Overview

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Title: Phase II Study of Dasatinib (BMS-354825) in Patients with Metastatic Adenocarcinoma of the Pancreas

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Author Summary: Abstract and Brief Discussion

Background
Src, erythropoietin-producing hepatoma (EphA2), and platelet-derived growth factor receptors (PDGFR)–alpha and –beta are dysregulated in pancreatic ductal adenocarcinoma (PDAC). Dasatinib is an oral multitarget tyrosine kinase inhibitor (TKI) that targets BCR-ABL, c-Src, c-KIT, PDGF-β receptor and EphA2. We conducted a phase II, single-arm study of dasatinib as first-line therapy in patients with metastatic PDAC.

Methods
Dasatinib (100 mg twice a day, later reduced to 70 mg twice a day due to toxicities) was orally administered continuously on a 28-day cycle. Primary endpoint was overall survival (OS). Response was measured using RECIST criteria. Circulating tumor cells (CTCs) were also collected.

Results
Fifty-one patients enrolled in this study. The median OS was 4.7 months (95% CI 2.8–6.9 months). The median progression-free survival was 2.1 months (95% CI 1.6–3.2 months). In 34 evaluable patients, the best response achieved was stable disease (SD) in 10 patients (29.4%). One patient had stable disease while on treatment for 20 months. The most common non-hematologic toxicities were fatigue and nausea. Edema and pleural effusions occurred in 29% and 6% of patients, respectively. The number of CTCs did not correlate with survival.

Conclusions

Single-agent dasatinib does not have clinical activity in metastatic PDAC.

Discussion

This study was a phase II study using a targeted agent as first-line monotherapy for metastatic PDAC. Despite being a chemotherapy-naïve study, the study met its accrual goal of 49 patients. At the time of this study, single-agent gemcitabine was considered the standard of care in the first-line setting for metastatic PDAC and with the postulated mechanism of action of dasatinib in preclinical PDAC models, this agent was felt to be promising. Unfortunately, single-agent dasatinib did not show clinical activity in patients with metastatic PDAC (median OS: 4.7 months, 95% CI 2.8–6.9 months) (Figure 1). A sustained durable response was observed in one patient who received 20 months of dasatinib. There were 6 patients who lived for more than 20 months after discontinuation of therapy. It is unknown if this could be attributed to sustained response from dasatinib, subsequent lines of therapy or disease biology. The adverse events at least possibly related to dasatinib were as expected based on prior studies with dasatinib [1–2]. Fluid retention is a common side effect of dasatinib. The rate of pleural effusion in this study was lower (6%) compared to prior studies with dasatinib (10%–26%) [1–2], possibly due to the short duration that patients were on dasatinib in this study (31–49.5 days) compared with patients on dasatinib for chronic myelogenous leukemia (CML) (42 weeks) [3]. The rates of grade 1–2 edema were higher in this study (29%) compared with studies of dasatinib in non-small cell lung cancer (3%) [1] and CML (9%) [2]. One possible explanation for worsening rates of edema observed in this study is that patients with PDAC often have low albumin levels, which can contribute to edema. For hematologic toxicities, the adverse events were comparable to other solid tumor studies with dasatinib [1]. In 19 patients with available samples, CTC number at baseline, measured by CellSearch technology (Veridex LLC, Raritan, NJ), did not correlate with survival. This was likely due to the small number of patients and lack of sensitivity of the detection platform in pancreas cancer (median: 1, range: 0–5 in 7 mL of blood). In conclusion, single-agent dasatinib did not show clinical activity as first-line therapy in patients with metastatic PDAC. The limited single-agent activity of dasatinib is likely due to the mechanisms of resistance to Src inhibition that have been associated with a lack of inhibition of activated STAT3 signaling [4].

Trial Information

Disease:	Pancreatic cancer
Stage of disease / treatment:	Metastatic / Advanced
Prior Therapy:	None
Type of study - 1:	Phase II
Type of study - 2:	Single Arm
Primary Endpoint:	Overall Survival
Secondary Endpoint:	Progression Free Survival
Secondary Endpoint:	Overall Response Rate
Secondary Endpoint:	Correlative Endpoint
Additional Details of Endpoints or Study Design:	Statistical Analysis: Overall survival (OS) was calculated from the start of treatment to the date of death and censored at the date of last follow-up for survivors. Time to disease progression (progression free survival-PFS) was calculated from the start of treatment to the date of disease progression or the date of death, whichever came first, and censored at the date of last follow-up for those alive and without disease progression. Assessments were performed every two cycles (8 weeks, 56 days). Probability of survival was estimated by Kaplan-Meier method [16] and the difference of survival between groups was examined by log-rank test. The predictive value of CTC on survival outcomes was evaluated by Cox proportional hazard models [17]. The difference of CTC between baseline and post-treatment time points was examined by paired T-test. All tests are two-sided and p-values $\leq$ 0.05 were considered statistically significant.
Investigator's Analysis:	Inactive because results did not meet primary endpoint

Drug Information

Drug 1:	
Generic/Working name:	Dasatinib
Trade name:	Sprycel
Company name:	Bristol-Myers Squibb
Drug type:	Small molecule
Drug class:	BCR-Abl
Dose:	per
Route:	
Schedule of Administration:	

Patient Characteristics

Number of patients, male:	17
Number of patients, female:	34
Stage:	IV
Age:	Median (range): 61 (43-80)
Number of prior systemic therapies:	Median (range): 0
Performance Status:	ECOG **0** — 23 **1** — 20 **2** — 6 **3** — **unknown** — 2
Other:	Not Collected
Cancer Types or Histologic Subtypes:	**Adenocarcinoma of the pancreas**: 51

Primary Assessment Method

Experimental Arm: Adenocarcinoma Of The Pancreas

Number of patients screened:	76
Number of patients enrolled:	51
Number of patients evaluable for toxicity:	49
Number of patients evaluated for efficacy:	34
Evaluation method:	Other
Response assessment CR:	0%
Response assessment PR:	0%
Response assessment SD:	29.4%
Response assessment PD:	70.6%
Response assessment other:	0%
(Median) duration assessments PFS:	2.1 months, CI: 1.6–3.2
(Median) duration assessments TTP:	
(Median) duration assessments OS:	4.7 months, CI: 2.8–6.9
(Median) duration assessments response duration:	
(Median) duration assessments duration of treatment:	

Experimental Arm: Total Patient Population

Number of patients screened:	
Number of patients enrolled:	
Number of patients evaluable for toxicity:	
Number of patients evaluated for efficacy:	
Evaluation method:	Other
Response assessment CR:	
Response assessment PR:	
Response assessment SD:	
Response assessment PD:	
Response assessment other:	
(Median) duration assessments PFS:	
(Median) duration assessments TTP:	
(Median) duration assessments OS:	
(Median) duration assessments response duration:	
(Median) duration assessments duration of treatment:	

Adverse Events

Name	*NC/NA	1	2	3	4	5	All Grades

*No Change from Baseline/No Adverse Event

Adverse Events Legend:	Please see table 2

Serious Adverse Events

Name	Grade	Attribution

Assessment, Analysis, and Discussion

Completion:	Study completed
Pharmacokinetics / Pharmacodynamics:	Not Collected
Investigator's Assessment:	Inactive because results did not meet primary endpoint

Discussion

Currently, the only targeted agent approved for used in metastatic PDAC is erlotinib in combination with gemcitabine, which showed minimal overall survival (OS) benefit over gemcitabine alone (HR 0.82) [5]. Based on preclinical studies, PDAC is thought to be driven by multiple perturbations of cell growth and regulation, including many of the proteins potentially affected by dasatinib. This was a phase II, open-label, single-agent, noncomparative trial designed primarily to determine overall survival in treatment-naïve patients with metastatic PDAC who received oral dasatinib on a 28-days continuous cycle. The justification for using survival rather than objective response as the primary endpoint was the historical low response rates (RR) observed in clinical trials with this malignancy (approximately 8%–10% complete + partial RR) [5] and the observation that patients may derive survival or clinical benefit without a tumor response [5–6].

Baseline patient characteristics of 51 patients treated with dasatinib are presented in Table 1. The study was opened in May 2007 and completed accrual in July 2011. Median age was 61 years (range: 43–80 years) and median follow-up was 4.7 months (range: 1–34 months). The study dose of dasatinib was based on phase I studies in solid tumors and differed from standard doses used in chronic myeloid leukemia (CML) (100–180 mg daily). The first 13 study patients received dasatinib 100 mg twice a day, but due to toxicities observed at this dose in other clinical trials with dasatinib, the starting dose was reduced to 70 mg twice a day ($n = 38$). Despite being a first-line nonchemotherapy study, the study met its accrual goal of 49 patients. This study was a rare example of a "window of opportunity" trial, which allowed evaluation of a new molecular entity in tumors unperturbed by previous therapies. With the superiority of current standard of care chemotherapy such as FOLFIRINOX [7] (OS = 11.1 months) and nab-paclitaxel/gemcitabine [8] (OS = 8.5 months) over gemcitabine alone (OS = 6 months) [9–12], the median OS of 4.7 months achieved with dasatinib in this study is lower than current standard benchmarks. Unfortunately, the search for molecular targets in metastatic PDAC remains elusive as promising preclinical models have not translated to an improvement in clinical outcomes.

There was no difference in duration of treatment, efficacy and survival in patients who initially received dasatinib 100 mg twice a day vs. 70 mg twice a day (data not shown). For treatment response in 34 evaluable patients in whom a second CT scan was obtained prior to cycle 3, the best response achieved was stable disease (SD) in 10 patients. Reasons for treatment discontinuation included: disease progression ($n = 35$), adverse events ($n = 9$), patient withdrawal ($n = 5$) and no initiation of therapy ($n = 2$). On long-term follow-up, there were 9, 6, and 2 patients who lived for more than 12, 20, and 30 months, respectively. Of the 6 patients who had an OS of $>$20 months, all 6 patients proceeded to gemcitabine-based second-line therapy and 3 patients received 5-FU-based third-line chemotherapy. It is uncertain if the prolonged survival could be attributed to sustained response from dasatinib, subsequent lines of therapy received or disease biology. The patient who had the longest OS of 34 months had a time-to-progression of 3 months with SD as the best response achieved. This patient was discontinued from study due to disease progression and subsequently received gemcitabine/erlotinib, capecitabine, nab-paclitaxel, and irinotecan. One patient had SD for up to 20 months while on study treatment and then progressed a proceeded to second-line therapy with gemcitabine. It was observed that patients who received second-line therapy had improved survival compared to those who did not proceed with second-line therapy (data not shown). This is likely a selection bias in view that those who were able to receive second-line therapy were likely to have better performance status and therefore obtained clinical benefit compared with those who were too debilitated to receive additional treatment.

The adverse events (AEs) at least possibly related to dasatinib were as expected based upon prior studies with dasatinib (Table 2) [1, 2]. Fluid retention is a common side effect of dasatinib. The rate of pleural effusion in this study was lower (6%) compared with prior studies of dasatinib (10%–26%) [1–2], likely due to the short duration of drug exposure in this study (31–49.5 days), compared with patients on dasatinib for CML (42 weeks)[3]. It was not surprising that the initial dose of dasatinib 100 mg twice a day was reduced to 70 mg twice a day due to toxicities, as it has been shown in CML that grade $\geq$3 pleural effusions occurred in 78% of patients with initial daily dasatinib of at least 140 mg [3]. The rates of grade 1-2 edema were higher with this study (29%) compared to studies with dasatinib in non-small cell lung cancer (3%) [1] and CML (9%) [2], possibly from low albumin levels often seen in this patient population. Low serum albumin has been associated with early mortality in pancreatic cancer [13]. Fatigue, nausea, vomiting, and diarrhea were noted to be much higher in this study compared with other studies of dasatinib [1,2]. For hematologic toxicities, the AEs were comparable to other solid tumor studies of dasatinib[1].

CTCs were detectable in this study. Mean number of CTCs per 7 mL was 1.58 (range: 0–5) and 3.1 (range: 0–13) in pretreatment ($n = 19$) and post-treatment (at 4 weeks) specimens ($n = 10$), respectively. No difference in survival was found when baseline CTCs were stratified by $<$3 vs. $\geq$3 ($p = 0.26$). Unlike in metastatic colorectal cancer [14] and breast cancer [15] where CTCs are independent predictors of survival, the prognostic role of CTCs remains unclear in pancreatic cancer.

In conclusion, single-agent dasatinib did not show clinical activity as first-line therapy in patients with metastatic PDAC. The limited single-agent activity of dasatinib is likely due to the mechanisms of resistance to Src inhibition which have been associated with a lack of inhibition of activated STAT3 signaling [4].

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Figures and Tables

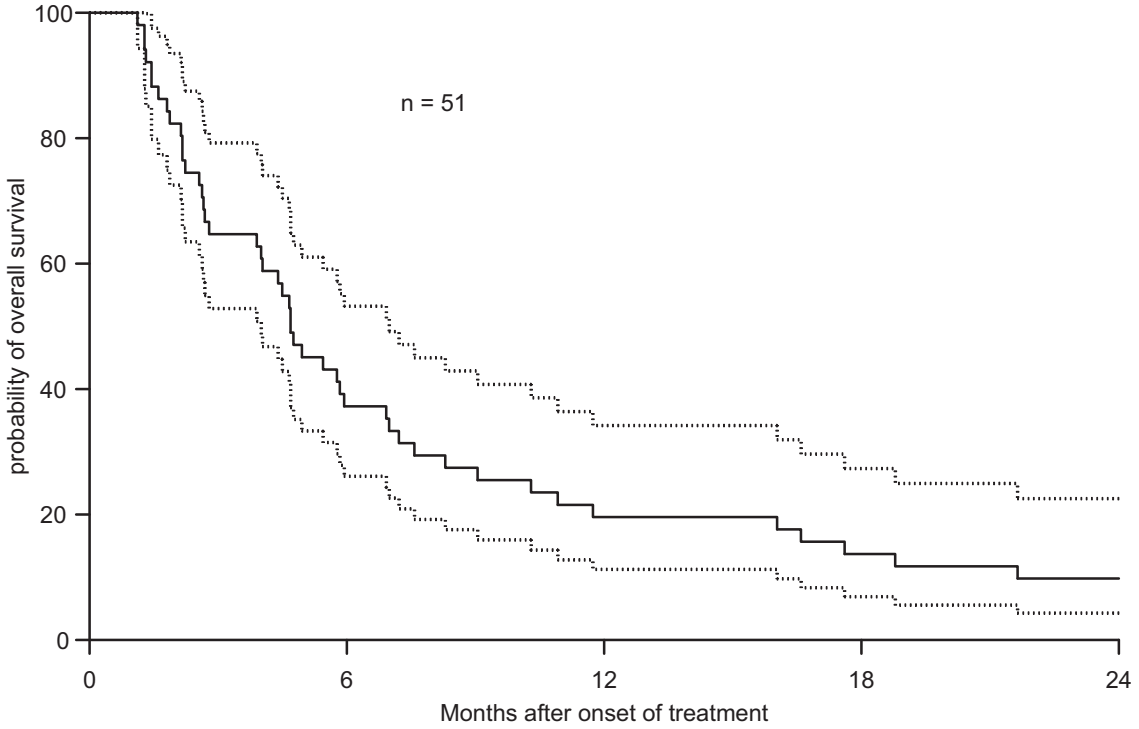

Figure 1. Kaplan-Meier estimates of overall survival with 95% confidence interval (dashed lines)
Overall Survival (median 4.7 months, 95% CI 2.8–6.9 months)

Table 1. Baseline characteristics.

Characteristic	No. of patients (n = 51)	%
Age, years		
< 65	29	57
≥ 65	22	43
Sex		
Female	34	67
Male	17	33
Ethnicity		
White	46	90
Black	4	8
Unknown	1	2
N stage		
N0	11	21
N1	9	18
Nx	31	61
M stage		
M0	10	20
M1	22	43
Mx	19	37
ECOG Performance status		
0	23	45
1	20	39
2	6	12
Unknown	2	4
CA 19-9 (U/mL)		
	7	14
	14	27
	23	45
	7	14

ULN = upper limits of normal.

Table 2. Drug-related adverse events.

	Grade 1/2		Grade 3		Grade 4		All grades	
Toxicity	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Respiratory								
Dyspnea	5	10					5	10
Pleural effusion	2	4	1	2			3	6
Gastrointestinal								
Nausea	26	51	2	4			28	55
Vomiting	20	39	3	6			23	45
Abdominal pain	13	25	3	6			16	31
Diarrhea	14	27	2	4			16	31
Anorexia	16	31	2	4			18	36
Dehydration	8	16	3	6			11	22
Weight loss	10	20					10	20
Small intestine obstruction			1	2			1	2
Elevated AST	15	29	3	6			18	35
Elevated ALP	12	24	2	4			14	28
Elevated bilirubin	2	4	1	2			3	6
Skin								
Edema	15	29					15	29
Rash	18	35					18	35
Hematologic								
Anemia	18	35	1	2			19	37
Lymphopenia	8	16	3	6			11	22
WBC decreased	9	18					9	18
Thrombocytopenia	11	22					11	22
Other								
Thromboembolic event	2	4	1	2	2	4	5	10
Generalized muscle weakness	6	12	1	2	1	2	8	16
Fatigue	22	43	6	12			28	55
Headache	5	10					5	10

* Only toxicities listed as least possibly related to study drug are listed.
**AST = aspartate aminotransferase; ALP = alkaline phosphatase; WBC = white blood cell.