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Title: Phase 2 Placebo-Controlled, Double-Blind Trial of Dasatinib Added to Gemcitabine for Patients with Locally-Advanced Pancreatic Cancer

Author list: T. R. J. Evans [1], E. Van Cutsem [2], M. J. Moore [3], I. S. Bazin [4], A. Rosemurgy [5], G. Bodoky [6], G. Deplanque [7], M. Harrison [8], B. Melichar [9], D. Pezet [10], A. Elekes [11], E. Rock [11], C. Lin [11], L. Strauss [12], P. J. O'Dwyer [13]

Affiliations: [1] CR-UK Beatson Institute, University of Glasgow, Glasgow UK; [2] University Hospitals Leuven and KU Leuven, Leuven, Belgium; [3] Princess Margaret Cancer, Toronto, ON, Canada; [4] Federal State Budgetary Institution, Dubna, Russia; [5] Florida Hospital, Tampa, Tampa, FL, USA; [6] St.László Teaching Hospital, Budapest, Hungary; [7] Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; [8] East and North Hertfordshire NHS Trust, Northwood, Middlesex, UK; [9] Lekarska Fakulta Univerzity Palackeho a Fakultni Nemocnice, Olomouc, Czech Republic; [10] CHU Estaing, Clermont-Ferrand, France; [11] Otsuka Pharmaceutical Development and Commercialization, Princeton, New Jersey, USA; [12] Lewis Strauss, Bristol-Myers Squibb Company, Princeton, NJ, USA; [13] Abramson Cancer Center, University of Pennsylvania, Philadelphia PA, USA.

Corresponding author:

Dr. T. R. Jeffrey Evans, M.D.

CR-UK Beatson Institute

University of Glasgow

Garscube Estate, Switchback Road

Glasgow, G61 1BD United Kingdom

Telephone: +44 141 330 4890; Email: J.Evans@beatson.gla.ac.uk

ABSTRACT

Background: Pancreatic ductal adenocarcinoma (PDAC) has a high mortality rate with limited treatment options. Gemcitabine provides a marginal survival benefit for patients with advanced PDAC. Dasatinib is a competitive inhibitor of Src kinase, which is overexpressed in PDAC tumors. Dasatinib and gemcitabine were combined in a phase 1 clinical trial where stable disease was achieved in 2 of 8 patients with gemcitabine-refractory PDAC.

Patients and methods: This placebo-controlled, randomized, double-blind, phase II study compared the combination of gemcitabine plus dasatinib to gemcitabine plus placebo in patients with locally advanced, non-metastatic PDAC. Patients received gemcitabine 1,000 mg/m2 (30-minute IV infusion) on days 1, 8, 15 of a 28-day cycle combined with either 100 mg oral dasatinib or placebo tablets daily. The primary objective was overall survival (OS), with safety and progression-free survival (PFS) as secondary objectives. Exploratory endpoints included overall response rate, freedom from distant metastasis, pain and fatigue progression and response rate, and CA19-9 response rate.

Results: There was no statistically significant difference in OS between the 2 treatment groups (HR = 1.16; 95% confidence interval [CI]: 0.81–1.65; p=0.5656). Secondary and exploratory endpoint analyses also showed no statistically significant differences. The burden of toxicity was higher on the dasatinib arm.

Conclusions: Dasatinib failed to show increased OS or PFS in patients with locally advanced PDAC. Alternative combinations or trial designs may show a role for src inhibition in PDAC treatment.

Key words: dasatinib, gemcitabine, pancreatic cancer, anticancer therapy

Key message: Adding dasatinib to gemcitabine did not improve progression-free or overall survival in patients with locally advanced inoperable, non-metastatic pancreatic cancer.

BACKGROUND

Pancreatic ductal adenocarcinoma (PDAC) is characterized by aggressive invasion and early metastases. Overall survival remains poor in patients with inoperable, locally advanced, or metastatic PDAC. Gemcitabine remains one therapeutic option for patients with advanced PDAC and provides a marginal survival advantage [1, 2]. Among other therapeutic options, two combination regimens have further extended survival prolongation of gemcitabine [3, 4]. Chemoradiation may increase locoregional control in PDAC (at the cost of considerable toxicity), but this approach does not address the principal mode of treatment failure in locally advanced PDAC, which is development of distant metastases.

Src-family kinases are non-receptor tyrosine kinases with a critical role in cellular proliferation [5-7]. Src is involved in many aspects of tumor cell behavior that influence metastatic capacity, such as survival, adhesion, migration, and invasion. Furthermore, Src is over-expressed in PDAC [8, 9]. Compared with normal pancreatic ducts, increased expression and activation of Src were observed in 74% and 60% of tumors, respectively, correlating with reduced survival in resected PDAC [10]. Moreover, gemcitabine chemo-resistance in PDAC cell lines was associated with increased Src kinase activity [11]. Src kinase inhibition enhances gemcitabine-induced cytotoxicity in vitro, and significantly increases tumor growth inhibition in orthotopic models in vivo in combination with gemcitabine compared to either agent alone [11].

Dasatinib, a competitive inhibitor of Src and Abl kinases [12, 13], represents an effective therapy for chronic myelogenous leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia [14-18]. Treatment of pancreatic cancer cell lines in vitro with dasatinib inhibits invasion and migration at concentrations that inhibit Src kinase activity [10, 19], as well as proliferation and anchorage-independent cell growth [19, 20]. Dasatinib inhibits pancreatic tumor growth in vivo in xenograft models [19, 20] and inhibits the development of metastases in vivo in

a genetically-engineered mouse model of pancreatic cancer [10], suggesting that this agent might best be used in patients without metastatic disease to prevent development of distant metastases. Unpublished data from the first author's laboratory suggests that there was a trend to improved overall survival with the combination of gemcitabine and dasatinib compared to dasatinib alone in a genetically-engineered mouse model of pancreatic cancer that did not reach statistical significance ($p = 0.08$).

Dasatinib and gemcitabine were combined in 2 phase 1 clinical trials. In the first study, recommended combination doses were dasatinib 100 mg by mouth (PO) daily and gemcitabine 600 mg/m2 intravenously (IV) weekly for the first 7 of 8 weeks, and dose limiting toxicities included fatigue and dehydration [21]. Stable disease was achieved in 2 of 8 patients with gemcitabine-refractory PDAC. In a second phase 1 combination trial, recommended combination doses were dasatinib 100 mg daily by mouth, and gemcitabine 1,000 mg/m2 for 3 weeks out of 4 and dose-limiting toxicities included neutropenia with infection, elevation of ALT, and pneumonitis [22]. The current phase 2 clinical trial compared the combination of gemcitabine plus dasatinib to gemcitabine plus placebo in patients with locally advanced, non-metastatic PDAC. The primary objective was overall survival (OS), with comparison of safety and progression-free survival (PFS) as secondary objectives. Exploratory objectives included freedom from distant metastases (FFDM), pain, fatigue, CA19-9 response rates, and objective responses.

PATIENTS AND METHODS

Patients

This placebo-controlled, randomized, double-blind, multi-center, phase II study was conducted in accordance with Good Clinical Practice (GCP) guidelines and approved by the research ethics committees at each of the participating institutions. All patients provided written, informed

consent prior to undergoing any study-related procedures.

Eligible patients had pathologically-proven PDAC with unresectable disease due to local extension, invasion, or lymph node involvement beyond the surgical field but had no evidence of metastatic disease based on imaging assessments. Additional eligibility criteria are included in supplementary information.

Study Design

Patients were randomized 1:1 to receive gemcitabine 1,000 mg/m2 (30-minute IV infusion) on days 1, 8, and 15 of a 28-day cycle combined with either 100 mg oral dasatinib (dasatinib group) or placebo tablets (placebo group) daily with breakfast (Figure 1). Stratification factors included baseline ECOG PS of 0 versus 1 and intent to administer radiotherapy (yes/no). At the investigator's discretion, patients without evidence of metastatic disease after 6 cycles of treatment had the option to receive radiotherapy with conventional fractionation with or without concomitant 5-FU or capecitabine chemotherapy starting within 3 weeks of cycle 6 study therapy. Gemcitabine and dasatinib/placebo were interrupted during radiotherapy and resumed within 6 weeks after radiotherapy completion. Study treatment continued until progressive disease (PD), withdrawal of consent, or unacceptable toxicity.

Dose delays and dose modifications were based on observed toxicities (supplementary methods Tables S1-S3) and subsequent treatment is described in supplementary information.

Evaluations and Response Assessment

Pre-treatment evaluation included a complete history and physical examination, vital signs, assessment of PS, blood counts, biochemical profile, coagulation screen, electrocardiograms, serum CA19-9 analysis, urinalysis, pregnancy test (if appropriate), and assessment of pain and fatigue (10-point numeric scales). Toxicity was graded using the National Cancer Institute

Common Toxicity Criteria (NCI-CTCAE) Version 3.0.

Radiologic studies to evaluate disease sites were performed within 14 days prior to dosing on day 1, and every 8 weeks until disease progression, determined by RECIST v1.1 [23]. Other assessments are included in supplementary information.

Statistical Hypothesis and Analyses

All analyses were performed on an intent-to-treat basis. OS was determined from the date of randomization until death (any cause) and analyzed by the log rank method. Hazard ratio was estimated using the Cox proportional hazards model with the following predictors: treatment, baseline ECOG, geographical region, CA19-9, and whether radiotherapy was received during the trial. A sample size of 200 patients was sufficient to demonstrate an increase in median OS from 10 to 13.3 months (Hazard Ratio [HR] = 0.75) with 79% power using a 1-sided α of 0.2. This sample size would have 88% power to detect an increase in PFS from 5 to 7 months (HR = 0.714; 1 sided α = 0.15).

PFS was defined as the time from randomization until local or distant disease progression (RECIST v1.1). Additional analyses are included in the supplementary information.

RESULTS

Patients

A total of 280 patients were screened, and 202 patients were enrolled at 79 trial sites in 15 countries in Australasia, Europe, and North America (Figure 2). Intent-to-treat groups for analysis consisted of 100 patients assigned to receive gemcitabine plus dasatinib (dasatinib group) and 102 assigned to receive gemcitabine plus placebo (placebo group). Three patients, 2 in the dasatinib group and 1 in the placebo group, did not receive study treatment and were not included in safety analyses.

Median age of enrolled patients was 65 years (range 37-87), and 51% were male (Table 1). A higher proportion of patients were male in the dasatinib arm (57% vs 45%). ECOG PS was evenly distributed between groups with approximately 61% of patients in each group having a score of 1. Other prognostic factors were balanced, except that more patients in the dasatinib group had stage II disease (75% vs 68%). Median treatment duration of treatment with dasatinib or placebo was 4 and 5 cycles, respectively. Dose reduction of dasatinib was required in 34% of patients, and of placebo in 23% of patients. Median gemcitabine treatment duration was 5 cycles in both dasatinib and placebo groups. Dose reduction of gemcitabine was required in 42% of patients in each of the two groups. Radiotherapy was administered in 37 patients (18, dasatinib group; 19, placebo group), and more than 90% of the planned radiotherapy dose was administered in 34 patients. Concomitant chemotherapy was administered in 31 patients (12, dasatinib; 19, placebo), and more than 90% of the planned radio-sensitizing chemotherapy was administered in 27 patients.

Efficacy Analyses

At the data cut-off date of December 2, 2013, there was no significant difference in OS between the dasatinib and placebo groups (375 days vs 393 days, HR = 1.16; 95% confidence interval [CI]: 0.81–1.65; p=0.5656) (Figure 3A, Table 2). There was also no significant difference in the median PFS of 167 and 166 days for dasatinib- and placebo-treated patients, respectively (HR = 1.03; 95% CI: 0.76–1.39; p=0.8731) (Figure 3B). Additionally, in a population exclusive of patients with treatment discontinuation for reasons other than disease progression, median PFS was 221 and 218 days for dasatinib- and placebo-treated patients, respectively (HR = 0.99; 95% CI: 0.68–1.43; p=0.7058).

Overall response rates were 11% in the dasatinib group and 8% in the placebo-treated group (p=0.4392) (Table 2). No statistical difference was observed in other exploratory endpoints,

including FFDM, pain progression, pain response, fatigue response, and CA19-9 response rates. A statistically non-significant difference was observed in median FFDM at 310 days for dasatinib- (n= 32/99) and 380 days for placebo- (n= 32/102) treated patients (p=0.7994). There was no difference in the CA 19-9 response.

Safety analysis

Treatment-emergent adverse events (TEAEs) of any cause occurred in 99% and 98% of patients in dasatinib and placebo groups, respectively (Table 3). In the dasatinib group, TEAEs Grade 3 occurring in ≥10% of patients include neutropenia (33% of patients), fatigue (16%), thrombocytopenia (13%), anemia (12%), and abdominal pain (10%); in the placebo group, they include neutropenia (26%) and thrombocytopenia (11%). Potential treatment-related AEs were more common in the dasatinib group (79% vs 64% of patients) (See supplemental results table). Overall, 31 patients (32%) in the dasatinib group discontinued treatment due to an AE versus 25 patients (25%) in the placebo group. The most common TEAEs leading to treatment discontinuation in dasatinib and placebo groups include pleural effusion (2 and 2 patients), peripheral edema (2 and 1), and vomiting (2 and 0), respectively.

Cardiopulmonary events have been noted for drugs in this class. No QT prolongation or ventricular arrhythmia events were reported. Hemorrhage, cardiac disorders, thromboembolic events, and pulmonary arterial hypertension were infrequent. Myelosuppression was frequent, occurring more within the dasatinib group (52% vs 29%). Fluid retention also occurred frequently, with both peripheral edema and pleural effusions being more common in the dasatinib group (34% vs 21% and 27% vs 7%, respectively). Additional safety analyses are included in the supplementary information.

DISCUSSION

In vitro and in vivo studies support a role for dasatinib in inhibiting the development of metastases in PDAC. Dasatinib decreases cell proliferation, cell cycle progression, anchorage independent growth, migration, and invasion in PDAC cell lines in vitro [10, 19] and significantly inhibited the development of metastases in vivo with no effect on overall survival, probably due to progression of the primary tumor. Thus, there is evidence to support the hypothesis that Src kinase inhibitors may function as anti-metastatic agents in PDAC [10]. Consequently, this study was designed to determine if dasatinib could inhibit the development of metastases and improve overall survival if the growth of the primary tumor could be adequately controlled by gemcitabine in patients with inoperable, locally advanced, non-metastatic PDAC. Combined chemotherapy and radiotherapy could be administered (intention to treat prior to randomisation) at the investigator's discretion to maximise recruitment across international sites in some of which chemo-radiation was standard of care for this patient population. Our study was closed to recruitment prior to the first presentation of the LAP-07 study [24]. Nevertheless, the hypothesis of our study was that the addition of dasatinib would inhibit the development of metastases, thereby improving survival, if local disease control was optimised. The combination of chemotherapy and radiotherapy may still have a role in optimising local control, even if the results of the LAP 07 study suggests that this does not lead to a survival benefit.

Addition of dasatinib to gemcitabine did not improve overall survival of patients with locally-advanced pancreatic cancer in this study versus placebo in combination with gemcitabine. Secondary and exploratory endpoint analyses, including PFS, overall response rate, FFDM, pain progression and response rate, fatigue progression and response rate, and CA19-9 response rate also showed no statistically significant differences between the two groups. Observed toxicities were consistent with the known safety profiles of dasatinib and gemcitabine

in patients with solid tumors and revealed no new safety concerns [13, 21, 25].

Several possible explanations account for the lack of a survival benefit in this study. First, recommended doses from the phase I study were dasatinib 100 mg PO daily and gemcitabine 600 mg/m2 IV weekly for 7 of the first 8 weeks [21]. We used a higher dose of gemcitabine (1,000 mg/m2 on days 1, 8, 15 of a 28-day cycle) as we were concerned that a dose of 600 mg/m2 IV weekly would be sub-therapeutic as first-line therapy of patients with PDAC when combined with a placebo in this double-blind study. Patients treated with 1,000 mg/m2 of gemcitabine in combination with dasatinib had a higher incidence of Grade 3 TEAEs, as well as of TEAEs that led to treatment discontinuation. In addition, fewer patients in the dasatinib group completed dosing cycles for both dasatinib and gemcitabine treatment compared with the placebo group. Therefore, it may be that because this combination was not well tolerated, administration of adequate chemotherapy for control of the primary tumor and of dasatinib to inhibit development of metastases may have been compromised.

Data on subsequent treatments administered was not routinely collected after disease progression, a trial-specific endpoint for treatment discontinuation, was met. However, we think it is unlikely that any imbalance in second-line treatments between the two treatment arms will have obscured any significant difference in overall survival in the absence of any significant difference in progression-free survival with study therapy, especially given the modest, if any, survival benefit with second-line therapy in this disease at the time that the study was conducted.

Newer combination chemotherapy regimens, such as FOLFIRINOX, generate higher objective response rates and disease control in patients with metastatic disease. A more appropriate future study design to test the hypothesis that dasatinib inhibits the development of metastases may be to administer dasatinib as “maintenance” therapy, sequentially rather than in combination, after optimal control of localized non-metastatic disease with this more active

chemotherapy regimen. For example, maintenance treatment with sunitinib in pancreatic adenocarcinoma may have inhibited the development of metastases and improved 2-year survival [26]. Alternatively, it may be more appropriate to evaluate dasatinib as a post-operative adjuvant treatment to improve overall survival by inhibiting metastases [2]. Although we enrolled patients without clinically- or radiologically-visible metastases in our study, it is possible that sub-clinical metastases were already present. Dasatinib may be more effective at inhibiting presumed micro-metastatic disease following potentially curative resection.

There is little evidence to support that Src pathway activation is a predictive marker for dasatinib activity. Given the paucity of archival tumour material that is invariably available for patients with inoperable, non-metastatic pancreatic cancer, and the lack of a robust predictive marker hypothesis, we did not think it justified to pursue mandatory additional pre-treatment tumor biopsies for exploratory research in this study

In conclusion, addition of dasatinib to gemcitabine failed to increase OS or PFS in patients with locally-advanced PDAC. Because this trial did not include pharmacodynamics, it is not possible to conclude whether dasatinib penetration of the tumor was adequate to inhibit tumoral Src. Conversely, the dasatinib-gemcitabine combination generated increased toxicity relative to gemcitabine alone. This toxicity burden led to earlier discontinuation of combination therapy and likely contributed to the failure to improve OS. Alternative clinical trial designs with other drug combinations or sequenced schedules of administration could be pursued to further define a role for Src inhibition in PDAC treatment via metastasis inhibition.

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Disclosure

B. Melichar served as a consultant and received honoraria from Lilly, Novartis, Roche, Pfizer, Bayer, BMS, Astellas, GSK, and Amgen. I. Bazin serve on Speakers' Bureau at Bayer and has research funding from Merck Serono and Bayer. G. Bodoky served as a consultant to Bayer, Roche, Novartis, Janssen, and Lilly. G. Deplanque: research funding from Bavarian Nordic, Genentech, Janssen Cilag, Roche, Lilly, Exelixis, Sotio, and Merck Serono. C. Lin, E. Rock, and A. Elekes are employees of Otsuka Pharmaceutical Development & Commercialization. L. Strauss is an employee of Bristol-Myers Squibb. M. J. Moore, E. Van Cutsem, A. Rosemurgy, and D. Pezet have no conflicts of interest to report. T.R.J. Evans' employing institution have received honoraria from Bristol-Myers Squibb and Celgene for whom he has served as a consultant and on Speakers' Bureau, and from whom he has received support to attend international scientific conferences.

REFERENCES

1. Burris HA, 3rd, Moore MJ, Andersen J et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997; 15: 2403-2413.

2. Cid-Arregui A, Juarez V. Perspectives in the treatment of pancreatic adenocarcinoma. World J Gastroenterol 2015; 21: 9297-9316.

3. Von Hoff DD, Ervin T, Arena FP et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013; 369: 1691-1703.

4. Conroy T, Desseigne F, Ychou M et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011; 364: 1817-1825.

5. Frame MC. Src in cancer: deregulation and consequences for cell behaviour. Biochim Biophys Acta 2002; 1602: 114-130.

6. Thomas SM, Brugge JS. Cellular functions regulated by Src family kinases. Annu Rev Cell Dev Biol 1997; 13: 513-609.

7. Summy JM, Gallick GE. Src family kinases in tumor progression and metastasis. Cancer Metastasis Rev 2003; 22: 337-358.

8. Lutz MP, Esser IB, Flossmann-Kast BB et al. Overexpression and activation of the tyrosine kinase Src in human pancreatic carcinoma. Biochem Biophys Res Commun 1998; 243: 503-508.

9. Hakam A, Fang Q, Karl R, Coppola D. Coexpression of IGF-1R and c-Src proteins in human pancreatic ductal adenocarcinoma. Dig Dis Sci 2003; 48: 1972-1978.

10. Morton JP, Karim SA, Graham K et al. Dasatinib inhibits the development of metastases in a mouse model of pancreatic ductal adenocarcinoma. Gastroenterology 2010; 139: 292-303.

11. Duxbury MS, Ito H, Zinner MJ et al. Inhibition of SRC tyrosine kinase impairs inherent and acquired gemcitabine resistance in human pancreatic adenocarcinoma cells. Clin Cancer Res 2004; 10: 2307-2318.

12. Lombardo LJ, Lee FY, Chen P et al. Discovery of N-(2-chloro-6-methyl- phenyl)-2-(6-(4-(2-hydroxyethyl)- piperazin-1-yl)-2-methylpyrimidin-4- ylamino)thiazole-5-carboxamide (BMS-354825), a dual Src/Abl kinase inhibitor with potent antitumor activity in preclinical assays. J Med Chem 2004; 47: 6658-6661.

13. Demetri GD, Lo Russo P, MacPherson IR et al. Phase I dose-escalation and pharmacokinetic study of dasatinib in patients with advanced solid tumors. Clin Cancer Res 2009; 15: 6232-6240.

14. Cortes J, Rousselot P, Kim DW et al. Dasatinib induces complete hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in blast crisis. Blood 2007; 109: 3207-3213.

15. Guilhot F, Apperley J, Kim DW et al. Dasatinib induces significant hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in accelerated phase. Blood 2007; 109: 4143-4150.

16. Hochhaus A, Kantarjian HM, Baccarani M et al. Dasatinib induces notable hematologic and cytogenetic responses in chronic-phase chronic myeloid leukemia after failure of imatinib therapy. Blood 2007; 109: 2303-2309.

17. Ottmann O, Dombret H, Martinelli G et al. Dasatinib induces rapid hematologic and

cytogenetic responses in adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia with resistance or intolerance to imatinib: interim results of a phase 2 study. Blood 2007; 110: 2309-2315.

18. Talpaz M, Shah NP, Kantarjian H et al. Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. N Engl J Med 2006; 354: 2531-2541.

19. Nagaraj NS, Smith JJ, Revetta F et al. Targeted inhibition of SRC kinase signaling attenuates pancreatic tumorigenesis. Mol Cancer Ther 2010; 9: 2322-2332.

20. Desgrosellier JS, Barnes LA, Shields DJ et al. An integrin alpha(v)beta(3)-c-Src oncogenic unit promotes anchorage-independence and tumor progression. Nat Med 2009; 15: 1163-1169.

21. Hong DS, Choe JH, Naing A et al. A phase 1 study of gemcitabine combined with dasatinib in patients with advanced solid tumors. Invest New Drugs 2013; 31: 918-926.

22. Uronis HE, Bullock K, Blobe G et al. A phase I study of gemcitabine plus dasatinib (GD) or gemcitabine plus dasatinib plus cetuximab (GDC) in refractory solid tumors J Clin Oncol 2009; 27: e15506.

23. Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-247.

24. Hammel P, Huguet F, van Laethem JL et al. Effect of chemoradiotherapy vs chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: The LAP07 Randomized Clinical Trial. JAMA 2016; 315: 1844-1853.

25. Chee CE, Krishnamurthi S, Nock CJ et al. Phase II study of dasatinib (BMS-354825) in patients with metastatic adenocarcinoma of the pancreas. Oncologist 2013; 18: 1091-1092.

26. Reni M, Cereda S, Milella M et al. Maintenance sunitinib or observation in metastatic pancreatic adenocarcinoma: a phase II randomised trial. Eur J Cancer 2013; 49: 3609-3615.

Table 1. Baseline Patient Characteristics.

	Dasatinib + Gemcitabine (n=100)	Placebo + Gemcitabine (n=102)	Total (n=202)
Age, median (range)	65 (37–86)	66 (38–87)	65 (37–87)
Sex, n (%)			
Male	57 (57)	46 (45)	103 (51)
Female	43 (43)	56 (55)	99 (49)
Race, n (%)			
White	96 (96)	93 (91)	189 (94)
Black	1 (1)	5 (5)	6 (3)
Asian	1 (1)	0	1 (1)
Other	2 (2)	4 (4)	6 (3)
ECOG performance score, n (%)			
0	37 (37)	39 (38)	76 (38)
1	61 (61)	62 (61)	123 (61)
Tumor stage, n (%) [a]			
≤ IIB	24 (24)	33 (32)	57 (28)
III	75 (75)	69 (68)	144 (71)
Tumor location, n (%) [b]			
Head	75 (75)	77 (76)	152 (75)
Body	25 (25)	32 (31)	57 (28)
Tail	9 (9)	8 (8)	17 (8)
Radiotherapy intent, n (%)			
Yes	49 (49)	49 (48)	98 (49)
No	51 (51)	53 (52)	104 (52)

ECOG, Eastern Cooperative Oncology Group.

a. In addition, 1 patient in the dasatinib + gemcitabine arm did not have locally advanced stage tumor.

b. Total numbers exceed the number of patients and percentages exceed 100 as the primary tumor location may be recorded as present at more than one site (e.g. head and body).

Table 2. Summary of Efficacy.

	Dasatinib + Gemcitabine (n = 100)	Placebo + Gemcitabine (n = 102)	HR [a] or Relative Risk [c] (95% CI)	P-value [b]
Progression-free survival				
Number of events, n (%)	85 (85)	91 (89)	1.03	0.8731
Median, days (95% CI)	167 (114, 212)	166 (158, 199)	(0.76, 1.39)	
Overall survival				
Number of events, n (%)	69 (69)	66 (65)	1.16	0.5656
Median, days (95% CI)	375 (310, 462)	393 (356, 467)	(0.81, 1.65)	
Freedom from distant metastasis				
Number of events/n (%)	32/99 (32)	32/102 (31)	1.24	0.7994
Median, days (95% CI)	310 (246, 910)	380 (267, NA)	(0.74, 2.07)	
Pain progression				
Number of events (%)	16 (16)	23 (23)	0.68	0.2897
Median, days (95% CI)	NA (371, NA)	NA (NA, NA)	(0.36, 1.31)	
Fatigue progression				
Number of events (%)	22 (22)	24 (24)	1.04	0.9305
Median, days (95% CI)	NA (329, NA)	NA (296, NA)	(0.58, 1.87)	
Overall response, n (%)				
Number of events (%)	11 (11)	8 (8)	1.41 (0.592, 3.351)	0.4392
Complete response				
Number of events (%)	0 (0)	0 (0)	NA	NA
Partial response				
Number of events (%)	11 (11)	8 (8)	1.41 (0.592, 3.351)	0.4392
Stable disease				
Number of events (%)	68 (68)	75 (74)	NA	NA

	Dasatinib + Gemcitabine (n = 100)	Placebo + Gemcitabine (n = 102)	HR [a] or Relative Risk [c] (95% CI)	P-value [b]
Progressive disease				
Number of events (%)	9 (9)	13 (13)	NA	NA
Pain response				
Number of events (%)	24 (24)	24 (24)	1.02 (0.622, 1.673)	0.9371
Fatigue response				
Number of events (%)	13 (13)	22 (22)	0.61 (0.328, 1.149)	0.1105
CA 19-9 response				
Number of events/n (%)	36/96 (38)	35/98 (36)	1.06 [d] (0.726, 1.537)	0.8538

CI, confidence interval.

a. Hazard ratio and its confidence interval is obtained from Cox proportional hazard model with treatment, baseline ECOG PS, region, CA 19-9 (<1000 iu/ml, >=1000 iu/ml), and RT received during the trial (yes or no) as predictors.

b. P-values are derived from log-rank test.

c. Relative risk, 95% confidence interval for relative risk and p-value were derived from Cochran-Mantel-Haenszel model stratified by radiotherapy received during the study (yes or no).

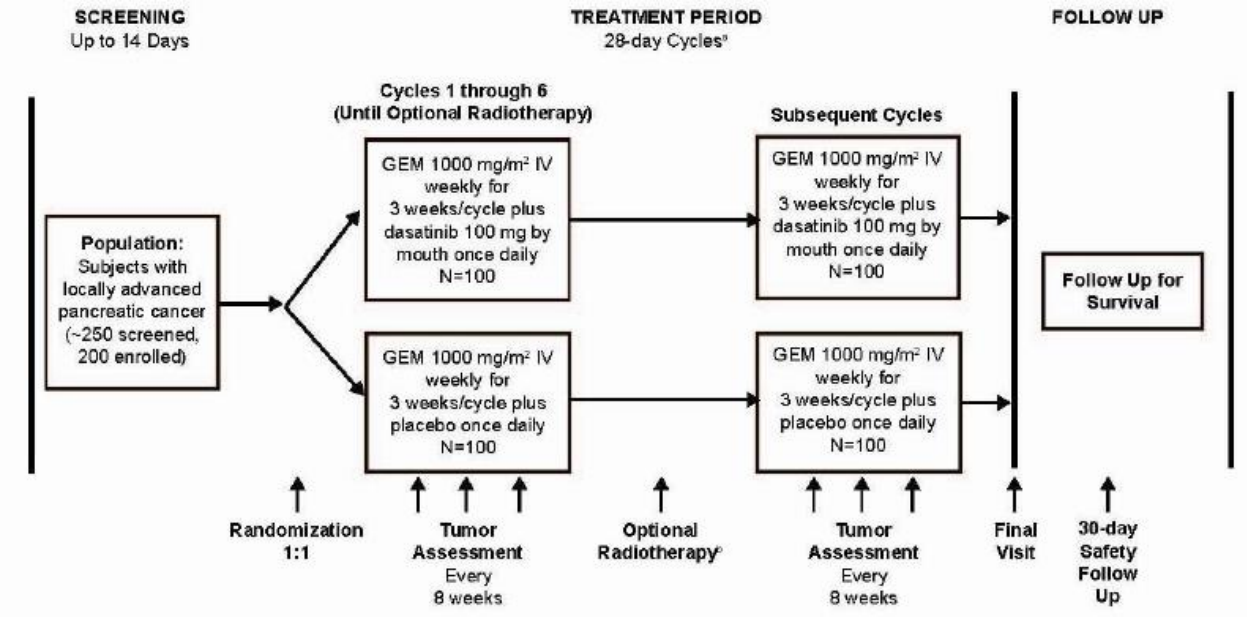
d. dRelative risk, 95% confidence interval for relative risk and p-value were derived from Cochran-Mantel-Haenszel model stratified by baseline CA 19-level (<1000 iu/ml, >=1000 iu/ml).

Table 3. Incidence of Treatment-Emergent Adverse Events Occurring in at Least 10% of Patients in Either Treatment Group (safety Population).

	Dasatinib +Gemcitabine (n = 98)		Placebo +Gemcitabine (n = 101)		Total (N=199)	
Adverse Event, n (%)	**All Grade**	**Grade ≥3**	**All Grade**	**Grade ≥3**	**All Grade**	**Grade ≥3**
Nausea	66 (67)	2 (2)	49 (49)	1 (1)	115 (58)	3 (2)
Neutropenia	53 (54)	32 (33)	49 (49)	26 (26)	102 (51)	58 (29)
Fatigue	48 (49)	16 (16)	46 (46)	9 (9)	94 (47)	25 (13)
Anemia	51 (52)	12 (12)	29 (29)	5 (5)	80 (40)	17 (9)
Vomiting	43 (44)	4 (4)	36 (36)	2 (2)	79 (40)	6 (3)
Thrombocytopenia	38 (39)	13 (13)	39 (39)	11 (11)	77 (39)	24 (12)
Abdominal pain	35 (36)	10 (10)	37 (37)	2 (2)	72 (36)	12 (6)
Diarrhea	42 (43)	6 (6)	29 (29)	1 (1)	71 (36)	7 (4)
Decreased appetite	46 (47)	2 (2)	23 (23)	2 (2)	69 (35)	4 (2)
Constipation	35 (36)	3 (3)	28 (28)	0 (0)	63 (32)	3 (2)
Peripheral edema	33 (34)	5 (5)	21 (21)	1 (1)	54 (27)	6 (3)
Pyrexia	22 (22)	1 (1)	31 (31)	2 (2)	53 (27)	3 (2)
Dyspnea	27 (28)	3 (3)	20 (20)	4 (4)	47 (24)	7 (4)
Increased alanine aminotransferase	22 (22)	9 (9)	14 (14)	3 (3)	36 (18)	12 (6)
Rash	20 (20)	0 (0)	14 (14)	0 (0)	34 (17)	0 (0)
Pleural effusion	26 (27)	6 (6)	7 (7)	0 (0)	33 (17)	6 (3)
Asthenia	16 (16)	4 (4)	16 (16)	4 (4)	32 (16)	8 (4)
Decreased weight	19 (19)	2 (2)	11 (11)	0 (0)	30 (15)	2 (1)
Abdominal pain upper	9 (9)	2 (2)	18 (18)	0 (0)	27 (14)	2 (1)
Increased aspartate	16 (16)	4 (4)	11 (11)	2 (2)	27 (14)	6 (3)

	Dasatinib +Gemcitabine (n = 98)		Placebo +Gemcitabine (n = 101)		Total (N=199)	
Adverse Event, n (%)	**All Grade**	**Grade ≥3**	**All Grade**	**Grade ≥3**	**All Grade**	**Grade ≥3**
aminotransferase						
Insomnia	11 (11)	1 (1)	14 (14)	0 (0)	25 (13)	1 (1)
Cough	12 (12)	0 (0)	13 (13)	0 (0)	25 (13)	0 (0)
Increased blood alkaline phosphatase	15 (15)	9 (9)	8 (8)	2 (2)	23 (12)	11 (6)
Hypokalemia	12 (12)	7 (7)	10 (10)	4 (4)	22 (11)	11 (6)
Leukopenia	8 (8)	5 (5)	13 (13)	7 (7)	21 (11)	12 (6)
Headache	12 (12)	0 (0)	9 (9)	0 (0)	21 (11)	0 (0)
Blood bilirubin increased	13 (13)	5 (5)	6 (6)	3 (3)	19 (10)	8 (4)
Dysgeusia	12 (12)	0 (0)	6 (6)	0 (0)	18 (9)	0 (0)
Flatulence	6 (6)	0 (0)	11 (11)	0 (0)	17 (9)	0 (0)
Alopecia	10 (10)	0 (0)	7 (7)	0 (0)	17 (9)	0 (0)
Dizziness	4 (4)	0 (0)	11 (11)	1 (1)	15 (8)	1 (1)
Anxiety	10 (10)	0 (0)	4 (4)	0 (0)	14 (7)	0 (0)

Figure 1. Study design.



GEM, gemcitabine.

a. Patients continued to receive trial treatment until disease progression, unacceptable toxicity, withdrawal of consent, or trial termination and were discontinued from trial treatment for disease progression when new cancer lesions were detected outside the loco-regional area (eg, in lung or liver) or when unequivocal evidence of local cancer progression was observed. Patients were followed for survival following cessation of trial therapy.

b. Radiotherapy performed at investigator's discretion for patients who showed no evidence of metastasis, beginning after Cycle 6 with trial treatment dosing interruption.

Figure 2. CONSORT diagram for the intent-to-treat analysis of data.

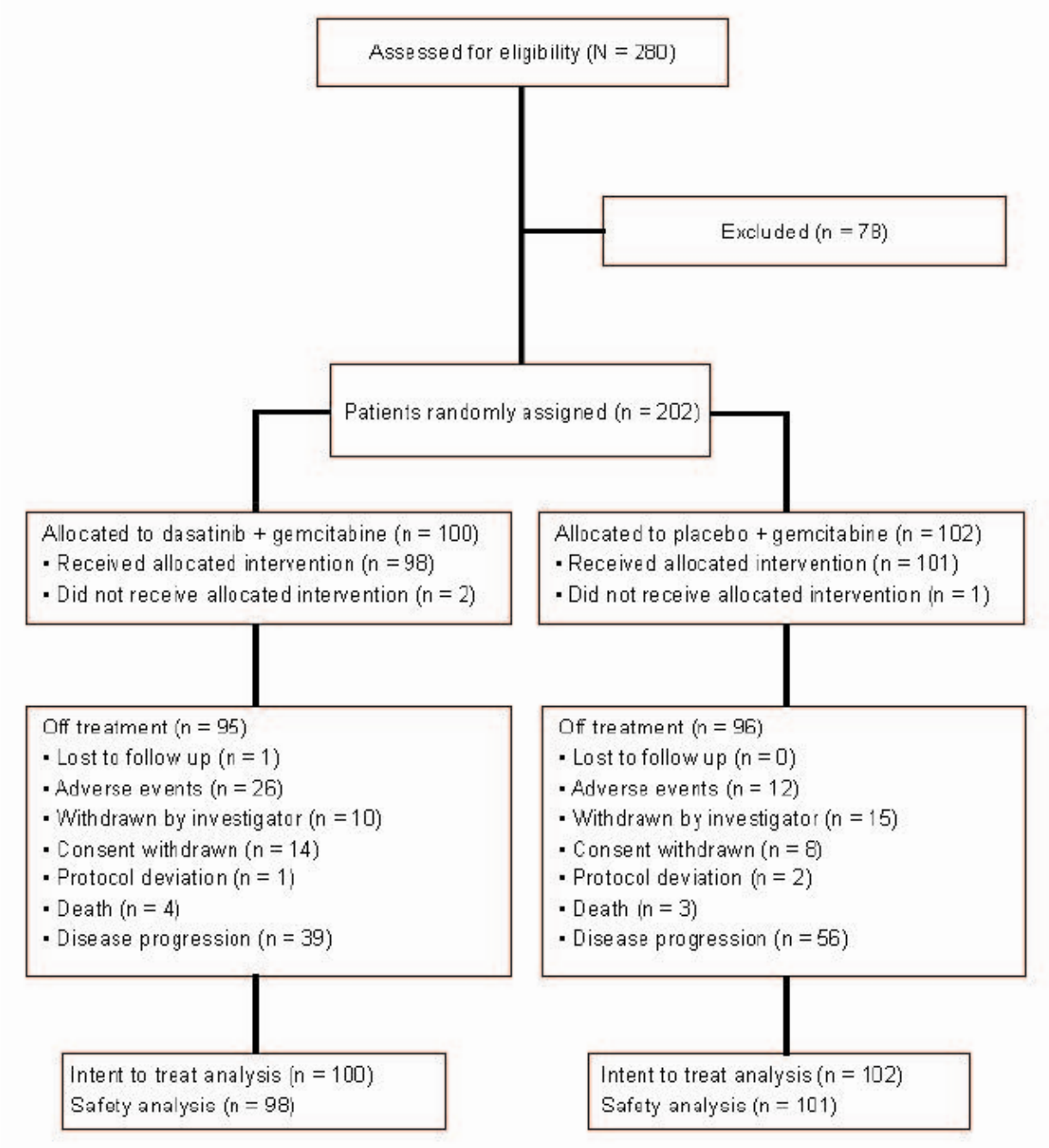
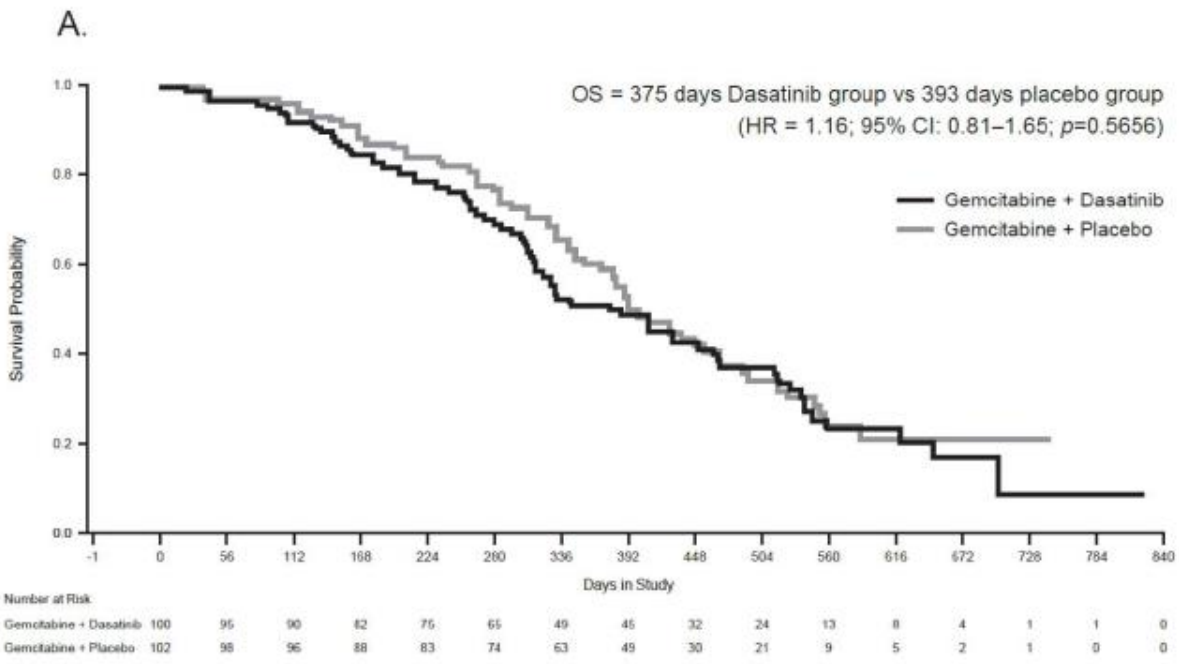
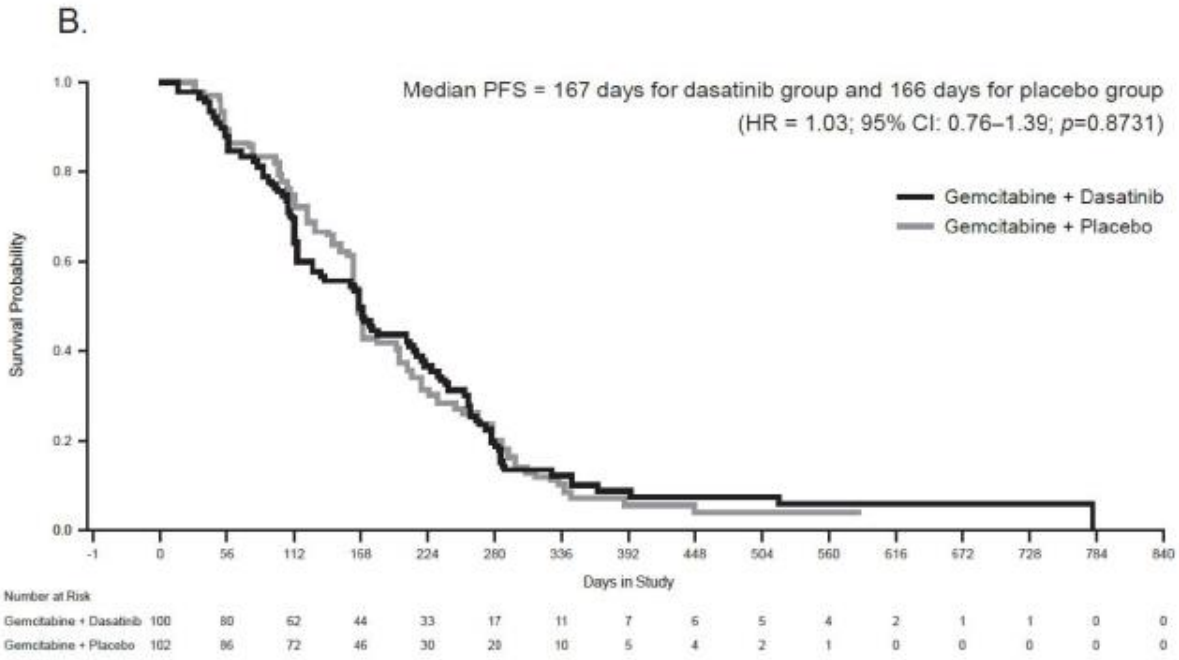


Figure 3. Kaplan-Meier Curve of Overall Survival (A) and Progression Free Survival (B).





SUPPLEMENTARY INFORMATION

Patients and Methods

Additional Eligibility Criteria

Patients were aged ≥18 years with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–1, adequate hematologic (absolute neutrophil count ≥100,000/μL), hepatic (bilirubin ≤2 x upper limit of normal [ULN]) aspartate transaminase (≤2.5 x ULN), and renal (creatinine ≤ 1.5 mg/dL) function, and had not received prior systemic treatment for pancreatic cancer.

Patients were excluded if they had significant cardiovascular disease (e.g. myocardial infarction, life-threatening arrhythmia, or QTc >470 msec within 6 months of study entry), a clinically significant bleeding disorder, requirement for a strong inhibitor of CYP3A4, or an inability to swallow or absorb oral medication. Patients who were pregnant or breastfeeding, or who were of childbearing potential but unwilling or unable to use adequate contraception, were also excluded.

Treatment following dose interruption

Following treatment interruptions for toxicity, missed doses of gemcitabine and/or dasatinib/placebo were not replaced. Study treatment was discontinued if there were treatment delays of both agents >4 weeks (other than for radiotherapy). If either agent was interrupted or discontinued due to drug-related toxicity, patients could continue on the other agent alone. If either agent was dose-reduced for toxicity, re-escalation could be considered if the adverse event (AE) was determined not to be drug-related.

Evaluations and Response Assessment

Pain response was defined as either a decrease of ≥2 points in pain score or 50% decrease in analgesia consumption along with stability of the other for ≥4 weeks. Fatigue response

was defined as a decrease of ≥2 points for ≥4 weeks, with progression defined as ≥2-point change for 4 weeks. Both pain and fatigue responses were recorded by the patients once weekly. CA19-9 was measured on day 1 of each cycle and response was defined as a ≥50% decrease in serum CA19-9 observed for at least 2 consecutive months.

Statistical Hypothesis and Analyses

Freedom from distant metastases (FFDM) was defined as the time from randomization until the unequivocal appearance of metastatic disease. Pain response, fatigue response, and CA19-9 response were analyzed by the Cochran-Mantel-Haenszel test, stratified by radiotherapy (pain and fatigue response analyses) and baseline CA19-9 (CA19-9 response analyses). Patients who discontinued for any reason other than death or progressive disease were followed for survival.

Results

Safety Analyses

Serious AEs were experienced by 53 patients (54%) in the dasatinib group and 48 patients (48%) in the placebo group. By the cutoff date of December 2, 2013, a total of 136 patients (67%) had died, including 9 patients (9%) in the dasatinib group and 10 patients (10%) in the placebo group who died as a result of TEAEs. Causes of deaths due to TEAE in the dasatinib and placebo groups included, respectively: cardiac failure and cardio-respiratory arrest (2 and 3 patients), gastrointestinal disorders including intestinal obstruction (1 and 1), multi-organ failure and sudden death (1 and 1), infections including peritonitis and pneumonia (0 and 2), renal failure (1 and 0), and respiratory disorders including pleural effusion and respiratory failure (1 and 1).