Dasatinib. This diary will help document study compliance.

You will be asked to tell your doctor about other medications and nutritional supplements that you take.

When I am finished taking D-ICE

After you are finished taking Dasatinib **(SPRYCEL®)**, the study doctor will ask you to visit the office for follow-up exams and tests. These exams, tests or procedures are all part of regular cancer care:

First year off-therapy (reporting every 6 months)
- Physical examination every month x 6 months then every 2 months x 6 months
- Imaging studies that were positive at study entry every 3 months

Second and subsequent years off-therapy (reporting every year)
- Physical examination every 3 months
- Imaging studies that were positive at study entry every 6 months

Biology Studies: Blood and Tumor

We would also like to do some extra tests called biology studies and tumor studies. These tests will help us learn more about Dasatinib **(SPRYCEL®)** and may help children who receive this drug in the future. The information learned will not change the way you are treated, and the results of these tests will not be returned to you. Although these tests are a very important part of how we will better learn to use this drug, it is your decision as to whether or not you agree to participate in these tests.

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.

During the study blood samples will be collected to evaluate the biological effects of Dasatinib on your blood cells. The amount of blood for each sample is about 10 mL (which is the about the same as 2 teaspoons) and will be collected on Day 14 - 21 or when WBC $\geq$ 500 of each course during pre-consolidation treatment, and on Day 14 - 21 or when WBC $\geq$ 500 of each course during post-consolidation treatment for all patients.

The tests will help us to better learn how Dasatinib **(SPRYCEL®)** may work.

Please indicate by checking and initialing below whether you choose to participate in the biology studies.

☐/_____ Yes, I agree to participate in the biology studies.

☐/____ No, I do not agree to participate in the biology studies.

Tumor biology studies:
If a biopsy is done for clinical reasons at any time before or during the study, we would like to have a piece of tumor tissue for research. The tumor samples will be sent to a research laboratory to measure the characteristics of the tumor cell and to evaluate the effect of Dasatinib **(SPRYCEL®)** on the tumor cells.

Please indicate by checking and initialing below whether you choose to participate in the tumor biology studies.

☐/____ Yes, I agree to participate in the tumor biology studies if a tumor biopsy is done for clinical reasons.

☐/____ No, I do not agree to participate in the tumor biology studies if a tumor biopsy is done for clinical reasons.

How long will I be in the study?

You will be asked to take D-ICE (Dasatinib (SPRYCEL®), Ifosfamide, Carboplatin and Etoposide) for as long as you show to have stable disease, or objective tumor response, you will be allowed to continue treatment as long as there is a clinical benefit that is observed.

Your doctor may decide to take you off study if any of the following occur:

- **The side effects of Dasatinib (SPRYCEL®) and ICE are too harmful for you**
- **You need a treatment that is not allowed on this study**
- **Your tumor does not improve or worsens**
- **You are not able to follow study-related treatment instructions**
- **New information becomes available**
- **The study is not in your best interest**
- **The study is stopped**

Can I stop being in the study?

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

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

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

What side effects or risks can I expect from being in the study?

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

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the DASATINIB (SPRYCEL®) include:

Likely

- **Headache**
- **Hemorrhage**
- **Thrombocytopenia (Low platelet count which may lead to bleeding or bruising)**
- **Pleural effusion**
- **Dyspnea**
- **Diarrhea**
- **Nausea**
- **Vomiting**
- **Abdominal pain**
- **Gastrointestinal hemorrhage**
- **Skin rash**
- **Musculoskeletal pain**
- **Superficial edema**
- **Fatigue**
- **Pyrexia**
- **Hypocalcemia**
- **Infection (including bacterial, viral, fungal, non-specified)**
- **Cough**

Less Likely

- **Pneumonia (including bacterial, viral, and fungal)**
- **Upper respiratory tract infection/inflammation**
- **Herpes virus infection**
- **Enterocolitis infection**
- **Febrile neutropenia**
- **Anemia**
- **Leukopenia**
- **Depression**
- **Insomnia**
- **Dizziness**
- **Neuropathy (including peripheral neuropathy)**
- **Dysgeusia**
- **Dry eye**
- **Congestive heart failure/ Cardiac dysfunction**
- **Pericardial effusion**
- **Arrhythmia (including tachycardia)**
- **Palpitations**
- **Hypertension**
- **Flushing**
- **Pulmonary edema**
- **Lung infiltration**
- **Pneumonitis**
- **Abdominal distension**
- **Mucosal inflammation (including Mucositis/stomatitis)**
- **Colitis (including neutropenic colitis)**
- **Gastritis**
- **Oral soft tissue disorder dyspepsia**
- **Constipation**

- **Dehydration**
- **Pruritus**
- **Alopecia**
- **Acne**
- **Dry skin**
- **Urticaria**
- **Hyperhydrosis**
- **Arthralgia**
- **Myalgia**
- **Muscle inflammation**
- **Muscular weakness**
- **Pain**
- **Chest pain**
- **Chills**
- **Weight decreased**
- **Weight increased**
- **Contusion**
- **Thrombophlebitis**
- **Sepsis (including fatal outcome)**
- **Pancytopenia**
- **Anorexia**
- **Hyperuricemia**
- **Somnolence**
- **Visual disorder (including visual disturbance, vision blurred, and visual acuity reduced)**
- **Pulmonary hypertension**
- **Dermatitis (including eczema)**
- **Musculoskeletal stiffness**
- **Asthenia**

Rare but serious

- **Tumor lysis syndrome**
- **Aplasia pure red cell**
- **Hypersensitivity (including erythema nodosum, a type of skin inflammation))**
- **Transient ischemic attack**
- **Reversible posterior leukoencephalopathy syndrome**
- **Convulsion**
- **Amnesia**
- **Tremor**
- **Syncope**
- **Central nervous system hemorrhage**
- **Cardiomegaly**
- **Angina pectoris**
- **Myocardial infarction**
- **Pericarditis**
- **Acute coronary syndrome**
- **Myocarditis**
- **Ventricular tachycardia**
- **Hypotension**
- **Livedo reticulares**
- **Asthma**
- **Acute respiratory distress syndrome**
- **Pancreatitis**

- **Upper gastrointestinal ulcer**
- **Ascites**
- **Dysphagia**
- **Hepatitis**
- **Cholestasis**
- **Cholecystitis**
- **Acute febrile neutrophilic dermatosis**
- **Photosensitivity reaction**
- **Pigmentation disorder**
- **Skin ulcer**
- **Bullous conditions (including Erythema multiforme)**
- **Nail disorder**
- **Palmar-plantar erythrodysesthesia syndrome**
- **Rhabdomyolysis**
- **Tendonitis**
- **Blood creatine phosphokinase increased**
- **Renal failure**
- **Urinary frequency proteinuria**
- **Gynecomastia**
- **Menstruation irregular**
- **Malaise**
- **Temperature intolerance**
- **Lethargy**
- **Lightheadedness**
- **Tinnitus**
- **Tendonitis**
- **Cor pulmonale**
- **Cerebrovascular accident**
- **Tendonitis**
- **Hypoalbuminemia**
- **Anxiety**
- **Confusional State**
- **Affect lability**
- **Libido decreased**
- **Conjunctivitis**
- **Vertigo**
- **Electrocardiogram QT prolonged**
- **Bronchospasm**
- **Anal fissure**
- **Esophagitis**
- **Panniculitis**

Risks and side effects related to the IFOSFAMIDE include:

Likely

- **Nausea**
- **Vomiting**
- **Hair loss**
- **Fewer red and white blood cells and platelets in the blood**
    - **A low number of red blood cells can make you feel tired and weak**
    - **A low number of white blood cells can make it easier to get infections**
    - **A low number of platelets causes you to bruise and bleed more easily**
- **Decreased ability of the body to fight infection**

- **Absence or decrease in the number of sperm which may be temporary or permanent which may decrease the ability to have children**
- **Slight decrease in kidney function**

Less Likely

- **Drowsiness**
- **Confusion**
- **Depression**
- **Loss of appetite**
- **Diarrhea or constipation**
- **Seizures**
- **Abnormal hormone function affecting levels of salt in the blood and urine**
- **Abnormal heartbeat or rhythm. This side effect may require frequent evaluations of the hearts function and a heart specialist consult**
- **Blood in the urine that is only seen under the microscope**
- **Body loss of certain important salts and minerals**
- **Failure of the ovaries to function normally which may be permanent and which may decrease the ability to have children**
- **Inflammation and burning along the vein where the medicine is given**
- **Temporary elevation in the blood of certain enzymes found in the liver**

Rare but Serious

- **Damage to brain tissue with very high doses that may lead to coma**
- **Kidney failure or damage**
- **Damage to the bladder, which can lead to large amounts of blood in the urine, pain and the urge to urinate frequently and also permanent scarring of the bladder**
- **A new cancer or leukemia resulting from this treatment**
- **Damage to heart muscle which may make you tired, weak, feel short of breath, and retain fluid**
- **Abnormal bone growth and development**

Risks and side effects related to the ETOPOSIDE include:

Likely

- **Nausea**
- **Hair loss**
- **A feeling of weakness or tiredness**
- **Fewer red and white blood cells and platelets in the blood**
    - **A low number of red blood cells can make you feel tired and weak**
    - **A low number of white blood cells can make it easier to get infections**
    - **A low number of platelets causes you to bruise and bleed more easily**

Less Likely

- **Loss of appetite**
- **Decreased blood pressure during the infusion which may require treatment**
- **Rashes**
- **Diarrhea or constipation**
- **Pain in the abdomen**
- **Mouth sores**
- **Tingling sensation or loss of sensation in fingers or toes**
- **A feeling of extreme tiredness or weakness**
- **The finger or toe nails may loosen from their nail beds**
- **Inflammation and burning along the vein through which the medication was given**
- **Chest pain**

Rare but Serious

- **Damage to the liver**
- **Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate chills and fever**
- **A new cancer or leukemia resulting from this treatment**
- **Temporary severe rashes which can result in loss of skin and damage to mucous membranes**
- **Absence or decrease monthly periods**
- **Damage to heart muscle which may make you tired, weak, feel short of breath, and retain fluid**

Risks and side effects related to the CARBOPLATIN include:

Likely

- **Bone Marrow Suppression (as described for Ifosfamide) - Fewer red and white blood cells and platelets in the blood**
  - **A low number of red blood cells can make you feel tired and weak**
  - **A low number of white blood cells can make it easier to get infections**
  - **A low number of platelets causes you to bruise and bleed more easily**
- **Nausea and vomiting**

Less Likely

- **Kidney and liver damage**

Rare but Serious

- **Tingling and discomfort in arms and legs and weakness may occur rarely**
- **Local allergic reactions at the IV site. Itching, a skin rash, lightheadedness, facial flushing or trouble breathing**
- **Hearing loss**
- **A new cancer or leukemia resulting from this treatment**

Risks and side effects related to the MESNA include:

Likely

- **Bad taste when taken by mouth.**

Less Likely

- **Nausea.**
- **Vomiting**
- **Stomach pain**
- **Headache**
- **Pain in arms, legs and joints**
- **Tired feeling**
- **Rash**
- **Temporary low blood pressure**
- **Diarrhea**
- **Fever**
- **Facial flushing with red cheeks**
- **Nervousness**
- **Dizziness**
- **Confusion**
- **Swelling around the eyes**

- **Coughing**
- **Rapid heart rate**

Rare but Serious

- **Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate chills and fever**

Risks and side effects related to the G-CSF (Growth factor, Filgrastim, Neupogen) include:

Most patients who receive G-CSF have little or no side effects. However, some patients may experience the following:

Likely

- **Mild to moderate aching or pain inside the bones**

Less Likely

- **Local irritation at the site of the injection**
- **Mild headache**
- **Higher than normal levels of liver enzymes**
- **Lower number of platelets in the blood**
- **Low fever**
- **Enlargement of the spleen**
- **Worsening of skin rashes**
- **Inflammation of a blood vessel in the skin leading to a raised purple rash and bruising**
- **Higher than normal white blood count**

Rare but Serious

- **Allergic reactions which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, hives and facial swelling**
- **If you are known to have sickle cell disease, filgrastim may cause a sickle cell crisis.**
- **A blood disorder or leukemia that has only been seen in patients with certain immune disorders who are treated for a very long time**
- **Severe damage to the spleen**
- **Difficulty breathing and lung damage that may be due to the white blood cells that are stimulated by filgrastim traveling to the lungs when they are inflamed or infected**

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. The long-term effects of Dasatinib on fertility are unknown. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. Pregnancy tests will be obtained in women interested in participating in this study.

Risks of blood drawing or placing an intravenous catheter for blood drawing:

Risks associated with drawing blood are slight, but some risks include: pain, excessive bleeding, fainting or feeling lightheaded, bruising, infection (a slight risk any time the skin is broken), and multiple punctures to locate veins.

Risk of Surgery

Some patients on this study will undergo surgery before starting therapy or during this study. You will be asked to sign a separate consent form for the surgical procedure. The planned surgery will be explained to you and your questions about it answered by your surgeon when you sign the consent for the surgical procedure.

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

Are there benefits to taking part in the study?

Taking part in this study may or may not make your tumor to stop growing. The potential benefit of the treatment with Dasatinib is that it may cause your cancer to stop growing or to shrink for a period of time. It may lessen the symptoms, such as pain, that are caused by the cancer. Because there is not much information about Dasatinib, we know that the information from this study will help doctors learn more about Dasatinib as a treatment for cancer in children. However, we do not know if you will benefit from taking part in this study. Information learned from this study may help future patients with cancer.

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

Your other choices may include:

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

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

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- **Pediatric Cancer Foundation**
- **Bristol-Myers Squibb (sponsor/supplier of Dasatinib)**
- **Representatives of the National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people**

What are the costs of taking part in this study?

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

Bristol-Myers Squibb (BMS) is supplying Dasatinib at no cost to you. However, you or your health plan may need to pay for costs of the supplies and personnel who give you the Dasatinib.

The study agent, Dasatinib, will be provided free of charge while you are participating in this study. However, if you should need to take the study agent much longer than is usual, it is possible that the supply of free study agent that has been supplied to *[the NCI or other study sponsor, as appropriate]* **could run out. If this happens, your study doctor will**

discuss with you how to obtain additional drug from the manufacturer and you may be asked to pay for it.

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

There will be no cost to you for any tissue collected and banked. You will not be paid for allowing your leftover tissue to be used in research, even though it is possible that new cancer tests or treatments may be developed as a result of the research.

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

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

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

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

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

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

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

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

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

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

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

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

Whether you participate or not, you will continue to get the best medical care this hospital can provide.

Who can answer my questions about the study?

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

For questions about your rights while taking part in this study, call the _____

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

Where can I get more information?

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

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

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

- **For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/**
- **For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/**

You will get a copy of this form. You will be given a copy of the protocol (full study plan) upon request.

If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all # pages of this form.
I have read it or it has been read to me.

I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Parent (or Guardian) _____

Date _____

Signature of Physician or Responsible Investigator

_____

Date _____

FOR SUBJECTS/PARTICIPANTS 7-17 YEARS OF AGE

The undersigned physician, _____, M.D., hereby certifies that he/she has discussed the research project with the subject/participant and has explained all the information contained in the informed consent form to the subject/participant, including any risks that may reasonably be expected to occur. The undersigned further certifies that the subject/participant was encouraged to ask questions and that all questions were answered.

_____ _____

Date **Physician's Signature**