Phase II study of 5-fluorouracil, oxaliplatin plus dasatinib (FOLFOX-D) in first-line metastatic pancreatic adenocarcinoma

Protocol ID#:	CA180-359
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Experimental Agent:	Dasatinib
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Commercially Available Agent:	Oxaliplatin Leucovorin 5-Fluorouracil
Participating Sites:	University of Florida, UF Health Cancer Center UF Health Cancer Center – Orlando Health

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PROTOCOL SYNOPSIS

Protocol Title:	Phase II study of 5-fluorouracil, oxaliplatin plus dasatinib (FOLFOX-D) in first-line metastatic pancreatic adenocarcinoma
Site Numbers & Names:	University of Florida, UF Health Cancer Center UF Health Cancer Center – Orlando Health
Research Hypothesis:	Reduction in metastatic spread, assessment of safety and activity of FOLFOX-D in patients with advanced pancreatic cancer
Study Schema: **Drugs / Doses / Length of Treatment)**	Dasatinib days 1-14 and mFOLFOX-6 day 1 of each 14 day cycle until progression or unacceptable toxicity.
Study Objectives: • **Primary:** • **Secondary:**	Primary Objective: Determine activity of 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) plus dasatinib on progression free survival (PFS) in patients with metastatic pancreatic adenocarcinoma Secondary Objectives: • To determine the response rate (RR) by RECIST criteria • To determine the rate of freedom from metastasis (FFM) • To determine the time to progression (TTP) • To determine overall survival (OS) • To determine the clinical benefit rate (CBR) • To determine the site of failure of this regimen in this population • To determine the safety profile and tolerability of this regimen in this population • To determine patient compliance with oral therapy • To determine the quality of life (QOL) of patients receiving this therapy • Exploratory tissue and serum correlative analyses to identify predictors of response.
Study Design:	This is a single arm, prospective open-label multicenter phase II clinical study.
Accrual Goal: **(Total number of subjects)**	42 patients
Accrual Rate: **(Number of subjects expected per month)**	One to two patients per month over a 42 month accrual period.
FPFV: **LPFV:** **Follow Up:**	January 2013 July 2016 July 2017

Correlative Studies: **(PK/PD, etc.)**	Plasma, mononuclear cells, circulating tumor cells, previously obtained tumor biopsy material. Evaluation of Src inhibition, pathway suppression, molecular markers for prognosis, prediction of response, and post hoc molecular testing.
Inclusion Criteria:	• Metastatic, measurable, biopsy-proven pancreatic adenocarcinoma • ECOG PS 0-2 • No prior chemotherapy or radiotherapy for metastatic pancreatic cancer. More than 6 months elapsed since prior treatment in adjuvant setting • Adequate organ and marrow function • Patent biliary system • Stable anticoagulation regimen • Ability to take oral medications
Exclusion Criteria:	• Known brain metastases or carcinomatous meningitis • Recent major surgery • Clinically significant pleural or pericardial effusion • Major cardiac conditions • Significant bleeding disorder • Inability to comply with contraceptive requirements
Criteria for Evaluation: **(Efficacy, safety, stopping rules, etc.)**	RECIST Radiographic criteria and clinical evaluations Standard AE monitoring and reporting
Statistics:	Prospective non-randomized phase II study with modified intention-to-treat

1 INTRODUCTION

1.1 Background

Pancreatic cancer represents a dismal prognosis when metastatic disease is diagnosed. Despite significant improvements in the understanding of pancreatic adenocarcinoma biology and pathophysiology, median survival for most patients with advanced disease remains at less than 6 months. It remains a highly lethal disease. In the U.S., pancreatic cancer will afflict nearly 43,000 patients and will result in 39,000 deaths, representing the 4th most common cause of cancer-related deaths in 2011. [1,2,3] Cytotoxic systemic therapy in advanced disease must balance risks of toxicity with benefits of disease control and symptom alleviation. New approaches to the management or prevention of metastatic disease represent a clinical unmet need for a large number of cancer patients.

Gemcitabine has served as the cytotoxic therapy foundation for numerous failed attempts to improve survival. This has been clearly demonstrated for both cytotoxic as well as biologic targeted combination therapies. However, a renewed interest has emerged in 5-fluorouracil (5-FU) and leucovorin (LV)-based combinations in advanced pancreatic cancer, with some recently published impressive results. Thus, a new platform to which novel combinations of active cytotoxic therapies in combination with biologic targeted agents appears to be available.

1.2 Pancreatic Cancer Therapy

Systemic cytotoxic therapy for metastatic pancreatic cancer was historically limited to 5-fluorouracil (5-FU) and leucovorin (LV). In the metastatic setting, these agents produced response rates of <10%, clinical benefit rates of <10% and a median overall survival (OS) of 4.5 months. [4,5] However, with the development of gemcitabine, clinical trials suggested an improvement in both the quality of life and survival of patients receiving this drug despite a relatively low objective response rate of still < 10%. [6] There was also a statistically significant, but not clinically meaningful, increase in the median survival (5.7 vs 4.4 months, p= 0.0025) and one year survival (18% vs 2%) favoring those treated with gemcitabine. Confirmatory studies rapidly established gemcitabine as the new standard of care. [7,8]

For the following decade, multiple trials have compared gemcitabine to combination therapy with multiple active cytotoxic agents. Unfortunately, none of these trials has proven positive for the primary endpoint of survival, although response rates are generally higher with the doublets, along with toxicity. [9] Two recent meta-analyses have suggested a possible survival improvement with gemcitabine-based doublets coupled to platinums or fluoropyrimidines, but with benefit restricted only to those with good performance status. [10,11] The incorporation of biologic therapies to a gemcitabine backbone have been similarly disappointing, with only a marginal improvement in survival noted (median OS 6.24 months vs 5.91 months; HR 0.82 [95% CI, 0.69-0.99]; p= 0.038) with the addition of the anti-epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) erlotinib. [12] Alternative approaches to gemcitabine-based combination therapy are desperately needed.

1.3 FOLFOX Activity and Safety

Systemic disease control using 5-fluorouracil (5-FU), leucovorin, and oxaliplatin as second-line therapy in patients with metastatic pancreatic cancer has been prospectively evaluated. [13, 14] In these previously treated patients, the combination resulted in a partial response rate of 23% with stable disease seen in an additional 17-30%. Median OS was 17-25 weeks with notable improvements in some patient's performance status. Toxicity was tolerable and consistent with previous experiences using this combination therapy in patients with colorectal cancer. Specifically, Grade 3/4 toxicity included leukopenia 16%, anemia 3.2%, thrombocytopenia 3.2%, diarrhea 14.2%, fatigue 16.1% and neurotoxicity 4.2%. There were no treatment related deaths. In a phase III RCT, the combination of 5-FU/LV/Oxaliplatin was determined to be superior to 5-FU/LV alone in patients with metastatic pancreatic cancer who progressed on gemcitabine therapy. [15] The specific combination of these agents (FOLFOX) has also been prospectively evaluated in the first-line setting with a similar response rate of 27%, stable disease in another 30% of patients, median PFS of 4 months and median OS of 7.4 months. [16, 17]

At the 2010 Annual Meeting of the American Society of Clinical Oncology, results were presented from the PRODIGE 4/ACCORD 11 trial. [18] This phase III controlled trial in patients with first line metastatic pancreatic cancer randomized gemcitabine against the combination of 5-FU/LV/oxaliplatin/irinotecan (FOLFIRINOX). At a median follow-up of 26 months, 342 randomized patients demonstrated superior OS for the combination therapy (11.1 months) compared to gemcitabine (6.8 months; HR 0.57; 95% CI, 0.45-0.73; $p < 0.001$). Progression free survival (PFS) (6.4 months vs 3.3 months; HR 0.47; 95% CI, 0.37-0.59; $p < 0.001$) and response rate (32% vs 9%; $p < 0.001$) also favored the combination treatment. However, toxicities were significantly increased with FOLFIRINOX including diarrhea (13% vs 2%), peripheral neuropathy (9% vs 0), thrombocytopenia (9% vs 3%), neutropenia (46% vs 21%), and febrile neutropenia (5% vs 1%). There were also trends towards worsening vomiting (14% vs 8%) and fatigue (23% vs 17%) with FOLFIRINOX. There was one toxicity-related death in each arm. [19] Despite the favorable clinical outcomes and incorporation of FOLFIRINOX into NCCN Guidelines, many clinical providers reject this therapy as a significantly toxic treatment in a disease where palliation of symptoms remains a primary goal. [20, 21]

Thus, 5-FU-based combination therapies reflect an opportunity to improve survival in advanced pancreatic cancer where dozens of gemcitabine-based combinations have repeatedly failed. In advanced pancreatic cancer, FOLFOX chemotherapy is active with significantly less toxicity than FOLFIRINOX therapy. It can therefore serve as a new backbone for the addition of novel targeted therapeutics, a place where prior attempts with gemcitabine combinations have failed to produce meaningful improvements. FOLFOX remains an internationally recognized combination treatment in widespread use for colorectal cancer and other gastrointestinal malignancies. [22] Academic, community, and institutional oncology providers are familiar with FOLFOX

dosing, administration, toxicities, and patient management with NCCN Guidelines supporting its use in first or second-line advanced pancreatic cancer. [21]

Toxicity of 5-FU, leucovorin, and oxaliplatin is well characterized and is outlined in more detail in Section 5.

1.4 Src Inhibition with Dasatinib, Activity and Safety

A number of studies have shown that Src tyrosine kinase activity is commonly activated and elevated in many human cancers, including pancreatic cancer, with prognostic implications as associated with disease stage and patient survival. [23,24,25,26,27,] The major consequence of increased Src activity is to promote an invasive and metastatic cancer phenotype characterized by breakdown of cell-cell adhesion, increased cell-matrix adhesion, mediation of lymph/angiogenesis, and formation of focal adhesions. [28,29,30,31] Intracellular cytoplasmic Src (c-Src) activates a number of substrates critical to these processes including focal adhesion kinase (FAK), signal transducers and activators of transcription 3 (STAT-3), vascular endothelial growth factor (VEGF), hypoxia-inducible factor-1 alpha (HIF), and other components of the epidermal growth factor (EGF) pathway. [28,32,33,34] Inhibition of Src activity in preclinical models restores cell-cell adhesion, inhibits cell migration and invasion, and reverses the Src-mediated invasive and metastatic cancer phenotype. [35,36,37,38]

Dasatinib (SPRYCEL®, Bristol-Myers Squibb [BMS]-354825) is a potent, broad spectrum inhibitor of 5 critical oncogenic tyrosine kinases/kinase families, including the Src family of kinases with sub-nanomolar inhibition constant (IC_{50}). Dasatinib is approved in the United States, Europe, and several other countries for chronic myeloid leukemia (CML) with resistance or intolerance to prior treatment including imatinib. Dasatinib has been studied in more than 2500 subjects with CML or Ph+ ALL and with solid tumors. Clinical pharmacokinetic (PK) data indicate that dasatinib has good oral absorption, is > 90% protein bound, and is predicted to have a large volume of distribution. The overall mean terminal half life is around 4 hours in subjects, and it is expected to be eliminated mainly through metabolism.

Dasatinib has an acceptable safety profile with most subjects having some degree of myelosuppression. Myelosuppression is common finding in most hematologic malignancies and is also a common side effect of most chemotherapeutic agents. Thrombocytopenia, neutropenia, leukopenia, and anemia were frequently reported as Grade 3 to 4 laboratory abnormalities in all subject populations studied. In cases of severe myelosuppression, recovery generally occurred following brief (2 to 4 weeks) dose interruptions or reductions. Other severe hematologic toxicities were uncommon. Most subjects continued treatment without further evidence of myelosuppression. The most common nonhematologic toxicities include gastrointestinal AEs, in particular diarrhea, nausea, and vomiting. Most gastrointestinal events were mild to moderate in severity. Other dasatinib toxicities to note included fluid retention, bleeding-related events, and QT prolongation. The incidence of edema associated with dasatinib treatment was similar across all phases of CML and Ph+ ALL, and pleural effusion in dasatinib-treated subjects mostly occurred in advanced stage CML and Ph+ ALL. Overall, one third of subjects had a bleeding event and of those, half were considered

study drug related. These events occurred mostly in subjects with thrombocytopenia. [39]

Given inherent hematologic toxicity differences between the hematologic malignancy and solid tumor population of patients, separate dose finding and toxicity studies have been undertaken. Indeed, results from the solid tumor phase I dasatinib studies demonstrated infrequent myelosuppression and thrombocytopenia, relative to those patients in the hematologic malignancy studies. This indicates that dasatinib is not likely to be directly or significantly toxic to the hemapoietic progenitor cells. However, those patients with pleural effusions in the solid tumor studies had dose-limiting toxicities of expansion of their effusions, and have subsequently been excluded from future enrollment on studies with dasatinib. [40]

Dasatinib toxicity is well characterized and is outlined in more detail in Section 1.7.

1.5 Combination of FOLFOX and Dasatinib

The role of single agent Src antagonists appears to be of limited clinical value in the salvage setting of metastatic pancreatic cancer. [40] This is consistent with pre-clinical data suggesting that dasatinib use can significantly inhibit migration and invasion, with marked inhibition in the development of metastases. However, there is no survival advantage in dasatinib treated animals owing to continued growth of their already established tumors. [41] Dasatinib is currently undergoing prospective investigation in a phase II study as monotherapy in first-line metastatic pancreatic cancer (Protocol ID# NCT00474812). [42] Nevertheless, incorporating dasatinib with cytotoxic therapies may improve clinical outcomes. Constitutively active Src is associated with increased gemcitabine and 5-FU chemoresistence in pancreatic cancer cells. [43,44] Inhibition of Src reduces tumor expression of thymidylate synthase (TS), the target enzyme of 5-FU. Lowering TS levels is associated with subsequent 5-FU chemoresistance reversal resulting in substantially decreased in vivo tumor growth and inhibition of distant metastases. [45] Dasatinib can synergistically inhibit oxaliplatin-induced Src activation. [45],[46] Src inhibition also increases oxaliplatin activity both in vitro and in vivo. [47]

Safety regarding the specific combination of FOLFOX and dasatinib in patients with previously treated metastatic colorectal cancer was presented at the 2010 Annual Meeting of the American Society of Clinical Oncology. [48] In this study of thirty total patients, all received FOLFOX plus cetuximab plus dasatinib in one of 3 dasatinib dosing cohorts. This phase IB prospective protocol with escalating doses of dasatinib including an expansion cohort included patients who had received a median of 3 prior regimens, making this a heavily pretreated population of subjects. Grade 3-4 toxicities included neutropenia (23%), fatigue (20%), pleural effusions (3%), and thrombocytopenia (3%). The dose limiting toxicity was fatigue and myelosuppression with maximum tolerated dose of dasatinib in combination with FOLFOX being 150 mg daily. The recommended dose for further phase II development was 100 mg based on myelosuppression. However, pharmacodynamic studies confirmed subtherapeutic inhibition of Src at 100 mg, thus 150 mg with growth factor support is recommended for this study. Interestingly, clinical activity was seen including in patients previously reported to be refractory to oxaliplatin.[49]

1.6 Summary of Results of Dasatinib Investigational Program

SPRYCEL®[50] (dasatinib, Bristol-Myers Squibb [BMS]-354825) is a potent, broad spectrum inhibitor of 5 critical oncogenic tyrosine kinases/kinase families (BCR-ABL, Src, c-KIT, PDGF receptor β [PDGFRβ], and ephrin [EPH] receptor kinases), each of which is linked to multiple forms of human malignancies, and was discovered and developed by BMS. SPRYCEL® is approved in the United States (US)[50], Europe (EU)[51], and several other countries for the treatment of adults in all phases of chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy including imatinib, and Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) who are resistant or intolerant to prior therapy.

The recommended starting dosage for subjects with chronic phase CML is 100 mg administered orally once daily (QD). The recommended starting dosage for accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL is 140 mg/day administered orally once daily. In clinical studies of adult CML and Ph+ ALL patients, dose escalation to 140 mg once daily (chronic phase CML) or 180 mg once daily (advanced phase CML and Ph+ ALL) was allowed in patients who did not achieve a hematologic or cytogenetic response at the recommended starting dosage.

1.6.1 Human Pharmacokinetics of Dasatinib

Dasatinib is rapidly absorbed following oral administration in subjects with leukemia.[52] Across all treatment regimens, disease status, and study days, mean C_{max} values were attained at median T_{max} values that ranged from 0.45 to 3.18 hours postdose. The overall median T_{max} value was approximately 1 hour. There was no influence of treatment regimens, disease status, or study days on the half-life (T-HALF) of dasatinib. The overall mean T-HALF value was approximately 3 to 5 hours. Dasatinib has an apparent volume of distribution of 2505 L, suggesting that the drug is extensively distributed in the extravascular space. There were no clinically meaningful relationships between steady state CLo and body weight or body surface area. Statistical linear regression analyses were performed on log (AUC) versus log (DOSE) to assess dose proportionality. The AUC of dasatinib is approximately dose proportional in the dose range of 15 to 240 mg/day, suggesting that the drug exhibited linear kinetics over the entire dose range. However, the 90% CIs are wide, indicating that the variability in AUC is high. There was no marked effect of disease state, age, gender, and race on the PK parameters CLo, Vz/F, and T-HALF, suggesting that dose adjustment in these subpopulations may not be necessary.[53] The geometric mean accumulation index (AI) ranged from 1.01 to 1.61 between days 5/8 and 26/29 and no consistent dose-related trends were observed in the accumulation of dasatinib after repeated administration. 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.[54] The observed food effects were not clinically relevant.

Dasatinib is extensively metabolized in humans. Unchanged dasatinib represented 29%

of circulating radioactivity in plasma after a 100 mg dose of [^{14}C]-labeled dasatinib was administered to 8 healthy subjects in study CA180019.[55] Elimination is predominantly in the feces, mostly as metabolites. Following a single oral dose of [^{14}C]-labeled dasatinib, approximately 85% of the dose was recovered in the feces within 10 days, and approximately 4% of the administered radioactivity was recovered in the urine.

The cytochrome p450 enzyme CYP3A4 plays a major role in the metabolism of dasatinib in the humans. Dasatinib has little potential to induce CYP3A4 and, at concentrations ≤ 25 μM (1 μM = 488 ng/mL), dasatinib did not induce CYP1A2, CYP2B6, CYP2C9, and CYP3A4 in primary cultures of human hepatocytes.[56] Based on these data and plasma concentrations observed in vivo, dasatinib is unlikely to decrease the exposure of co-administered drugs that are metabolized by CYP1A2, CYP2B6, CYP2C9, or CYP3A4. In human liver microsomes, dasatinib did not inhibit CYP1A2, CYP2B6, CYP2C19, CYP2D6, or CYP2E1 at concentrations up to 50 μM.[57] It inhibited CYP2A6 (IC50 = 35 μM), CYP2C8 (IC50 = 12 μM), CYP2C9 (IC50 = 50 μM), and CYP3A4 (IC50 values of 18 and 10 μM for midazolam and testosterone substrates, respectively).

1.6.2 Clinical Experience with Dasatinib in Solid Tumors

Studies in the solid tumor program for dasatinib include four Phase 1 studies (CA180003, CA180021, CA180004, CA180086) and three Phase 2 studies (CA180059, CA180088, CA180085). CA180003 and CA180021 were exploratory studies in refractory solid tumors and advanced solid tumors, respectively, and have been completed. CA180004, CA180059, and CA180088 are ongoing in breast cancer, and CA180085 and CA180086 are ongoing in prostate cancer (ongoing as of November 2008).

The efficacy and safety observations in the solid tumor studies are presented in the following sections.

1.7 Safety of Dasatinib in Clinical Studies

1.7.1 Experience in CML and Ph+ ALL Clinical Trials

The data presented in Table 1.7.1 reflect exposure to dasatinib in 2182 patients with leukemia in clinical studies (starting dosage 100 mg once daily, 140 mg once daily, 50 mg twice daily, or 70 mg twice daily). The median duration of therapy was 11 months (range 0.03-26 months).

The majority of dasatinib-treated patients (1,864 [85%]) experienced at least 1 drug-related adverse reactions at some time. Drug was discontinued for adverse reactions in 14% (296/2182) of subjects. Drug related AEs leading to discontinuation in any 1 category occurred in ≤ 1% of the subjects with the exception of pleural effusion (85/2182; 4%). In subjects with chronic phase CML, drug-related pleural effusion accounted for discontinuation in 52 of the 1150 subjects. Only 1 subject in the 100 mg QD group had discontinuation due to drug-related pleural effusion compared with 35 subjects in the 70 mg BID group. In subjects with advanced phase CML or Ph+ ALL, drug-related pleural effusion accounted for discontinuation in 33 of the 1032 subjects. Six subjects in the 140 mg QD group had discontinuation due to drug-related pleural effusion

compared with 27 subjects in the 70 mg BID group.

Overall, 59% (1287/2182) of subjects across all disease phases reported SAEs (any grade). Drug-related SAEs were reported in 53% (681/2182) of subjects. In subjects with chronic phase CML, notable common drug-related AEs included dyspnea, pleural effusion, congestive heart failure, febrile neutropenia, and thrombocytopenia. In most cases, a lower proportion of subjects in the 100 mg QD group reported drug-related SAEs than subjects in the 70 mg BID or other dose groups. In subjects with advanced phase CML or Ph+ ALL, notable common drug-related AEs included dyspnea, pleural effusion, diarrhea, and hematological toxicities. In most cases, there was little difference in these SAEs between the 140 mg QD and 70 mg BID groups. Rates of severe drug-related pleural effusion were lower in the 140 mg QD group (3%) vs the 70 mg BID (6%).

The most frequently reported AEs are presented in Table 1.7.1

Table 1.7.1: Very Common and Common AEs Reported in Subjects in Clinical Studies

	All Subjects (N= 2182) Percent (%) of Subjects	
	All Grades	**Grades 3/4**
Nervous system disorders *Very common*: headache	25	1
Common: neuropathy (including peripheral neuropathy)	7	<1
dizziness	5	<1
dysgeusia	2	0
somnolence	2	<1
Respiratory, thoracic and mediastinal disorders *Very common*: pleural effusion	27	7
dyspnea	24	5
cough	10	<1
Common: pulmonary edema	2	<1
lung infiltration	2	<1
pneumonitis	2	<1
pulmonary hypertension	1	<1
Gastrointestinal disorders *Very common*: diarrhea	33	4
nausea	23	1
vomiting	13	1
abdominal pain	11	<1
Common: gastrointestinal bleeding	8	4
mucosal inflammation (including mucositis/stomatitis)	7	<1
dyspepsia	6	0
abdominal distension	5	0

Table 1.7.1: Very Common and Common AEs Reported in Subjects in Clinical Studies

	All Subjects (N= 2182) Percent (%) of Subjects	
	All Grades	**Grades 3/4**
constipation	5	<1
gastritis	2	<1
colitis (including neutropenic colitis),	2	<1
oral soft tissue disorder	2	0
Skin and subcutaneous tissue disorders *Very common*: skin rash[a]	23	<1
Common: pruritus	7	<1
acne	5	<1
alopecia	5	0
dry skin	3	0
hyperhidrosis	2	0
urticaria	1	<1
dermatitis (including eczema)	1	0
Musculoskeletal and connective tissue disorders *Very common*: musculoskeletal pain	15	1
Common: arthralgia	9	<1
myalgia	8	<1
muscle inflammation	3	<1
muscular weakness	1	<1
musculoskeletal stiffness	1	0
Metabolism and nutrition disorders *Common*: anorexia	9	<1
appetite disturbances	2	<1
hyperuricaemia	1	<1
Infections and infestations *Very Common*: infection (including bacterial, viral, fungal, nonspecific)	11	3
Common: pneumonia (including bacterial, viral, fungal)	5	3
upper respiratory tract infection/inflammation	5	<1
herpes viral infection	1	<1
enterocolitis infection	1	<1
sepsis (including fatal outcome)	1	<1
Cardiac Disorders *Common*: pericardial effusion	5	1
arrhythmia (including tachycardia)	3	<1
congestive heart failure/cardiac dysfunction[b]	3	2

Table 1.7.1: Very Common and Common AEs Reported in Subjects in Clinical Studies

	All Subjects (N= 2182) Percent (%) of Subjects	
	All Grades	**Grades 3/4**
palpitations	2	0
Vascular disorders *Very common:* hemorrhage[c]	16	2
Common: flushing	4	0
hypertension	2	<1
Blood and lymphatic system disorders *Common:* febrile neutropenia,	5	5
pancytopenia	1	<1
General disorders and administration site conditions *Very common*: fatigue	23	2
superficial edema[d]	22	1
pyrexia	14	1
Common: asthenia	9	<1
pain	8	<1
chest pain	6	<1
generalized edema	4	<1
chills	3	<1
Psychiatric disorders *Common:* insomnia	2	0
depression	2	<1
Eye disorders *Common:* visual disorder (including visual disturbance, vision blurred, and visual acuity reduced)	2	<1
dry eye	1	<1
Ear and labyrinth disorders *Common:* tinnitus	1	0
Investigations *Common*: weight increased	5	<1
weight decreased	5	<1
Injury, poisoning, and procedural complications *Common:* contusion	2	<1

Source: SPRYCEL® (dasatinib) BMS-354825, Bristol-Myers Squibb Investigator Brochure, Version 8, 200858

[a] Includes drug eruption, erythema, erythema multiforme, erythrosis, exfoliative rash, fungal rash, generalized erythema, genital rash, heat rash, milia, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin exfoliation, skin irritation, and urticaria vesiculosa.

[b] Includes ventricular dysfunction, cardiac failure chronic, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and ventricular failure.

[c] Excludes gastrointestinal bleeding and CNS bleeding; These adverse drug reactions are reported under the gastrointestinal disorders system organ class and the nervous sytem disorders system organ class, respectively.

[d] Includes auricular swelling, conjunctival edema, eye edema, eye swelling, eyelid edema, face edema, gravitational edema, lip edema, localized edema, mascular edema, edema genital, edema mouth, edema peripheral, orbital edema, penile edema, periorbital edema, pitting edema, scrotal edema, swelling face, and tongue edema.

1.7.2 Experience in Phase 2 Breast Cancer Studies

Drug related AEs in ≥ 25% of the subjects in the completed Phase 2 studies in breast cancer are given in Table 1.7.2. [53]

Table 1.7.2: Drug Related Adverse Events in ≥ 25% Subjects for Phase 2 Breast Cancer Studies CA180059 and CA180088

Preferred Term	CA180059, n (%)		CA180088, n (%)	
	70 mg BID (N=21)	70 mg BID (N=21)	70 mg BID (N=44)	100 mg BID (N=23)
Nausea	14 (67)	10 (44)	15 (34)	8 (35)
Fatigue	14 (67)	10 (44)	15 (34)	3 (13)
Diarrhea	7 (33)	12 (52)	23 (52)	10 (44)
Rash	5 (24)	11 (48)	10 (23)	9 (39)
Asthenia	0 (0)	0 (0)	13 (30)	9 (39)
Dyspnea	6 (29)	11 (48)	10 (23)	9 (39)
Pleural effusion	7 (33)	9 (39)	12 (27)	9 (39)
Anorexia	3 (14)	9 (39)	0 (0)	0 (0)
Headache	4 (19)	8 (35)	15 (34)	9 (39)
Cough	5 (24)	7 (30)	0 (0)	0 (0)
Abdominal pain	2 (10)	7 (30)	13 (30)	5 (22)
Vomiting	6 (29)	7 (30)	8 (18)	8 (35)
Flushing	6 (29)	3 (13)	0 (0)	0 (0)

1.7.3 Anticipated Adverse Events with Dasatinib

Myelosuppression

Treatment with dasatinib is associated with severe (NCI CTCAE 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. Myelosuppression was generally reversible and usually managed by withholding dasatinib temporarily or dose reduction.[51] In a Phase 3 dose-optimization study in patients with chronic phase CML, Grade 3 or 4 myelosuppression was reported less frequently in patients treated with 100 mg once daily than in patients treated with 70 mg twice daily. At doses of 150 mg in combination with FOLFOX, empiric growth factor use is recommended. (Personal Communication, Kopetz S.)

Bleeding Related Events
Severe CNS hemorrhages, including fatalities, occurred in ≤ 1% of patients receiving dasatinib. Severe gastrointestinal hemorrhage occurred in 4% of patients and generally required treatment interruptions and transfusions. Other cases of severe hemorrhage occurred in 2% of patients. Most bleeding events were associated with severe thrombocytopenia. (Incidences in this paragraph reflect drug-related adverse reactions based on investigator's attribution.)

Patients were excluded from participation in dasatinib clinical studies if they took medications that inhibit platelet function or anticoagulants. In some trials, the use of anticoagulants, aspirin, and non-steroidal anti-inflammatory drugs (NSAIDs) was allowed concurrently with dasatinib if the platelet count was 50,000 to 75,000. Caution should be exercised if patients are required to take medications that inhibit platelet function or anticoagulants.[51]

Fluid Retention
Dasatinib is associated with fluid retention. In all clinical studies, severe fluid retention was reported in 10% of patients, including pleural and pericardial effusion reported in 7% and 1% of patients, respectively. Severe ascites and generalized edema were each reported in < 1% of patients. 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. (Incidences in this paragraph reflect drug-related adverse reactions based on investigator's attribution).[52]

In the Phase 3 dose-optimization study in patients with chronic phase CML, fluid retention events were reported less frequently in patients treated with 100 mg once daily than in patients treated with 70 mg twice daily.[51]

QT Prolongation
A comprehensive evaluation of data from Phase 2 studies (N = 865) examined the possible effect of dasatinib on ECG parameters, particularly the QTc interval. The mean QTc interval changes from baseline using Fridericia's method (QTcF) were 4 to 6 msec; the upper 95% confidence intervals for all mean changes from baseline were < 7 msec. On-study, a total of 5 subjects (< 1%) reported a QTcF > 500 msec; 1 of these 5 subjects reported a QTcF > 500 msec on both Day 1 and Day 8. No events of torsade de pointes were reported.[52]

Nine of the 1150 subjects with chronic phase CML had QTc prolongation reported as an adverse event. Of these 9 subjects, 7 were considered related to drug. None of the 9 subjects who reported QTc prolongation were from the 100 mg QD group compared with 8 subjects from the 70 mg BID group. Ten of the 1032 subjects with advanced disease had QTc prolongation reported as an adverse event. Of these 10 subjects, 7 were considered drug-related. All 10 of the subjects who reported QTc prolongation were from the 70 mg BID group. Overall, of the 2182 subjects treated with dasatinib, 21 (1%) subjects across the studies reported a QTcF > 500 msec.[68]

1.8 Overall Risk/Benefit Assessment

The clinical studies discussed in Section 1 indicate that the safety profile for dasatinib in solid tumor subjects has been similar to that in chronic phase 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.

Preliminary analysis indicated modest clinical efficacy in the completed Phase 2 breast cancer study. Also, ongoing prostate cancer studies appear to be promising. The characterization of clinical efficacy of dasatinib in solid tumor cancer is pending completion of the ongoing studies and data analysis.

Adequate safety data exists to support the use of FOLFOX plus dasatinib in patients with advanced pancreatic cancer. There is not expected to be more severe toxicity in this population that is different from that seen in previously treatment solid tumor patients with this combination. Given the poor outcomes based on standards of care in this disease, new clinical management approaches are desperately needed.

1.9 Study Rationale

Systemic control of pancreatic cancer remains a clinical unmet need. The recent superiority of 5-FU based combination therapies over the historical standard gemcitabine represents an opportunity to develop novel combinations of synergistic and effective cytotoxic and biologic targeted therapies. Src excess activity has been demonstrated in pancreatic cancer and is implicated in the invasive and metastatic phenotype clearly represented by this disease. Inhibition of Src activity is associated with numerous biologic modifications capable of positively modifying this phenotype and appears to have synergy with restoring inherent chemosensitivity. The addition of dasatinib to FOLFOX (FOLFOX-D) represents a novel therapeutic regimen in pancreatic cancer with safety and pharmacokinetic data already having been established in colorectal cancer. This protocol will test the safety and activity of this combination in pancreatic cancer where current clinical outcomes remain far from optimal.

2 STUDY OBJECTIVES

2.1 Primary Objective

Determine activity of 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) plus dasatinib on progression free survival (PFS) in patients with metastatic pancreatic adenocarcinoma.

2.2 Secondary Objectives

Clinical Objectives

- To determine the response rate (RR) by RECIST criteria

- To determine the rate of freedom from metastasis (FFM)
- To determine the time to progression (TTP)
- To determine overall survival (OS)
- To determine the clinical benefit rate (CBR)
- To determine the site of failure of this regimen in this population
- To determine the safety profile and tolerability of this regimen in this population
- To determine patient compliance with oral therapy
- To determine the quality of life (QOL) of patients receiving this therapy

Exploratory Objectives

- Exploratory tissue and serum correlative analyses in this population receiving this regimen.
- Plasma, mononuclear cells, circulating tumor cells, previously obtained tumor biopsy material. Evaluation of Src inhibition, pathway suppression, molecular markers for prognosis, prediction of response, and post hoc molecular testing.

3 ETHICAL CONSIDERATIONS

3.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol, any amendments, and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion before initiation of the study.

All potential serious breaches must be reported to Bristol-Myers Squibb (BMS) immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure; debarment). Systems with procedures that ensure the quality of every aspect of the study will be implemented.

3.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (eg, advertisements), and any other written information to be provided to subjects. The investigator should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects, and any updates. The investigator should provide the IRB/IEC with reports, updates, and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

3.3 Informed Consent

Investigators must ensure that subjects (or, in those situations where consent cannot be given by subjects, the legally acceptable representative) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. Freely given written informed consent must be obtained from every subject (or, in those situations where consent cannot be given by subjects, the legally acceptable representative) before clinical study participation, including informed consent for any screening procedures conducted to establish subject eligibility for the study.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

Subjects unable to give their written consent (eg, stroke patients, or those with severe dementia) may be enrolled in the study only with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with the subjects' understanding, and should they become capable, they must personally sign and date the consent form as soon as possible. The explicit wish of a subject unable to give his or her written consent, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time, should be considered by the investigator.

4 INVESTIGATIONAL PLAN

4.1 Study Design and Duration

This is a single arm, prospective open-label multicenter phase II clinical study in the first-line setting of patients with metastatic pancreatic adenocarcinoma treated with FOLFOX plus dasatinib (FOLFOX-D) with primary and secondary endpoints as noted in Section 2.

4.1.1 Number of Patients Planned

A total of 42 patients is planned to be included in this study, from three investigational sites, over a 30 month accrual period.

4.1.2 Duration of Treatment

Patients will continue with protocol therapy until one of the criteria for study treatment discontinuation is met as described in Section 4.2.3.

4.1.3 Duration of Follow Up

Patients will be contacted for survival status every 8 weeks until death or patient withdrawal. Subsequent therapies will also be collected and recorded.

4.2 Study Population

For entry into the study, the following criteria MUST be met.

4.2.1 Inclusion Criteria

Signed Written Informed Consent

a) Before any study specific procedures are performed, subjects will have the details of the study described to them, and they will be given a written informed consent document to read. Then, if subjects consent to participate in the study, they will indicate that consent by signing and dating the informed consent document in the presence of study personnel.
b) Written consent should include HIPAA language according to institutional guidelines.

Target Population

a) Histologically or cytologically proven pancreatic adenocarcinoma with evidence of metastatic disease on diagnostic imaging studies.
b) Measurable disease (per RECIST 1.1 criteria)
c) ECOG Performance Status 0-2 (See Appendix I)
d) No prior chemotherapy or radiotherapy for metastatic pancreatic cancer. Patients may have received prior chemotherapy or radiotherapy for non-metastatic disease; however the diagnosis of metastatic disease must have been made more than 6 months after completion of prior treatment. Prior radiation therapy for palliation of symptomatic primary tumors (ie. for pain control) is allowable at the discretion of the Principal Investigator. Radiated lesions may not be used as target (measurable) lesions for RECIST purposes.
e) Patients may have had a history of other malignancies if there is no current evidence of persistent or recurrent disease and they are not undergoing any active therapy (including hormonal).
f) Patent biliary system. Surgical bypass or internal stent is preferred if clinical concern for obstructive potential during duration of study participation.
g) Patients receiving anti-coagulation treatment with an agent such as Coumadin or heparin may be allowed to participate, provided the following criteria are met;
    i) Receiving low- molecular weight heparin, or a stable dose of Coumadin for at least 3 weeks. If on coumadin, an INR between 2 and 3 must be documented on two sequential occasions prior to enrollment.

ii) No active bleeding or pathological condition that carries a high risk of bleeding (e.g. active GI mucosal ulceration or history of known variceal bleeding).

iii) Patients temporarily (<3 weeks) placed on prophylactic doses of heparin or low-molecular weight heparin related routine inpatient hospital stays or post-hospital rehabilitation are eligible.

h) Adequate organ and marrow function

i) Total bilirubin < 1.5 times the institutional Upper Limit of Normal (ULN)

ii) AST, ALT and Alk Phos ≤ 2.5 times the institutional ULN (≤ 5 x ULN for patients with known liver metastases)

iii) Serum Creatinine < 1.5 time the institutional ULN

iv) Hemoglobin ≥ 9.0 g/dL (patient may be transfused to maintain or exceed this level)

v) Absolute neutrophil count (ANC) ≥ 1,500/mm^3

vi) Platelet count ≥ 100,000/mm^3

vii) No other clinically significant lab abnormalities

i) Ability to take oral medication (dasatinib must be swallowed whole)

j) Concomitant Medications

i) Patient agrees to discontinue St. Johns Wort while receiving dasatinib therapy (discontinue St. Johns Wort at least 5 days before starting dasatinib)

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

iii) Patient agrees to discontinue use of potent CYP3A4 inhibitors or Category 1 anti-arrhythmic agents (see exclusion criteria section or Section 5.7 for detailed lists) at least 7 days prior to starting dasatinib.

Age and Sex

k) Subject, age ≥ 18 years.

l) Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the study and for at least 4 weeks after the last dose of study drug to minimize the risk of pregnancy. Prior to study enrollment, women of childbearing potential must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy.

WOCBP include any woman who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or who is not post-menopausal. Post-menopause is defined as:

- Amenorrhea that has lasted for ≥ 12 consecutive months without another cause, or
- For women with irregular menstrual periods who are taking hormone replacement therapy (HRT), a documented serum follicle-stimulating hormone (FSH) level of greater than 35 mIU/mL.

Women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or

mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or who are practicing abstinence or where their partner is sterile (eg, vasectomy) should be considered to be of childbearing potential.

WOCBP must have a negative serum pregnancy test within 7 days prior to the start of protocol therapy.

A male subject of fathering potential must use an adequate method of contraception to avoid conception throughout the study [and for at least 4 weeks after the last dose of study drug] to minimize the risk of pregnancy.

4.2.2 Exclusion Criteria

Sex and Reproductive Status

a) WOCBP who are **unwilling or unable** to use an acceptable method to avoid pregnancy for the entire study period and for at least 4 weeks after the last dose of study drug.
b) Women who are pregnant or breastfeeding.
c) Women with a positive pregnancy test.
d) Sexually active fertile men not using effective birth control if their partners are WOCBP.

Target Disease Exceptions

e) History of known brain metastases or carcinomatous meningitis

Medical History and Concurrent Diseases

a) Recent major surgery (within 4 weeks) or minor surgery (within 2 weeks), excluding placement of a vascular access device or biliary stent
b) Uncontrolled diabetes in the opinion of the treating physician
c) Any sensory neuropathy > grade 1 at baseline
d) Serious active or uncontrolled infection
e) Concurrent medical condition which may increase the risk of toxicity, including:
    i) Clinically significant pleural or pericardial effusion requiring therapeutic thoracentesis or chest tube placement, pericaridocentesis, or causing ≥ grade 2 dyspnea
    ii) Patients with known dihydropyrimidine dehydrogenase deficiency
    iii) Patients with a history of allergic reactions attributed to oxaliplatin, 5-FU or leucovorin
f) Cardiac Symptoms; any of the following should be considered for exclusion:
    i) Unstable angina or stable angina markedly limiting ordinary physical activity (angina occurs on walking one to two blocks and/or climbing one flight of stars in normal conditions and at a normal pace)
    ii) New York Heart Association class III or IV congestive heart failure
    iii) Myocardial infarction or stroke within 6 months of study enrollment
    iv) Diagnosed congenital long QT syndrome
    v) Any history of clinically significant ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or Torsades de pointes)
    vi) Prolonged QTc interval on pre-entry electrocardiogram (> 475 msec)

vii) Clinically significant peripheral vascular disease

g) Subjects with hypokalemia or hypomagnesemia if it cannot be corrected prior to dasatinib administration

h) History of significant bleeding disorder unrelated to cancer, including:
   i) Diagnosed congenital bleeding disorders (e.g., von Willebrand's disease)
   ii) Diagnosed acquired bleeding disorder within one year (e.g., acquired anti-factor VIII antibodies)
   iii) Ongoing or recent (≤ 3 months) significant gastrointestinal bleeding

i) History of any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of protocol therapy or that might affect the interpretation of the results of the study or that puts the subject at high risk for treatment complications, in the opinion of the treating physician.

Prohibited Treatments and/or Therapies

j) Category I 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; see Section 5.7 for details)
   i) quinidine, procainamide, disopyramide
   ii) amiodarone, sotalol, ibutilide, dofetilide
   iii) erythromycin, clarithromycin
   iv) chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide
   v) cisapride, bepridil, droperidol, methadone, arsenic, chloroquine, domperidone, halofantrine, levomethadyl, pentamidine, sparfloxacin, lidoflazine.

k) Potent CYP3A4 inhibitors that significantly increase dasatinib exposure. Patients must discontinue drug 7 days prior to starting dasatinib; see Section 5.7.1.1 for details).

Other Exclusion Criteria

l) Prisoners or subjects who are involuntarily incarcerated.

m) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

n) Inability to comply with study and/or follow-up procedures

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

4.2.3 Discontinuation of Subjects from Treatment

Patients who discontinue participation in the clinical study on their own or patients who are withdrawn by the investigator, for reasons other than disease progression or toxicity, will be defined as premature withdrawals.

Patients who are not initiated on study drug, but sign informed consent and undergo at least some of the screening procedures will be considered screening failures. A record of these patients will be maintained by the study site.

Subjects MUST discontinue study treatment for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Progressive disease at any time
- Patient meets criteria for stopping study medication due to toxicity as outlined in Section 5.5
- Any clinical adverse event (AE), laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- The patient uses illicit drugs or other substances that may, in the opinion of the Investigator, have a reasonable chance of contributing to toxicity or otherwise interfering with results
- Pregnancy
  - Instruct WOCBP to contact the investigator or study staff immediately if they suspect they might be pregnant (eg, 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 BMS if a study subject becomes pregnant. The mechanism for reporting pregnancy is described in Section 7.6.
- Termination of the study by BMS.
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Substantial non-compliance with the requirements of the study
- The patient is lost to follow up

The Investigator will make every reasonable effort to keep each patient in the study unless it is in the patient's best interests to discontinue participation. If a patient is removed from the study or declines further participation, all End of Treatment evaluations should be performed if the patient is willing and able to be assessed. A description of the reason(s) for withdrawal from the study must be recorded on the case report form (CRF). The Investigator should also ensure that all patients are followed up for survival status after the Final Visit. Patients who elect to withdraw from treatment prematurely may still be followed per the study calendar with their permission.

Relevant visit data should be entered on the CRF and any unused study medication will be accounted for and returned for all patients participating in the study, even for a brief period of time. Patients who discontinue following entry will have relevant information completed and recorded on the CRF. All patients who discontinue because of adverse events or clinically significant laboratory abnormalities should be followed up until they recover or stabilize, and the subsequent outcome will be recorded. If any patient should die during the trial or within 30 days of stopping study treatment, the Investigator will inform the BMS representative. The cause of death should be recorded in detail, within 24 hours, on a serious adverse event (SAE) form and reported to the sponsor Drug Safety Unit (refer to Section for SAE reporting).

5 TREATMENTS

5.1 Study Treatment

An investigational product, also known as investigational medicinal product in some regions, is defined as follows: A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form. In this protocol, the investigational product is dasatinib.

Other medications used in the study for therapeutic reasons as components of a given standard of care are considered non-investigational products. In this protocol, non-investigational products include oxaliplatin, 5-fluorouracil, and leucovorin.

5.1.1 Agent Administration

One treatment cycle is equal to 14 days.

Agent	Dose	Route/Duration	Schedule
Dasatinib*	150 mg	Oral	Daily on days 1-14
Oxaliplatin^{+}	85 mg/m^2	IV over 120 minutes	1 every 14 days
Leucovorin^{+}	400 mg/m^2	IV over 120 minutes	1 every 14 days
5-fluorouracil bolus^{+}	400mg/m^2	IV push over less than 5 minutes	1 every 14 days
5-fluorouracil infusion^{+}	2400mg/m^2	IV continuous infusion for 46 hours	1 every 14 days
* If the start of a cycle is delayed due to scheduling, logistical issues or non-dasatinib related toxicities, dasatinib may be continued in the interim. $^{+}$Administer sequentially as written, except oxaliplatin and leucovorin, which may be administered concurrently in separate bags using a Y-line. In the event that oxaliplatin is discontinued, leucovorin can be administered alone and the administration duration may be shortened to 15 min. See section 5.5 for levoleucovorin substitution.			

5.1.2 mFOLFOX-6

Doses should be based on actual body weight. Body surface area (BSA) will be calculated prior to each treatment cycle from body weight in kg, recorded up to 72 hrs prior to day 1 of each cycle, and height in cm, recorded at baseline. The formula for BSA calculation should remain consistent throughout treatment. Pre-medications should be administered per institutional practice.

5.1.3 Dasatinib

Dasatinib should be taken in the morning at approximately the same time every day. The medication may be taken with or without food. Patients should not consume greater than one 8 oz glass per day of grapefruit or pomegranate juice per day while taking dasatinib. Crushing or cutting dasatinib is prohibited. If vomiting occurs, the dose should not be replaced. Short-acting antacid agents may be taken, but it is recommended that these not be taken from 2 hours before to 2 hours after dosing of dasatinib.

On days of chemotherapy administration, dasitinib should be taken at least 3 hours prior to chemotherapy, even if this represents a time different from the patient's usual administration time. Please note, there is no dose adjustment for BSA.

5.1.4 Supportive Care

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

Nausea: Antiemetics should be administered per institutional guidelines.

Diarrhea: Patients should be provided with instructions on use of loperamide (Imodium) in the event of diarrhea, as well as instructions to contact the treating physician. Other anti-diarrheals are also allowed. Patients should be given mouth care instructions per institutional guidelines.

Neutropenia: Prophylactic use of G-CSF or Peg-G-CSF is not permitted. Please refer to table 5.5.2 for neutropenia adverse event guidelines. When needed, either G-CSF 5mcg/kg/dose (total dose rounded per institutional guidelines) SQ on days 4-10 of each cycle or Peg-G-CSF 6mg SQ on day 4 of each cycle are acceptable options.

Peripheral Nerve Cold Hypersensitivity: When appropriate, intravenous calcium gluconate plus magnesium sulfate, may be administered immediately before and after each dose of oxaliplatin per institutional protocol (see table 5.5.3 for details).

Infusional Hypersensitivity: Platinum hypersensitivity can cause dyspnea, bronchospasm, itching and hypoxia. Appropriate treatment includes supplemental oxygen, steroids, antihistamines and epinephrine; bronchodilators and vasopressors may be required. Platinum hypersensitivity is an extremely rare event (approximately 0.5% of patients) and should be treated promptly.

Pharyngo-laryngeal Dysesthesias: Oxaliplatin may cause discomfort in the larynx or pharnyx associated with dyspnea, anxiety and/or swallowing difficulty and is exacerbated by cold. Appropriate therapy includes use of anxiolytics and cold avoidance. If grade 1 (mild) pharyngo-laryngeal dysesthesias occurs while treatment is being administered, increase the duration of infusion to 6 hours. If grade 2 (moderate) or grade 3 (severe) pharyngo-laryngeal dysesthesias occurs during treatment administration, stop oxaliplatin infusion, administer benzodiazepine, reassure the patient and monitor. At the discretion of the

investigator, the infusion may be re-started at 1/3 original infusion rate. Increased duration of infusions is not required for subsequent treatment administration.

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

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

See also additional details in Section 5.7.3.

5.2 Dasatinib

5.2.1 Identification

Dasatinib will be provided in 2 different strengths for this trial:

Table 5.1.1: Description of Dasatinib Dosage Forms

Strength	Description
20 mg	white to off-white, biconvex, round, film coated tablet with either “20” or “BMS” debossed on one side and “527” on the other side
50 mg	white to off-white, biconvex, oval, film coated tablet with either “50” or “BMS” debossed on one side and “528” on the other side

5.2.2 Packaging and Labeling

Dasatinib is supplied as 5 mg, 20 mg, and 50 mg film-coated tablets containing dasatinib with lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The tablet coating contains hydroxypropyl methylcellulose, titanium dioxide, and polyethylene glycol (triacetin in the 5 mg film-coated tablet). Tablets for clinical studies are supplied in high-density polyethylene bottles containing a desiccant and cotton. The bottles are heat-induction sealed with child resistant caps.

Each bottle is labeled in an open label manner. Labels contain, at a minimum, the

following information: product name, tablet strength, batch number, directions for use, storage conditions, and appropriate caution statements.

5.2.3 Storage, Handling, and Dispensing

5.2.3.1 Storage

Bottles containing dasatinib tablets should be stored at 15° - 25°C.

All investigational product should be stored in a secure area according to local regulations. The investigator is responsible for ensuring that it is dispensed only to study subjects and only from official study sites by authorized personnel, as dictated by local regulations.

The investigator is responsible for ensuring that the investigational product is stored under the appropriate environmental conditions (temperature, light, and humidity.

If concerns regarding the quality or appearance of the investigational product arise, do not dispense the investigational product, and contact BMS immediately.

5.2.3.2 Handling and Dispensing

Procedures for proper handling and disposal of anticancer drugs should be considered.

Dasatinib tablets consist of a core tablet (containing the active drug substance), surrounded by a film coating to prevent exposure of pharmacy and clinical personnel to the active drug substance. If tablets are crushed or broken, pharmacy and clinical personnel should wear disposable chemotherapy gloves. Personnel who are pregnant should avoid exposure to crushed and/or broken tablets.

The Investigator (or assigned designee, i.e., study pharmacist) will dispense the proper number of each strength tablet to 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.

5.3 Drug Ordering and Accountability

5.3.1 Initial Orders

Initial Orders of dasatinib should be requested by completing the Dasatinib (Sprycel®) Drug Supply Form for Investigator Sponsored Studies and submitting the request form electronically via e-mail at least 5-7 business days before the expected delivery date. Deliveries will be made Tuesday through Friday.

Initial drug supply will be provided for a 12-week treatment period per subject.

5.3.2 Re-Supply

Re-supply requests should be sent to srcsupply@bms.com.

Please check "Re-supply" on the drug supply form. Re-supply requests should be submitted at least 5-7 business days before the expected delivery date. Deliveries will be made Tuesday through Friday.

5.3.3 Drug Accountability

Please refer to Section 9.2 for drug accountability requirements.

5.3.4 IND Status

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

5.4 Method of Assigning Subjects to a Treatment

This is a single arm phase II study where all subjects receive the same treatment.

5.5 Dose Modifications

All toxicities should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Dose modifications are based on dose level administered on the last treatment day. Dose adjustments of each agent may be made independently based on the specific types of toxicities observed. If oxaliplatin is discontinued due to toxicity dasatinib, 5-FU and LV may be continued. If dasatinib is discontinued due to toxicity oxaliplatin, 5-FU and LV may be continued. If more than two dose reductions are required for 5-FU/LV, the patient must discontinue protocol therapy. In general, a dose reduction of 5-FU is always associated with an equal dose reduction of LV, except in the setting of a LV-specific AE. Levoleucovorin can be substituted for LV, with the appropriate pharmacologic equivalent dose (ie, 50%), at the discretion of the treating physician. If treatment is held for greater than 2 cycles (28 days) the patient must discontinue protocol therapy, unless otherwise approved by the Principal Investigator.

If criteria for treatment discontinuation is met, but the treating oncologist feels that it is in the best interest of the patient to receive additional therapy (for example, if the patient has

demonstrated a response to therapy), additional therapy may only be given after discussion with the Principal Investigator following a resolution of the toxicity to Grade 1 or to baseline level.

If a dasatinib dose is not taken due to an error, it may be taken up to 12 hours later. If vomiting occurs, the dose should not be replaced.

If a dose level had been reduced due to toxicity, re-escalation is not permitted.

5.5.1 Dose Modification Table

Agent	Starting Dose	Dose Level -1	Dose Level -2
Dasatinib	150 mg	120 mg	100 mg*
Oxaliplatin	85 mg/m^2	65 mg/m^2	50 mg/m^2
Leucovorin	400 mg/m^2	300 mg/m^2	200 mg/m^2
5-fluorouracil bolus	400mg/m^2	300 mg/m^2	200 mg/m^2
5-fluorouracil infusion	2400mg/m^2	1800 mg/m^2	1200 mg/m^2

* Additional dose reductions may be instituted at the Principal Investigator's discretion for exceptional responders (subjects demonstrating stable disease at or beyond 32 weeks of treatment). Dose Level -3: 80mg. Dose Level -4: 60mg.

5.5.2 Dose Modifications Due to Combined Drug Toxicity

Table 5.5.2: Dose Modifications for Associated Combined Toxicities

Toxicity – NCI Grade (v.4)	Suggested Dose Modification
Hematologic **Neutrophils/ granulocytes** Grade 3,4	Hold treatment and check weekly until ANC ≥ 1500/mm^3. ▪ Upon recovery, initiate standard empiric therapy with colony stimulating factors to prevent recurrence on subsequent cycles. Resume treatment at same dose level. ▪ 2nd occurrence - ↓ 5-FU/LV bolus one dose level ▪ 3rd occurrence - ↓ 5-FU infusion one dose level ▪ 4th occurrence - ↓ 5-FU/LV bolus and infusion a second dose level and oxaliplatin one dose level ▪ 5th occurrence - discontinue protocol therapy Either GCSF or Peg-GCSF is permitted when appropriate (see Section 5.1.4).
Thrombocytopenia Grade 2 (1st Event)	Hold treatment and check weekly until platelets are ≥ 75,000/mm^3. Resume treatment at same dose level.
Grade 2 (2nd Event) Grade 3, 4	Hold treatment and check weekly until platelets are ≥ 75,000/mm^3. ▪ Upon recovery - ↓ oxaliplatin one dose level ▪ 2nd occurrence - ↓ 5-FU/LV bolus one dose level ▪ 3rd occurrence - ↓ oxaliplatin and 5-FU/LV bolus second dose level

	▪ 4th occurrence – discontinue 5-FU/LV bolus ▪ 5th occurrence - ↓ dasatinib one dose level ▪ 6th occurrence - discontinue protocol therapy
Other hematologic toxicities do not require dose modification. However, red blood cell transfusion should be considered for hemoglobin < 8 g/dL or significant symptoms of anemia.	
Gastrointestinal **Diarrhea or mucositis** Grade 1	For any GI toxicity, verify and provide supportive care as described in section 5.1.4
Grade 2, 3	Hold treatment until ≤ grade 1 ▪ 1st occurrence - ↓ 5-FU/LV bolus one dose level ▪ 2nd occurrence - ↓ 5-FU/LV bolus second dose level and 5-FU infusion one dose level ▪ 3rd occurrence - ↓ dasatinib one dose level ▪ 4th occurrence - ↓ dasatinib second dose level ▪ 5th occurrence - discontinue protocol therapy
Hepatic **Total bilirubin, AST, or Alk Phos** Grade 3	Hold treatment until ≤ grade 2 – provide/replace biliary stent if needed ▪ 1st occurrence – resume at previous dose ▪ 2nd occurrence - ↓ 5-FU/LV bolus and oxaliplatin one dose level ▪ 3rd occurrence - ↓ 5-FU/LV bolus and oxaliplatin second dose level ▪ 4th occurrence – discontinue protocol therapy
Grade 4	Discontinue protocol therapy.
Fatigue Grade 3,4	Hold treatment until ≤ grade 2 ▪ 1st occurrence - ↓ 5-FU/LV bolus one dose level ▪ 2nd occurrence - ↓ 5-FU/LV bolus second dose level and 5-FU infusion one dose level ▪ 3rd occurrence - ↓ dasatinib one dose level ▪ 4th occurrence - ↓ dasatinib second dose level ▪ 5th occurrence - discontinue protocol therapy
Other Clinically Significant Toxicities*	
Grade 3	Hold treatment until AE resolves to ≤ grade 1. Reduce suspected offending drug one dose level. ▪ 2nd occurrence – suspected offending drug second dose level ▪ 3rd occurrence – discontinue protocol therapy
Grade 4	Hold treatment until AE resolves to ≤ grade 1. Reduce suspected offending drug one dose level. ▪ 2nd occurrence – discontinue protocol therapy
* Determination of "clinically significant" AEs and "offending drug" is at the discretion of the treating physician.	

5.5.3 Dose Modifications due to Oxaliplatin Toxicity

Dose modifications and delays due to single drug toxicities should follow the defined dose modifications as described in Table 5.5.1 as well as below. Descriptions of individual drug AEs are provided in more detail in the oxaliplatin package insert.

Table 5.5.3: Dose Modifications for Oxaliplatin-specific Toxicities

Suggested Dose Modifications for Oxaliplatin Toxicity			
Toxicity – NCI Grade (v.4)	**Duration of Event**		**Persistent between cycles**
	< 7 days	**> 7 days**	
Neuropathies Grade 1: Paresthesias/ dysesthesias of short duration that resolve and do not interfere with function	No change	No change	No change
Grade 2: Paresthesias/ dysesthesias interfering with function, but not activities of daily living (ADL)	No change	1st time: ↓oxaliplatin one dose level 2nd time: ↓oxaliplatin second dose level	↓ oxaliplatin one dose level
Grade 3: Paresthesias/ dysesthesias with pain or with functional impairment that also interfere with ADL	1st time: ↓oxaliplatin one dose level 2nd time: ↓oxaliplatin second dose level	Discontinue oxaliplatin	Discontinue oxaliplatin
Grade 4: Persistent paresthesias/dysesthesias that are disabling or life-threatening	Discontinue oxaliplatin	Discontinue oxaliplatin	Discontinue oxaliplatin
Pharyngo-laryngeal dysesthesias	Please refer to section 5.1.4		
Hypersensitivity reaction	In the event of an acute oxaliplatin hypersensitivity reaction, the treating physician may attempt to administer subsequent oxaliplatin doses with steroid and antihistamine pre-medication, and lengthening of the oxaliplatin infusion time to 4-6 hours. Partial dose reduction in oxaliplatin is not undertaken for hypersensitivity reaction. In the event of a hypersensitivity reaction that the treating physician believes warrants discontinuation of oxaliplatin, the other agents should be continued without dose modification		
Pulmonary fibrosis	Signs and symptoms associated with PF (cough, dyspnea, rales, hypoxia, tachypnea) should be investigated to rule out PF as their cause. If suspected, hold oxaliplatin until PF is ruled out or an alternate diagnosis is confirmed. Oxaliplatin may then be resumed at previous dose. If PF is confirmed, discontinue oxaliplatin.		

5.5.4 Dose Modifications due to Dasatinib Toxicity

Table 5.5.4: Dose Modifications for Dasatinib Toxicity

Single Drug Clinically Significant Toxicities*	
Grade 3	Hold treatment until AE resolves to ≤ grade 1. Reduce dasatinib one dose level.

	▪ 2nd occurrence – decrease dasatinib to the second dose level ▪ 3rd occurrence – discontinue protocol therapy#
Grade 4	Hold treatment until AE resolves to ≤ grade 1. Reduce dasatinib one dose level. 2nd occurrence – discontinue protocol therapy
* Determination of "clinically significant" is at the discretion of the treating physician. # Exceptional responders (see section 5.5.1) may continue protocol therapy at the discretion of the Principal Investigator	

If clinically relevant pleural effusion is noted, confirm with imaging and consider thoracentesis. Initiation of methylprednisolone (Medrol Dose Pack™ or equivalent; 24mg PO daily x 1 followed by 20mg followed by 16mg followed by 12mg followed by 8mg followed by 4mg then done) with or without lasix is recommended. For symptomatic effusion, dasatinib requires treatment hold for a minimum of 2 days during initiation of steroid use, prior to dose reduction.

Chest discomfort or dyspnea may also be related to pericardial effusion; an echocardiogram may be indicated. Dose reduction of dasatinib is required if fluid retention is severe or recurrent.

5.5.5 Myelosuppression

See Table 5.5.2.

5.5.6 Non-hematological Adverse Events

See above Tables 5.5.2, 5.5.3, and 5.5.4.

See also supportive care guidelines for symptom management in Section 5.1.4.

5.5.7 Adverse Event Information

For the most current safety updates, please refer to the current Prescribing Information for oxaliplatin, 5-fluorouracil and leucovorin. Please refer to section 1.7.3 and the most recent Investigator's Brochure for more information on dasatinib.

5.6 Blinding/Unblinding

Not applicable to this protocol.

5.7 Concomitant Treatments

5.7.1 Prohibited and/or Restricted Treatments

No other systemic therapy for treatment of pancreatic cancer is permitted while subject is on study. Concomitant palliative radiotherapy is not permitted for disease progression on treatment, but may be allowed for pre-existing non-target lesions with approval of BMS

Medical Monitor. Bisphosphonate treatment may not be initiated during study; if already begun, it may be continued at Investigator discretion (see Sections 4.2.1).

Subjects requiring any prohibited therapy should not be enrolled. If enrolled, the prohibited agent(s) will be withdrawn prior to first dose of study drug.

5.7.1.1 Potent CYP3A4 Inhibitors

Dasatinib is primarily metabolized by the CYP3A4 enzyme. In drug-drug interaction studies, concomitant use of ketoconazole (a potent CYP3A4 inhibitor) produced an increase of > 5-fold in dasatinib exposure. Therefore, **potent** inhibitors of CYP3A4 are prohibited during study; for such medications, a wash-out period of ≥ 7 days is required prior to starting dasatinib. Subjects should be advised not to consume substantial quantities of grapefruit or pomegranate juice. (Less-potent inhibitors, inducers and substrates of CYP3A4 are restricted, see Section 5.7.2.1.) Most commonly-used potent CYP3A4 inhibitors are:

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

5.7.1.2 Medications that prolong QT Interval

Subjects enrolled in this study may not take concomitant medications **known** to prolong the QT interval (Class I; see http://www.qtdrugs.org/medical-pros/drug-lists/drug-lists.htm). For such medications, a wash-out period of ≥ 7 days is required prior to starting dasatinib. Agents which possibly prolong the QT interval are restricted; see Section 5.7.2.2. Medications known to prolong the QT interval are:

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

5.7.2 Other Restrictions and Precautions

The following restricted therapies are not recommended, but are permitted with caution when clearly medically indicated.

5.7.2.1 CYP3A4 Inducers, Inhibitors, Substrates

Drugs that induce CYP3A4 activity may decrease dasatinib plasma concentrations. In subjects in whom enzyme-inducing anticonvulsants (eg, phenytoin, carbamazepine, phenobarbital) are used, alternative agents with lesser enzyme-induction potential should be considered.

Dasatinib is predominantly metabolized by the CYP3A4 isoenzyme. Potent inhibitors are prohibited, but less-potent inhibitors may also increase exposure to dasatinib. If

administration of a CYP3A4 inhibitor cannot be avoided in subjects receiving dasatinib, close monitoring for toxicity and dasatinib dose reduction should be considered. Subjects should be advised not to consume substantial quantities of grapefruit or pomegranate juice.

Other 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 subjects receiving dasatinib. Note: subjects treated with a fentanyl patch are eligible for this trial.

As warfarin is metabolized through the CYP450 system, therapeutic anticoagulation with warfarin (eg, Coumadin® or Cournadine®) is not recommended. As an alternative, therapeutic anticoagulation may be accomplished using low-molecular weight heparin (eg, Lovenox®) or heparin. Mini Dose Coumadin® (eg, 1 mg QD) is permitted for prophylaxis of central venous catheter thrombosis.

5.7.2.2 Medications that may Prolong QT Interval

Concomitant medications known to prolong the QT interval are prohibited (Section 5.7.1); medications which may possibly prolong the QT interval (non-Class I; see http://www.qtdrugs.org/medical-pros/drug-lists/drug-lists.htm) are restricted. Should the Investigator believe that beginning therapy with a potentially QT-prolonging medication (other than those prohibited) is vital to an individual subject's care, the Investigator must check that the prior on-therapy ECG does not show QTc ≥ 475 msec or an increase in QTc ≥ 60 msec over the baseline value.

5.7.2.3 Antacids

Nonclinical data demonstrate that the solubility of dasatinib is pH dependent and a clinical study has shown that dasatinib exposure is substantially and durably reduced after treatment with famotidine. Administration of dasatinib with H2 inhibitors or proton pump inhibitors should therefore be avoided. If antacid therapy is needed, a locally-acting antacid may be used, and should be administered at least 2 hours before or after the dose of dasatinib.

5.7.2.4 St. John's Wort (Hypericum perforatum)

Data suggests that St. John's Wort may decrease dasatinib plasma concentrations unpredictably. Subjects receiving dasatinib should not take St. John's Wort. Subjects should discontinue St. John's Wort at least 5 days before starting dasatinib.

5.7.2.5 Medications that Inhibit Platelet Function and Anticoagulants

Src-family kinase inhibition potentially reduces platelet aggregation. Caution should thus be exercised if subjects are required to take medications that inhibit platelet function or anticoagulants. Such medications include:

- aspirin or aspirin-containing combinations, clopidogrel, dipyridamole
- tirofiban, dipyridamole, epoprostenol, eptifibatide, cilostazol, abciximab, ticlopidine, cilostazol
- warfarin, heparin/low molecular weight heparin [eg, danaparoid, dalteparin, tinzaparin, enoxaparin]
- exceptions are low-dose warfarin for prophylaxis to prevent catheter thrombosis and heparin for flushes of intravenous lines.

5.7.2.6 Bisphosphonates

Subjects who had been receiving bisphosphonates prior to study entry may continue on therapy with caution. Bisphosphonates should be temporarily discontinued during the first 8 weeks of protocol therapy however they may be resumed after that time at the discretion of the treating physician. Please refer to section 4.2.1 for protocol required treatment modifications. Although concomitant use of bisphosphonates is not recommended, clinically-significant hypocalcemia has been uncommon. Oral serum calcium (Ca^{+2}) supplementation, including Vitamin D if appropriate, is warranted.

5.7.3 Additional Supportive Care Guidance for Dasatinib

Supportive care, especially pain control, will be optimized in all subjects. Guidance is provided for management of common side effects of dasatinib in order to maximize opportunity for benefit. Investigators are strongly urged to discuss with Medical Monitor and/or the Principal Investigator prior to discontinuing study treatment for reasons other than radiographic PD.

Non-hematologic side effects are typically CTCAE v4.0 Grade 1 - 2. Interruption and/or dose reduction may be necessary, especially if Grade ≥ 2. Usual supportive care measures should be used for nausea/emesis, diarrhea, pain, fever or headache. Neither clinically significant myelosuppression nor use of hematopoietic growth factors is expected.

Osteoclast inhibition is expected; therefore, calcium supplementation (eg, calcium carbonate 500 mg PO TID) may be warranted to maintain serum Ca^{+2} above LLN during dasatinib treatment. Vitamin D supplementation (eg, ergocalciferol 400 IU PO QD) may be appropriate for persistent hypocalcemia. Bisphosphonate therapy should be deferred in the presence of hypocalcemia.

Fluid retention, including clinically-significant pleural effusion, has been observed during dasatinib treatment. Refer to Section 5.1.4 for treatment recommendations.

5.8 Treatment Compliance

Patients will be required to return all bottles of study medication at the beginning of each cycle. The number of tablets remaining should be documented and recorded on the Case Report Form. In addition, each patient will complete a dasatinib pill diary to document compliance with each cycle of therapy (see Appendix II). When possible, drug reconciliation will take place in the presence of the patient in order to account for

possible discrepancies. Deviations from prescribed therapy will be recorded. Deviations greater than 10% from the expected dose (accounting for delays and dose modifications per protocol) will be considered deviations for IRB reporting purposes.

6 STUDY ASSESSMENTS AND PROCEDURES

6.1 Time and Events Schedule

Table 6.1: Study Schedule and Procedures

Evaluation	Screening[a]	Treatment Phase (1 cycle = 14 days)			Follow Up
		Before each cycle	Every fourth cycle	End of treatment	
History & Physical	X	X		X	X[k]
Performance Status	X	X		X	
Vital Signs[b]	X	X		X	
AE Assessment	X	X		X	X[l]
ECG	X[c]	X[c]			
Drug Dispensation		X[d]			
Pregnancy test[a]	X				
CMP[e,f]	X	X		X	
CBC w/Diff[e]	X	X		X	
PT/INR[g]	X				
CA19-9[e]	X	X			[r]
CT or MRI[h]	X		X		X
QOL questionnaires	X[i]		X[i]	X[i]	
Research Blood Collection	X[j]	X[j]		X	
FFPE Tumor Block Retrieval	X				
Survival Status					X[m]

a. All screening procedures should be completed within 28 days of treatment except for serum pregnancy testing which should be completed within 7 days of treatment. History & Physical, Vital Signs, ECOG PS, CMP, CBC w Diff and CA19-9 are not required to be repeated at treatment initiation if they were completed within 7 days prior to Cycle 1 Day 1.

b. Vital signs include height, weight, blood pressure, pulse, temperature and pain level (subjective 1-10 self-reported scale). Height should be obtained at screening only.

c. ECGs will be obtained at screening as well as prior to cycle #3 (day 28; +/- 7 days). Patients who are placed on QT prolonging medications while on study should have ECGs performed at regular intervals (interval timing is at the discretion of the treating investigator).

d. Only enough dasatinib for 2 cycles of therapy (28 days) may be given to a patient prior to reassessment.

e. Laboratory testing may be performed up to 72 hours prior to day 1 of the next cycle of therapy.

f. CMP: Na, K, Cl, CO_2, Glucose, BUN, Creatinine, Ca, Albumin, Total Bilirubin, Alk Phos, Total Protein, AST, ALT.

g. PT/INR should be followed closely for patients on warfarin.

h. CT of the chest, abdomen and pelvis or CT of the chest and MRI of the abdomen and pelvis are allowed. Consistent imaging modality should be used throughout the study. Imaging should be performed every 8 weeks (+/- 7 days) until disease progression.

i. FACT-Hep should be completed at screening, every fourth cycle starting at cycle 5, and at EOT. CTSQ should be completed at C2, every fourth cycle starting at cycle 5, and at EOT.

j. Baseline blood sample will be collected prior to first dose of therapy administered. Additional blood samples will be collected at completion of cycle 1 infusional 5-FU (day 3; cycle 1 only), day 1 of every cycle starting with cycle 2, and at EOT. Reasonable efforts to obtain the C1D3 sample will be made however collection is optional. Red, green top and cell prep tubes will be collected at all time points. EDTA tubes will be collected once, preferably at screening.

k. H&P is required at 30 days (+ 7 days) following the last dose of study drug. Additional H&Ps are required as needed to follow ongoing AEs.

l. Adverse events should be followed for 30 days after the last dose of protocol therapy or until the initiation of subsequent treatment. AEs continuing > 30 days should be monitored until resolution.

m. Patients or providers should be contacted every 8 weeks to assess survival status and subsequent therapies.

6.2 Study Materials

Bristol-Myers Squibb (BMS) will provide dasatinib at no cost for this study. Oxaliplatin, 5-fluorouracil and leucovorin will be obtained from commercial supply and will be billed to the patient or patient's insurance.

6.3 Safety Assessments

Subjects must undergo a history and physical examination by a licensed provider at the beginning of each treatment cycle. Vital signs and AE assessments should be done concurrently with the H&P.

Laboratory testing should be completed as outlined in the study schedule and procedures table as outlined above. Additional laboratory testing may be done at the Investigator's discretion.

An ECG is required pre-treatment (baseline) and prior to cycle 3 (day 28). Additional ECGs may be done at the Investigator's discretion to ensure the subject's safety. Concomitant medications should be monitored by the Investigator. In the event the subject undergoes an on-study drug treatment modification with a potentially QT prolonging medication, ECGs should occur at regular intervals throughout treatment.

6.4 Efficacy Assessments

6.4.1 Tumor response

Tumor response will be assessed using RECIST 1.1[59] criteria.

Tumor measurement

- Measurable disease: the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
- Measurable lesions: lesions that can be accurately measured in at least one dimension (the longest diameter), and with a minimum size of 10 mm by CT scan, or 10 mm by caliper measurement during clinical exam, or 20 mm by chest X-ray.
  - A malignant lymph node may be considered pathologically enlarged and measurable if it is ≥ 15 mm in short axis by CT scan.
  - A lytic or mixed blastic-lytic bone lesion, with identifiable soft tissue component which is evaluable by CT or MRI, may be considered as measurable lesion if the soft tissue component meets the criteria for measurable lesions.
  - Cystic metastases may be considered as measurable lesions if they meet the criteria for measurable lesions, however, non-cystic lesions, if present, are preferred as target lesions.

- Tumor lesions in an area previously subjected to loco-regional treatment, may be considered measurable if there has been demonstrated progression.

- Non-measurable lesions: all other lesions, including simple cysts, small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) and other truly non-measurable lesions. These include: leptomeningeal disease; ascites; pleural/pericardial effusion; inflammatory breast disease; lymphangitis cutis/pulmonis; abdominal masses that are not measurable by reproducible imaging techniques; blastic bone lesions.

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes), and ≥ 10 mm diameter using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesions is recommended. Whenever possible, imaging evaluation should be preferred over clinical exam.

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint. The measurability of lesion by CT scan is based on the assumption that CT slice thickness is ≤ 5 mm.

Baseline documentation of target and non-target lesions

- When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longer diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically).
- A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.
- All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’ ‘absent’, or in rare cases ‘unequivocal progression’. Multiple non-target lesions involving the same organ may be recorded as a single item.

Response criteria

Evaluation of target lesions

- Complete Response (CR): disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to < 10 mm.
- Partial Response (PR): at least a 30% decrease in the sum of diameters of the target lesions taking as reference the baseline sum diameters.
- Progression (PD): at least a 20% increase in the sum of diameters of the target lesions taking as reference the smallest sum on study, and an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.
- Stable Disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum diameters while on the study.

Evaluation of non-target lesions

- Complete Response (CR): disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological (< 10 mm short axis).
- Non-complete response (non-CR)/non-progression (non-PD): persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
- Progressive disease (PD): unequivocal appearance of one or more new malignant lesions. Unequivocal progression of existing non-target lesions. Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by a review panel (or study chair/primary investigator).

Evaluation of best overall response

- The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.
- Table 6.4.1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 6.4.2 should be used.

Table 6.4.1: Evaluation of Best Overall Response: Patients with Target Disease, with or without Non-target Disease

Target Lesion	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
PR	Non-PD or not at all evaluate	No	PR
SD	Non-PD or not at all evaluated	No	SD

Table 6.4.1: Evaluation of Best Overall Response: Patients with Target Disease, with or without Non-target Disease

Target Lesion	Non-target Lesions	New Lesions	Overall Response
Not at all evaluated	Non-PD	No	Inevaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Table 6.4.2: Evaluation of Best Overall Response: Patients with Non-target Disease Only

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/ non-PD	No	Non-CR/ non-PD[a]
Not all evaluated	No	Inevaluable
Unequivocal PD	Yes or No	PD
Any	Yes	PD

[a] 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

- When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes.
- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring.
- For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is

confirmed, the date of progression should be the earlier date when progression was suspected.

Confirmation

- In non-randomized trials where response is the primary endpoint, confirmation of PR or CR must be confirmed by repeat measurements that should be performed no less than 4 weeks after the criteria for response are first met.
- In randomized trials or studies where the primary endpoints are stable disease or progression, confirmation of response is not required. Elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, particularly in studies which are not blinded.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6-8 weeks.

6.4.2 Primary Efficacy Assessment

Determine activity of 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) plus dasatinib on progression free survival (PFS) in patients with metastatic pancreatic adenocarcinoma.

6.4.3 Secondary Efficacy Assessments

Determine the radiographic response rate by RECIST 1.1 criteria, the rate of freedom from metastasis (FFM), the time to progression (TTP), the overall survival (OS), the clinical benefit rate (CBR), the site of failure of this regimen in this population, the safety profile and tolerability of this regimen in this population, the patient compliance with oral therapy, and the quality of life (QOL) of patients receiving this therapy. All radiographic images and responses will be reviewed and confirmed by a 3rd party investigator-independent radiographic review.

Quality of life and Satisfaction measurements will be collected and recorded by patients (see Appendix III) with subsequent analysis performed on all patients. Specifically, the Cancer Quality Satisfaction Survey (CTSQ, 2007)[60] and the FACT-Hep (Functional Assessment of Chronic Illness Therapy; Hepatobiliary Cancer - Version 4.0) [61] will be employed as previously validated patient self-reporting tools in this population of patients. Analysis will be undertaken in consultation with cancer behavioral scientists.

Additional exploratory tissue and serum correlative analyses in this population receiving this regimen are further detailed in Section 6.5

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6.5 Other Assessments

The correlative science goal is to identify biomarkers predictive of response, ideally from analysis of the serum or more likely via molecular analysis of the neoplasm. We plan to collect blood products for the following purposes: 1) serially collected blood specimens to measure alterations in circulating factors during therapy, identify potential non-invasive biomarkers of Src inhibition, and to assess correlations with outcome; and 2)

DNA to identify relevant pharmacogenetic markers. Biospecimens will be banked and stored until funding can be secured from the industry sponsor of the trial and/or other sources. Approximately 40mL of whole blood will be collected and processed for future use at study enrollment as well as periodically throughout the period of active study participation. An additional 20mL of whole blood will be collected at one time point during the study, preferably screening, for genomic analysis (see Table 6.1).

Extracted mononuclear cells will be analyzed with regard to thymidylate synthase (TS) expression and correlated with tissue/tumor expression. Src levels and downstream targets in mononuclear cells will also be analyzed to document inhibition during treatment. Blood will be analyzed for specific pathway molecules see below, evidence of tumor injury, and predictive factors which may correlate to therapeutic outcomes or target selection, including plasma deoxyuridine levels as an indirect measure of TS inhibition. Additional molecular or chemical analyses may also be undertaken either during the study progress or in a post-hoc fashion, including assessment of circulating tumor cells.

Previously obtained and stored individual patient tumor samples will be requested and retrieved. Specifically, formalin fixed paraffin-embedded (FFPE) tissue will be sought. No additional biopsies are required as part of this protocol, however, if biopsies are obtained for clinical reasons, submission of this tissue block for analysis is included in the standard protocol consent document and is required. Subsequent molecular or genomic analyses may also be undertaken either during the study progress or in a post-hoc fashion (see below).

All collected tissue will undergo immunohistochemical (IHC) analysis of expression and when relevant, phosphorylation status for c-Src , thymidylate synthase (TS), ribonuclease reductase (RNR), dihidrofolate reductase (DHFR), integrins, EGFR, AKT, STAT, MET, FAK, HIF, and TRAIL pathway molecules. Additional molecules may also be examined either during the study progress or in a post-hoc fashion pending novel discoveries. When adequate sample is available, mutational analysis of *k-ras* and *b-raf* will be performed. While beyond feasible scope at this time, high quality microRNA should be extractable from these specimens, and microarray expression patterns with confirmatory PCR of relevant MiRNAs of interest may be analyzed in the future.

Collection, handling and storage of whole blood specimens:

1. Fill serum separator tubes (red top, approximately 20mL total), plasma separator tubes (sodium heparin green top, 10mL total), cell prep tubes (sodium heparin green/red top, 16mL total), and EDTA tubes (purple top, 20mL total) completely
2. Do not spin or manipulate the green top or cell prep tubes other than ensuring good distribution in the tube
3. Transfer green top and cell prep tubes to lab immediately for further processing
4. Red top and EDTA tubes will be processed and stored per CTSI guidelines

7 ADVERSE EVENT REPORTING

7.1 Adverse Events

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

7.1.1 Serious Adverse Events

A ***Serious Adverse Event (SAE)*** is any untoward medical occurrence that at <u>any dose</u>:

- results in death
- is life-threatening (defined as an event in which the subject 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 (see note below for exceptions)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (eg, medical, surgical) to prevent one of the other serious outcomes listed above. Examples of such events include but are not limited to intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

All pregnancies, regardless of outcome, must be reported to BMS, **including pregnancies that occur in the female partner of a male study subject. <u>All</u> pregnancies must be followed to outcome.** See Section 7.6 for instructions on reporting pregnancies.

Although overdose and cancer are not always serious by regulatory definition, these events should also be reported to BMS in an expedited manner, as described in Section 7.2.

NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an "important medical event" or a life-threatening event)
- elective surgery planned before signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health

status (eg, routine colonoscopy)

- medical/surgical admission for purpose other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases.
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative).

7.1.2 Nonserious Adverse Events

Nonserious adverse events are all adverse events that are not classified as SAEs.

7.2 Assignment of Adverse Event Intensity and Relationship to Investigational Product

All adverse events, including those that are serious, will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0.

The following categories and definitions of causal relationship to investigational product as determined by a physician should be used:

- **Related:** There is a reasonable causal relationship to investigational product administration and the adverse event.
- **Not Related:** There is not a reasonable causal relationship to investigational product administration and the adverse event.

The expression "reasonable causal relationship" is meant to convey in general that there are facts (eg, evidence such as de-challenge/re-challenge) or other arguments to suggest a positive causal relationship.

7.3 Collection and Reporting

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. To prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more adverse events.

If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. The following information should be captured for all AEs: onset, duration, intensity, seriousness, relationship to investigational product, action taken, and treatment required. If treatment for the event was administered, it should be recorded in the medical record. The investigator must supply BMS and the IRB/IEC with any additional information requested, notably for reported deaths of subjects.

7.3.1 Serious Adverse Events

Following the subject's written consent to participate in the study, all SAEs must be collected, including those thought to be associated with protocol-specified procedures.

Collection of all SAEs must continue for 30 days after the last administration of the investigational product. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy). The investigator should notify BMS of any SAE occurring after this time period that is believed to be related to the investigational product or protocol-specified procedure.

All SAEs, whether considered related or unrelated to dasatinib, must be reported to BMS (by the investigator or designee) within 24 hours of study personnel 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 Food and Drug Administration (FDA) as soon as possible **and no later than 7 days** (for a death or life-threatening event) **or 15 days** (for 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 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
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)
http://www.accessdata.fda.gov/scripts/medwatch/

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

If the investigator believes that an SAE is not related to the investigational product but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the potential relationship should be specified in the narrative section of the SAE report.

If an ongoing SAE changes in its intensity or relationship to the investigational product, a follow-up SAE report should be sent within 24 hours to BMS. As follow-up information becomes available it should be sent within 24 hours using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization.

7.3.2 Handling of Expedited Safety Reports

In accordance with local regulations, BMS will notify investigators of all SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the Investigator Brochure). In the European Union, an event meeting these criteria is termed a Suspected Unexpected Serious Adverse Reaction (SUSAR). BMS will send investigators an expedited safety report (ESR) to notify them of such an event.

Other important findings that BMS may report as ESRs include increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety findings from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or the decision by BMS to end or temporarily halt a clinical study for safety reasons.

Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the Investigator Brochure. Where required by local regulations or when there is a central IRB/IEC for the study, BMS will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. When BMS has a written agreement with a local IRB/IEC, BMS will directly submit ESR(s). The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

In addition, BMS will report suspected serious adverse reactions (whether expected or unexpected) to the relevant health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

7.3.3 Nonserious Adverse Events

The investigator will begin collecting nonserious adverse event (NSAE) information once administration of the investigational product is initiated. This NSAE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

All identified NSAEs must be recorded and described in the medical record. If an ongoing NSAE worsens in its intensity, or if its relationship to the investigational product changes, a new NSAE entry for the event should be completed. NSAEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for NSAEs that cause interruption or discontinuation of investigational product, or those that are present at the end of study participation. Subjects with NSAEs at study completion should receive post-treatment follow-up as appropriate.

7.4 Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. In general, non-clinically significant laboratory deviations are not considered adverse events. Laboratory deviations which require treatment delay, modification or discontinuation or are otherwise clinically significant should be reported as adverse events. When reporting a test result that constitutes an adverse event, the

clinical term should be used; for example, the event should be reported as "anemia" not "low hemoglobin." Test results that constitute SAEs should be documented and reported as such.

7.5 Overdose

An overdose is defined as the accidental or intentional ingestion or infusion of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

7.6 Pregnancy

Sexually active WOCBP must use an effective method of birth control during the course of the study, in such a manner that the risk of failure is minimized. (See Section 4.2.1 for the definition of WOCBP.) Before enrolling WOCBP in this study, investigators must review the BMS-provided information about study participation for WOCBP. The topics include the following:

- General Information
- Informed Consent Form
- Pregnancy Prevention Information Sheet
- Drug Interactions with Hormonal Contraceptives
- Contraceptives in Current Use
- Guidelines for the Follow-up of a Reported Pregnancy.

Before study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during study participation and of the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

7.6.1 Requirements for Pregnancy Testing

All WOCBP MUST have a negative pregnancy test within 7 days before receiving dasatinib. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG. If the pregnancy test is positive, the subject must not receive dasatinib and must not continue in the study.

In addition, all WOCBP must be instructed to contact the investigator and/or other study personnel immediately if they suspect they might be pregnant (eg, missed or late menstrual period) at any time during study participation.

7.6.2 Reporting of Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). The investigator must immediately notify BMS of this event and record the pregnancy on the Pregnancy Surveillance Form (not on an SAE

form). Initial information on a pregnancy must be reported immediately to BMS, and information on the outcome provided once it is available. Completed Pregnancy Surveillance Forms must be forwarded to BMS according to SAE reporting procedures.

Note: Any pregnancy that occurs in a female partner of a male study subject must be reported to BMS using the Pregnancy Surveillance Form.

Protocol-required procedures for study discontinuation and follow-up must be performed for the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. Information regarding the course of the pregnancy, including perinatal and neonatal outcome, must be reported to BMS on the Pregnancy Surveillance Form.

7.7 Other Safety Considerations

Any significant worsening of the subject's condition noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded in the medical record.

7.8 Data Safety Monitoring Plan

This protocol will adhere to the policies of the University of Florida Shands Cancer Center Data and Safety Monitoring Plan, in accordance with NCI regulations. The Data and Safety Monitoring Committee will review all serious adverse events and toxicity reports as well as annual reviews. The investigator will continuously monitor the progress of the study and the safety of the participants. All adverse events will be evaluated for causality and reported to the appropriate oversight committees as required.

7.9 Data Management System

To provide data collection we will utilize the ONCORE database for both accrual entry and trial data management. ONCORE is a Clinical Trials Management System designed with the capability for: study setup, activation, tracking, reporting, data monitoring and review and eligibility verification. It is housed on secured servers maintained at the University of Florida Health Science Center on the University of Florida campus. The e-CRFs on ONCORE are 21 CFR part 11 compliant, and all users are assigned password protected user accounts.

8 STATISTICAL CONSIDERATIONS

The primary statistical analysis will use the modified Intention-to-Treat (mITT) population consisting of patients who are enrolled and received any dose of study medication. The mITT population will be included in summary tables of patient demographics and disease characteristics, and in analysis of efficacy.

Statistical analyses will be conducted by the study biostatistician using SAS v9.1 (SAS

institute, Cary, NC).

Routine data listing or tabulation review during the study conduct will be performed to identify missing data, anomalies, outliers, etc. Missing data will generally not be imputed. Baseline is defined as the last non-missing measurement for a variable prior to the initial dose of any investigational product.

Descriptive statistics will be provided to summarize demographic and baseline characteristic parameters. Categorical data will be summarized as frequency and its corresponding percentage. For continuous data, frequency (n), mean, standard deviation, median (as appropriate), minimum, and maximum will be provided for each parameter.

8.1 Sample Size Determination

The sample size of 42 patients for this prospective non-randomized phase 2 study is based on the assumptions of a 30-month accrual period and a follow-up of 6 months after the last patient is enrolled. This sample size will allow detection of median PFS of 6 months or greater with a 50% increase in comparison to historical controls (4 months), with a one-sided log-rank test at the 0.05 significance level and a power of 80%. At an attrition rate of 5%, 48 patients will be recruited.

8.2 Analysis of Primary Endpoint

PFS is defined as the time from treatment start to the first of either (1) documented disease progression or (2) death as a result of any cause. Patients who did not progress nor die or are lost to follow-up will be censored at the day of their last objective tumor assessment. The Kaplan-Meier method will be used to estimate the median PFS time, together with a 95% confidence interval (CI). PFS will be determined by RECIST criteria.

8.3 Analysis of Secondary Endpoints

The objective RR is equal to the proportion of patients achieving a best overall response of partial or complete response (CR + PR), according to RECIST from the start of the treatment until disease progression/recurrence. Clinical benefit rate is equal to the objective RR plus the proportion of patients attaining stable disease (CR + PR + SD). Patients who do not have a tumor response assessment for any reason will be considered nonresponders and will be included in the denominator when calculating the response rate. The number of patients achieving a response will be divided by the total of patients treated to yield the proportion responding. Exact confidence bounds (95% CI) will be calculated.

Overall survival is defined as the time from the date of treatment start to the date of death from any cause. If the patient is alive at the end of the follow-up period or is lost to follow-up, OS will be censored on the last date the patient is known to be alive. OS will be evaluated by the Kaplan-Meier method and a 2-sided 95% CI will be provided for the median OS.

The time to progression (TTP) for responders only is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that the criteria for PD are met, or death. TTP will be estimated with the Kaplan-Meier method; a 90% CI will be provided for the median TTP. Patients who do not relapse are censored at the day of their last objective tumor assessment. The freedom from metastasis rate is defined below and will be calculated based on an intention to treat principle. Determination of the anatomic site of first failure for patients with PD will be recorded and analyzed. Duration of response is also defined below.

Proportion and exact confidence boundaries (95% CI) will be estimated for toxicity and compliance with oral therapy. Mean and 95% confidence interval will be estimated for quality of life (QOL). QOL measurements will be analyzed with regards to changes from baseline including total scores as well as subscores consistent with the previously validated instruments in use.

8.4 Analysis of Safety Data

Safety analyses will be performed on all patients who receive any dose of study medication. Adverse events that occur more than 30 days after the administration of the last dose of treatment will not be included.

The safety and tolerability of study drug is determined by reported AEs, physical examinations, laboratory tests, and ECGs. All patients will be assessed regularly for potential occurrence of AEs from the time that treatment starts until 30 days after the last dose of study therapy. AEs will be summarized with the incidence and percentage of patients with at least one occurrence of a preferred term (according to the most severe NCI-CTCAE Version 4.0 grade) will be included. The number of AEs reported will also be summarized. Causality (relationship to study drug) will be summarized separately. Duration of AE will be determined and included in listings along with action taken and outcome. Laboratory AEs will be monitored from the time that treatment starts until 30 days after the last dose of study therapy. Laboratory results will be classified according to NCI-CTCAE, Version 4.0. Incidence of laboratory abnormalities will be summarized; laboratory results not corresponding to an NCI-CTCAE Version 4.0 term will not be graded. Laboratory toxicity shifts from baseline to worst grade will also be provided. The results from physical examination and vital sign measurement will be tabulated. Descriptive statistics will be provided as appropriate.

8.5 Duration of Response and Other Endpoint Definitions

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

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

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

Rate of freedom from metastasis (FFM) is defined as the proportion of patients with documentation of progression of disease, during study participation, in whom no new lesions appeared.

In rare situations where PD or other endpoints could not be clearly assessed, the PI will review the records with the treating physician and provide a clinical judgment for purposes of endpoint documentation.

9 ADMINISTRATIVE SECTION

9.1 Compliance with the Protocol

The study must be conducted as described in the final IRB/IEC-approved protocol. Documentation of approval, signed by the IRB/IEC chairperson or designee, will be sent to the BMS protocol manager.

All protocol amendments and revisions to the informed consent will be submitted to the BMS protocol manager and to the IRB/IEC. No protocol amendments will be implemented until written approval has been given by the IRB/IEC, except when necessary to eliminate an immediate hazard to study subjects. Administrative letters should also be sent to the BMS protocol manager and IRB/IEC; however, they do not require approval.

If a protocol amendment mandates a revision to the informed consent, the revised consent must be used to obtain consent from subjects currently enrolled in the study if it affects them (eg, if it contains new information regarding safety), and the revised consent must be used to obtain consent from new subjects before enrollment.

9.2 Records Retention

The investigator will retain, in a confidential manner, all data pertinent to the study for all treated subjects as well as those entered as control subjects. The investigator will retain source documents and accurate case histories that record all observations and other data pertinent to the investigation (eg, the medical record) for the maximum period required by applicable regulations and guidelines or following institutional procedures. If the investigator withdraws from the study (eg, relocation or retirement), the records will be transferred to a mutually agreed upon designee, such as another investigator or an IRB. Written documentation of such transfer will be provided to BMS.

The investigator will ensure that a current record of disposition of investigational product is maintained at each study site where the 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 identification number or batch number and use date or expiry date
- dates and initials of person responsible for each 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 (eg, lost, wasted, broken)
- amount destroyed at study site, if applicable, and
- 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.

9.3 Destruction of Investigational Product

If the investigational product is to be destroyed on site, 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.

Consult with the PI for instructions on disposal of unused dasatinib tablets.

10 GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or the sponsor to be related to the investigational product
Expedited Safety Report	Rapid notification to investigators of all SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the Investigator Brochure), or that could be associated with the study procedures.
SUSAR	Suspected, Unexpected, Serious Adverse Reaction as termed by the European Clinical Trial Directive (2001/20/EC).
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product)

11 LIST OF ABBREVIATIONS

AE	Adverse event
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
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EKG	Electrocardiogram
ESR	Expedited Safety Report
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
HCG	Human Chorionic Gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HRT	Hormone Replacement Therapy
IB	Investigators' Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IST	Investigator-Sponsored Trial
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NSAE	Non-Serious Adverse Event
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
SUSAR	Suspected Unexpected Serious Adverse Reaction
TNM Staging	Tumor, Node and Metastasis Staging
ULN	Upper Limit of Normal
WBC	White Blood Count
WOCBP	Women of Child-Bearing Potential

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APPENDIX I. Performance Status

ECOG PERFORMANCE SCALE

0 - Fully active, able to carry on all predisease activities without restriction *(Karnofsky 90-100)*.

1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work *(Karnofsky 70-80)*.

2 - Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours *(Karnofsky 50-60)*.

3 - Capable of only limited self-care, confined to bed or chair 50% or more of waking hours *(Karnofsky 30-40)*.

4 - Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair *(Karnofsky 10-20)*.

5 – Deceased.

APPENDIX II. Dasatinib patient pill diary

Patient Pill Diary

	Dasatinib			
Day of Treatment	**Time**	**# 50mg pills taken**	**# 20mg pills taken**	**Comments**
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				

Patient's name_____Cycle # _____

Patient's signature_____Date_____

_____

Physician's Office will complete this section:

1. Complete dates: Start date_____End date _____
2. Total number of Dasatinib pills to be taken (per protocol) (50mg)_____(20mg)_____
3. Total number of Dasatinib pills taken (per protocol) (50mg)_____(20mg)_____
4. Compliance rate_____%

Physician/Nurse/Research Staff's Signature:

_____

APPENDIX III. Pancreatic Cancer Patient Quality of Life and Satisfaction Questionnaires

FACT-Hep (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-Hep (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel sad	0	1	2	3	4
GS2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GS3	I am losing hope in the fight against my illness	0	1	2	3	4
GS4	I feel nervous	0	1	2	3	4
GS5	I worry about dying	0	1	2	3	4
GS6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Hep (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C1	I have swelling or cramps in my stomach area	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C3	I have control of my bowels	0	1	2	3	4
C4	I can digest my food well	0	1	2	3	4
C5	I have diarrhea (diarrhoea)	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
Hep 1	I am unhappy about a change in my appearance	0	1	2	3	4
CNS 7	I have pain in my back	0	1	2	3	4
Cx6	I am bothered by constipation	0	1	2	3	4
H17	I feel fatigued	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
Hep 2	I am bothered by jaundice or yellow color to my skin	0	1	2	3	4
Hep 3	I have had fevers (episodes of high body temperature)	0	1	2	3	4
Hep 4	I have had itching	0	1	2	3	4
Hep 5	I have had a change in the way food tastes	0	1	2	3	4
Hep 6	I have had chills	0	1	2	3	4
HN 2	My mouth is dry	0	1	2	3	4
Hep 8	I have discomfort or pain in my stomach area	0	1	2	3	4

Cancer Therapy Satisfaction Questionnaire
US English

The following pages ask some questions about your cancer therapy (IV/pills). Within this questionnaire, "Cancer therapy (IV/pills)" refers to your current or most recent cancer therapy or cancer pills (including: hormonal therapy, IV therapy, and cancer pills). Please read each question and answer as honestly as you can without the help of anyone. There are no right or wrong answers; the answers should be based on your own personal experiences.

Your Thoughts about Cancer Therapy (IV/pills)

The following statements ask you to share your **thoughts about cancer therapy (IV/pills)**. Please answer each question below by *checking the box* that best represents your opinion (check only one box per question).

	In general, in the last four weeks, how *often did you feel*:	**Always**	**Most of the time**	**Some-times**	**Rarely**	**Never**
1.	That cancer therapy (IV/pills) would help you to return back to a normal life?	☐	☐	☐	☐	☐
2.	That cancer therapy (IV/pills) would get rid of the cancer?	☐	☐	☐	☐	☐
3.	That cancer therapy (IV/pills) would help prevent the cancer from coming back?	☐	☐	☐	☐	☐
4.	That cancer therapy (IV/pills) would stop the cancer from spreading?	☐	☐	☐	☐	☐
5.	That your cancer therapy (IV/pills) limited your daily activities?	☐	☐	☐	☐	☐
6.	Upset about the side effects?	☐	☐	☐	☐	☐
7.	That cancer therapy (IV/pills) was worth taking even with the side effects?	☐	☐	☐	☐	☐
8.	That cancer therapy (IV/pills) would help you live longer?	☐	☐	☐	☐	☐

9. In general, **in the last four weeks**, how often did you think about stopping your cancer therapy (IV/pills)?

☐ Always ☐ Most of the time ☐ Sometimes ☐ Rarely ☐ Never

Satisfaction with Cancer Therapy (IV/pills)

The following statements are about your satisfaction with your **most recent cancer therapy (IV/pills)**. Please answer each question below by *checking the box* that best describes your level of satisfaction (check only one box per question).

10. **Overall**, how worthwhile was your cancer therapy (IV/pills)?

☐	☐	☐	☐	☐
Very worthwhile	Quite worthwhile	Moderately worthwhile	A little worthwhile	Not worthwhile at all

11. **Overall,** was taking cancer therapy (IV/pills) as difficult as you expected?

☐	☐	☐	☐	☐
Much more difficult than I thought it would be	Somewhat more difficult than I thought it would be	As difficult as I thought it would be	Somewhat easier than I thought it would be	Much easier than I thought it would be

12. **Overall,** how well did the **benefits** of cancer therapy (IV/pills) meet your expectations?

☐	☐	☐	☐	☐
Much better than my expectations	Somewhat better than my expectations	Met my expectations	Somewhat worse than my expectations	Much worse than my expectations

13. **Overall,** were the **side effects** of cancer therapy (IV/pills) as you expected?

☐	☐	☐	☐	☐
Much better than I expected	Somewhat better than I expected	Exactly as I expected	Somewhat worse than I expected	Much worse than I expected

14. How satisfied were you with the **form** of your cancer therapy (IV/pills)?

☐	☐	☐	☐	☐
Very satisfied	Satisfied	Neither satisfied nor dissatisfied	Dissatisfied	Very dissatisfied

15. **Overall,** how satisfied were you with your most recent cancer therapy (IV/pills)?

☐	☐	☐	☐	☐
Very satisfied	Satisfied	Neither satisfied nor dissatisfied	Dissatisfied	Very dissatisfied

16. Taking everything into consideration, if given the choice again, would you decide to take this cancer therapy treatment?

☐	☐	☐	☐	☐
Yes, definitely	Probably Yes	I don't know	Probably not	Definitely not

Thank you.