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Once-daily Dasatinib: Expansion of Phase II Study Evaluating Safety and Efficacy of Dasatinib in Patients With Metastatic Castration-resistant Prostate Cancer

Evan Y. Yu, Christophe Massard, Mitchell E. Gross, Michael A. Carducci, Stephane Culine, Gary Hudes, Edwin M. Posadas, Cora N. Sternberg, George Wilding, Géralyn C. Trudel, Prashni Paliwal, and Karim Fizazi

Division of Oncology, University of Washington, Seattle, Washington; Department of Medical Oncology, Institut Gustave Roussy, University of Paris, Villejuif, France; Cedars-Sinai Medical Center, Los Angeles, California; Department of Oncology, Johns Hopkins Kimmel Cancer Center, Baltimore, Maryland; Department of Oncology, CRLC Val d'Aurelle, Montpellier, France; Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania; Sections of Hematology/Oncology and Urology and Urology, University of Chicago, Chicago, Illinois; Department of Medical Oncology, San Camillo Fortanini Hospital, Rome, Italy; Department of Oncology, University of Wisconsin, Carbone Cancer Center, Madison, Wisconsin; and Bristol-Myers Squibb Research and Development, Wallingford, Connecticut, United States

Abstract

OBJECTIVES—To determine the activity and tolerability of 100-mg once-daily (QD) dasatinib in patients with metastatic castration-resistance prostate cancer (CRPC). Dasatinib, an oral Src family kinase inhibitor, has demonstrated both preclinical and clinical activity with twice-daily dosing in patients with metastatic CRPC.

METHODS—Chemotherapy-naive men with metastatic CRPC and increasing prostate-specific antigen levels were treated with dasatinib 100 mg QD. The primary measurement was a composite lack of disease progression, according to the Prostate Cancer Working Group 2 criteria, determined every 12 weeks during the study. The other analyses included changes in the prostate-specific antigen level, bone lesions, soft tissue disease, and bone turnover markers (urine N-telopeptide and bone alkaline phosphatase).

RESULTS—The present trial was designed before the publication of the recent Prostate Cancer Working Group 2 criteria; however, the analyses are presented to conform to the updated guidelines. A total of 48 patients received dasatinib. A lack of disease progression was observed in 21 patients (44%) at week 12 and in 8 (17%) at week 24. Urine N-telopeptide was reduced by 40% from baseline in 22 (51%) of 43 patients, and bone alkaline phosphatase was decreased in 26 (59%) of 44 patients. Dasatinib was well-tolerated, with only 6 patients (13%) with drug-related grade 3–4 adverse events and 3 (6%) with grade 3 adverse events. The most common treatment-related adverse events (20%) were fatigue, nausea, diarrhea, headache, and anorexia.

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Reprint requests: Evan Y. Yu, M.D., Division of Oncology, University of Washington School of Medicine, Seattle Cancer Care Alliance, Box 358081, 825 Eastlake Avenue East, G4-800, Seattle, WA 98109. evanyu@u.washington.edu.

G. C. Trudel is an employee of, and owns stocks in, Bristol-Myers Squibb; and P. Paliwal is an employee of Bristol-Myers Squibb.

E. Y. Yu, M. A. Carducci, E. M. Posadas, and G. Wilding are members of the Department of Defense-Sponsored Prostate Cancer Clinical Trials Consortium.

CONCLUSIONS—Dasatinib 100 mg QD has a favorable safety profile and maintains a similar degree of activity as the previously reported twice-daily dosing schedules. These data support additional study of dasatinib 100 mg QD for metastatic CRPC.

Prostate cancer (CaP) is the second-leading cause of cancer-related deaths in men in the Western world.¹ Metastases to the bone are common (~80%) and result in pain, fractures, hypercalcemia, spinal cord compression, and bone marrow insufficiency.² The current standard for the treatment of metastatic castration-resistant CaP (CRPC) is docetaxel chemotherapy, offering a modest survival benefit.^{3,4} Bone-targeting agents, such as bisphosphonates and denosumab, a nuclear factor- κ B ligand inhibitor, reduce the incidence of skeletal complications in patients with bone-metastatic CRPC.^{4–10} However, well-tolerated targeted therapies for metastatic CRPC are needed that offer dual antitumor and positive bone effects, delaying the time until chemotherapy initiation.

Dasatinib (Sprycel, Bristol-Myers Squibb, New York, NY) is an oral tyrosine kinase inhibitor with potent activity against the nonreceptor tyrosine kinases, c-Src and other Src family kinases.¹¹ Src and Src family kinase are located within several signaling pathways involved in CaP and promote tumor cell proliferation, survival, migration, and transition to androgen-independent growth.^{12,13} Dasatinib inhibits cancer cell proliferation, reduces CaP xenograft growth, and inhibits formation of lymph node metastases in androgen-sensitive and androgen-resistant tumors.^{11,12,14} In a C42B orthotopic nude mouse model of prostate bone tumors, dasatinib decreased the prostate-specific antigen (PSA), increased bone mineral density, decreased serum calcium, and potentiated the activity of docetaxel chemotherapy.¹⁵ In bone resorption assays, dasatinib reduced osteoclast proliferation and calcium release.¹⁶

A Phase II study (CA180085) was conducted to determine the clinical activity and safety of dasatinib. Yu et al¹⁷ reported the safety and activity of dasatinib at 100 mg and 70 mg twice-daily (BID). At these doses, dasatinib demonstrated biologic activity, as evidenced by decreases in bone turnover markers; however, toxicities (40% of patients) developed, including pleural effusions, fatigue, nausea, and diarrhea.¹⁷ Because of these toxicities and evidence from a dose-optimization study of chronic myelogenous leukemia that once-daily (QD) dasatinib can offer equal efficacy yet less toxicity,¹⁸ the trial was amended. In the present expansion cohort of patients, the goal was to determine whether 100 mg QD dosing would improve tolerability while maintaining the biologic (bone markers) and clinical (Prostate Cancer Working Group 2 [PCWG2] criteria¹⁹ of a lack of progression) activity.

MATERIAL AND METHODS

Patients

Male patients with histologically confirmed CaP, metastasis, and 2 serial increases in the PSA level with a castrate serum testosterone level of <50 ng/dL, were eligible. The patients with pleural or pericardial effusion were excluded. Other key inclusion/exclusion criteria have been previously described by Yu et al.¹⁷ Concomitant luteinizing hormone-releasing hormone agonists were continued for patients without surgical castration. The patients already receiving bisphosphonates were allowed to continue their use throughout the study. However, the treatment could not begin within 3 weeks of study entry or during the study period.

All patients provided written informed consent before enrollment into the trial. The ethics committees of all participating sites approved the study protocol. The clinical trials registry number was NCT00385580.

Study Design

The original study (CA180085) was a Phase II, open-label study conducted at 12 centers in the United States, Italy, and France. The protocol was amended to include the present cohort of patients who received dasatinib 100 mg QD.

Adverse events (AEs) were classified according to the National Cancer Institute Common Toxicity Criteria, version 3.0.²⁰ Dosing interruptions for drug-related toxicity were allowed, and patients could continue dasatinib when the toxicities had recovered to baseline or grade 1 or less. If unacceptable toxicity recurred despite optimal supportive care or if the toxicity was grade 3 or greater, the treatment was discontinued. Unlike the previously reported BID dosing regimen, dose reductions were not allowed for the new cohort.

Evaluation of Clinical Activity

The primary study endpoint was a composite endpoint (referred to as the composite response/stable disease [SD] rate), developed before the PCWG2 recommendations and defined as any of the following: (a) confirmed >50% PSA decline; (b) SD for any duration using the Response Evaluable Criteria in Solid Tumors (RECIST); (c) confirmed complete response or confirmed partial response using RECIST; or (d) confirmed disappearance of the lesions by radionuclide bone scan, at any point during the study period, including week 12. To follow the recent PCWG2 guidelines¹⁹ suggesting that Phase II trials should alter the focus from the measurement of response to the lack of progression, the data were reanalyzed and reported. The RECIST response and SD were considered in the definition of the lack of progression. The lack of progression using bone scans was assessed in combination with RECIST at multiple points. PSA changes were not included as a marker of response or progression and have been reported separately.

Tumor progression was defined according to the RECIST or as 1 definite new lesion on a bone scan. Patients continued therapy with asymptomatic increases in the PSA level or the appearance of new lesions on a bone scan before 24 weeks, provided they had no other evidence of progression (eg, RECIST findings or clinical symptoms). However, new lesions on a bone scan have been reported as progression, even if before the 24-week assessment.

The secondary endpoints included changes in the bone scan findings, RECIST, PSA level, and bone turnover markers (bone alkaline phosphatase [BAP] and urine N-telopeptide [uNTX]). The PSA levels were measured at the screening visit and every 4 weeks during the study. Serial bone scans were obtained approximately every 12 weeks, and the findings were classified as the disappearance of lesions, SD, or the appearance of new lesions. Investigators performed tumor assessments for the patients with measurable lesions at baseline and every 12 weeks using the modified RECIST.²¹ An analysis of the tumor measurements and a determination of the lack of response excluded pelvic lymph nodes <2 cm, according to the PCWG2 recommendations.¹⁹

The serum BAP and uNTX were measured at screening and every 4 weeks during the study to assess for treatment-related changes in bone metabolism. A 40% decrease in uNTX at 3 months was previously reported to be associated with a significant (17%) reduction in the risk of death, regardless of the baseline level.⁷ Therefore, patients with a 40% decrease in uNTX from baseline are reported. Additionally, because treatment-associated normalization of elevated uNTX has been shown to correspond with a 59% reduction in death and 49% increase in skeletal-related event (SRE)-free survival in men with CRPC,⁷ the proportion of patients with baseline uNTX levels greater than the upper limit of normal (63 nM/mmol creatinine), with a reduction to normal limits (3–63 nM/mmol creatinine) is also presented.

Statistical Analysis

Analyses of efficacy and safety were performed using all available data from patients treated with dasatinib. A 2-sided 95% exact confidence interval for the composite response/SD rate was calculated. The lack of progression was evaluated at 12 and 24 weeks, depending on the availability of the assessments. Statistical comparisons between the BID and QD groups were not predesignated in the protocol and were exploratory. Selected AE rates were compared using Fisher's exact test, and *P* values were calculated for descriptive purposes only. Therefore, no adjustment was made for multiple comparisons.

RESULTS

Patient Characteristics

From October 2006 to July 2008, 48 additional patients were enrolled and received 100 mg dasatinib QD. The median therapy duration was 3.98 months (range 0.10–14.7). At the database lock, February 19, 2009, 7 patients were continuing dasatinib. The last patient finished the study in January 2010. The baseline characteristics and demographic data are listed in Table 1. A flow chart is provided in Figure 1.

Efficacy

The original predefined primary endpoint of the composite response/SD rate, which included assessments at 12 weeks, was achieved in 12 (25%) of 48 patients (95% confidence interval 13.6%–39.6%). The protocol pre-specified that if the composite response/SD rate was 10% that additional study with dasatinib for this patient population would be futile. The PCWG2-defined endpoint of a lack of progression using both the RECIST and bone scan findings was met by 21 (44%) of 48 patients at week 12 and 8 (17%) of 48 patients at week 24. However, 6 patients (13%) continued with the study for >1 year without progression. The median interval to disease progression was 4.7 months (95% confidence interval 2.8–5.5).

All 48 patients had undergone a bone scan at baseline. Of the 40 patients evaluated by bone scan at week 12, 25 (52%) were reported to have no new lesions. At week 24, 21 patients were evaluated by bone scan, and 12 (25%) were reported to have no new lesions.

Of the 48 patients, 20 had RECIST-evaluable lesions at baseline. The disease control rate with confirmed measurable lesions by RECIST (complete response plus partial response, plus SD) was 40% (8 of 20) after 12 weeks. All 8 patients had SD. Of the remaining 12 patients, 8 (40%) had progression, and 4 (20%) were not evaluable. The 8 patients with SD at week 12 were evaluated again at week 24, for a disease control rate by RECIST of 15% (3 of 20, 1 with a confirmed partial response and with 2 SD); 3 (15%) others had progression, and 2 (10%) were not evaluable. The maximal percentage of change from baseline in tumor size is presented for the 16 men with measurable disease at baseline and 1 tumor assessment during the study period (Fig. 2A).

A confirmed PSA decline of 50% from baseline was observed in 1 patient (2%) with no other signs of clinical or radiographic progression. The maximal PSA change from baseline in the individual patients is shown in Figure 2B.

The patients receiving dasatinib exhibited decreased uNTX, independent of bisphosphonate use (Fig. 2C). The number of patients who achieved any decline in uNTX during the study was 33 (77%) of 43 patients. The number of patients who achieved a 40% reduction in uNTX during study was 22 (51%) of 43 patients. Of these 22 patients, 6 (50%) of 12 had received bisphosphonates and 16 (52%) of 31 had not. Seventeen patients had uNTx levels

greater than the upper limit of normal at baseline. Of these 17 patients, the only patient who was taking bisphosphonates and 9 (56%) of 16 who were not had a decline of uNTX into the normal range. All but 1 patient receiving bisphosphonates had started bisphosphonate therapy (zoledronate in 9 [75%] and aledronate in 3 [25%] of 12) >4 months before the initiation of dasatinib.

The maximal percentage of change in BAP for individual patients is presented in Figure 2D. The number of patients who achieved any decline of BAP during the study was 26 (59%) of 44. Reductions in BAP were achieved in 7 (58%) of the 12 patients taking bisphosphonates and 19 (59%) of the 32 patients who did not. Sixteen patients had levels greater than the upper limit of normal of BAP at baseline. Of these 16 patients, 2 (67%) of the 3 taking bisphosphonates had declines in BAP into the normal range, and 2 (15%) of the 13 who were not taking bisphosphonates had declines into the normal range.

Safety and Tolerability

The 100 mg QD dose of dasatinib was generally well-tolerated, and most AEs were grade 1 or 2, reversible, and clinically manageable. Grade 3–4 treatment-related serious AEs were reported in 3 men (6%): 1 (2%) grade 3 pleural effusion, 1 (2%) grade 4 anemia, and 1 (2%) grade 3 ischemia. Grade 1–2 hypocalcemia was experienced by 19 patients (40%); 1 patient (2%) developed transient grade 4 hypocalcemia. Other grade 3 laboratory AEs included hypokalemia in 2 (4%), hyponatremia in 1 (2%), and hypophosphatemia in 2 (4%). All laboratory-related AEs resolved without treatment or discontinuation of dasatinib. Two deaths (4%) unrelated to dasatinib (1 [2%] from septicemia/infection and 1 [2%] reported as unknown) were recorded within 30 days of the last dose of dasatinib.

COMMENT

In the present study, dasatinib, administered at a dose of 100 mg QD to patients with chemotherapy-naïve metastatic CRPC, produced signals of clinical activity. The PCWG2-defined endpoint of a lack of progression at 12 and 24 weeks was observed in 21 (44%) of 48 and 8 (17%) of 48 patients with QD dosing. The previously reported results were 20 (43%) of 47 and 9 (19%) of 47 patients with BID dosing.¹⁷

The present trial was designed before the publication of the PCWG2 criteria¹⁹ and did not require confirmation of bone scan progression. More specifically, only 1 new lesion was considered progression before the use of the PCWG2 criteria, which has recommended 2 new lesions, generally confirmed 6 weeks later with an additional 2 new lesions. Thus, dasatinib's effect in preventing tumor progression might have been underestimated compared with contemporary clinical trials using the PCWG2 criteria. The median duration of therapy was 3.98 months for the 100 mg QD dose and 2.78 and 2.68 months for the previously reported 70 mg and 100 mg BID doses, respectively.

Given the high incidence of bone morbidity in patients with CaP, we studied the biologic activity of dasatinib by evaluating the bone turnover markers. The reduction of SREs and bone pain associated with bone metastases are important goals to improve the quality of life and potentially extend the survival of patients with CRPC.^{4,7,17,22–26} Increased levels of the bone resorption marker, uNTX, has been correlated with the presence and extent of bone metastases.⁷ Moreover, normalization of uNTX in response to treatment has been associated with significant palliative responses, delays in bone disease progression, a trend toward fewer fractures, and a trend toward improved overall survival.^{4,7,27,28} The uNTX results with QD dasatinib (51% of patients achieved a 40% decrease in uNTX at 12 weeks) was exactly the same with the previously reported BID dosing.¹⁷

Osteoblastic activity was also measured using the prognostic marker, BAP, whose levels have been correlated with the risk of SREs²⁹ and interval to disease progression³⁰ in patients with CaP. In the present analysis, 59% of patients demonstrated a reduction in BAP. This result also agrees with the previously published BID results showing 63% of patients with a reduction in BAP levels.

In a post hoc analysis of these 2 separate cohorts, the safety profile (any drug-related AEs) of the 100 mg QD dose was generally more tolerable than the pooled 70 and 100 mg BID doses ($P = .06$; Tables 2 and 3). By reducing dasatinib from BID to QD, the number of patients experiencing drug-related grade 3 or 4 AEs decreased from 32% to 13% ($P = .03$). The occurrence of pleural effusion decreased from 51% to 19% ($P = .001$) for the pooled 70 and 100 mg BID and 100 mg QD dosing, respectively. Although the differences between the QD and BID dosing are apparent in Table 2, the present study was not designed to compare safety across the different doses and the P values are for descriptive purposes only.

CONCLUSIONS

The final results from the present study have demonstrated the biologic activity and tolerability of dasatinib at a dose of 100 mg QD. The bone and potential anti-tumor effects of dasatinib support the clinical and pre-clinical results that dasatinib is a potent inhibitor of Src and other Src family kinases.^{12,14,15} Additionally, the 100 mg QD dose demonstrated activity with a more acceptable toxicity profile than the previously pooled BID doses. Future clinical trials with dasatinib evaluating survival, bone biomarkers, and SREs are proceeding with 100 mg QD dosing.

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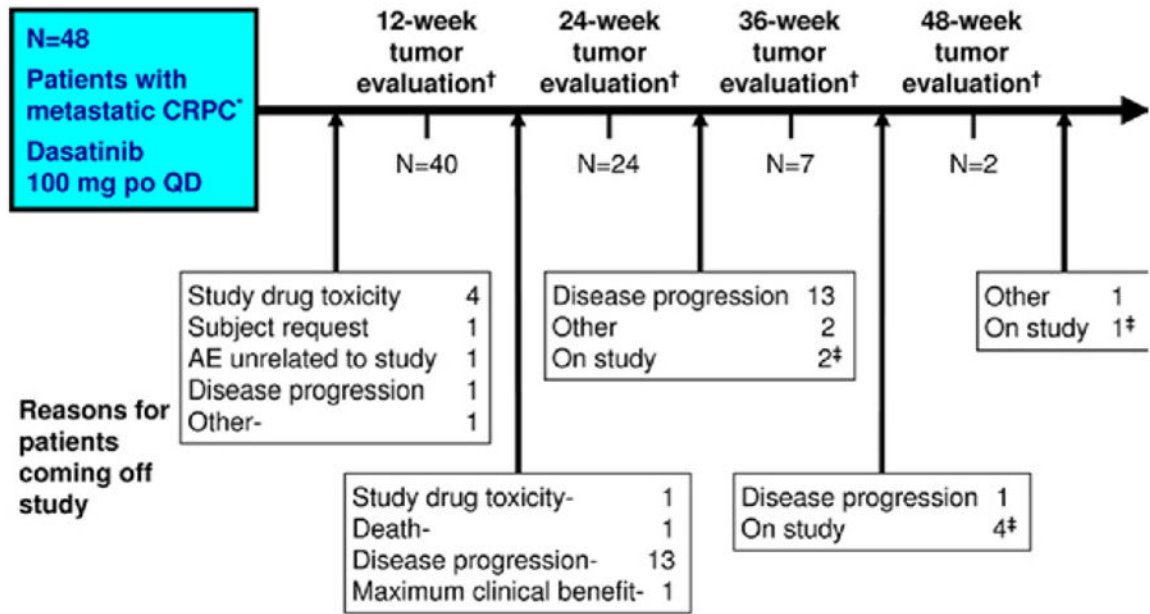
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* CRPC = castration resistant prostate cancer

† Follow-up assessments by bone scan, CT scan, and/or PSA as applicable; also includes end of study assessments.

‡ 6 out of 7 subjects that were on-study continued on study for more than 1 year

Figure 1.

Study schema showing number of patients with 12-week efficacy assessments (including end of study assessment) at which bone scan, computed tomography scans, and/or PSA levels were obtained. Between these 12-week assessments, a list of reasons for patients coming off study is given. Note, 6 of 7 patients still in the study at Clinical Study Report data lock in February 2009 eventually remained with the study with a lack of progressive disease for >1 year. po, oral; CT, computed tomography.

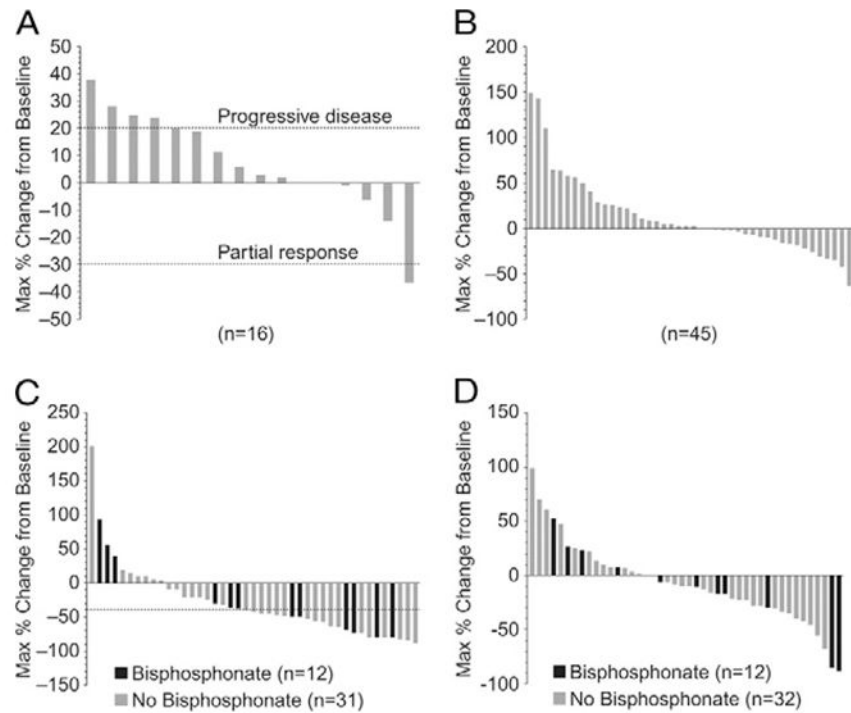


Figure 2.

(A) Maximal percentage of change in tumor size from baseline. Dashed line at 20% represents RECIST progression; dashed line at -30% represents RECIST partial response. RECIST could only be reported for 16 (80%) of 20 patients with baseline measurable disease, because 4 patients did not remain with the study long enough to undergo 12-week computed tomography imaging assessment. (B) Maximal PSA change from baseline. PSA level in 2 patients (4%) declined by >50%, and 1 had confirmation of >50% decline. (C) Maximal percentage of change in uNTX levels from baseline. Twelve patients were receiving bisphosphonates. Dashed line represents 40% reduction from baseline. (D) Maximal percentage of change in BAP from baseline. Twelve patients were receiving bisphosphonates.

Table 1

Patient baseline demographics and disease characteristics

Characteristic	Value
Total assessable patients (n)	48
Age (y)	
Median	68
Range	47–85
Age ≥ 65 y (n)	36 (75)
Race/ethnicity (n)	
White	46 (96)
Black	1 (2)
Other	1 (2)
Interval since diagnosis (mo)	
Median	79
Range	13–238
ECOG performance status (n)	
0	35 (73)
1	13 (27)
PSA (ng/mL)	n = 48
Median	43.6
Range	5.7–471
uNTX (nM/mmol creatinine)	n = 46
Median	46.0
Range	8.0–535.0
BAP (U/L)	n = 47
Median	35.0
Range	14.0–563.0
Previous therapy (n)	
Surgery	32 (67)
Radiotherapy	37 (77)
Bisphosphonates	12 (25)
RECIST-evaluable disease (n)	20 (42)
Bone metastases (n)	34 (71)
Disease sites, target lesions (n)	
Lymph node	18 (38)
Pelvis	1 (2)
Prostate mass	1 (2)
Skin/soft tissue	1 (2)
Visceral, lung	1 (2)
Visceral, liver	1 (2)

ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen; RECIST, Response Evaluable Criteria in Solid Tumors; uNTX, urine N-telopeptide; BAP, bone alkaline phosphatase.

Data in parentheses are percentages.

Table 2

Safety summary for subjects receiving either 100 mg QD dasatinib or pooled 70 mg and 100 mg BID dasatinib doses

Variable	QD (100 mg; n = 48)	Pooled BID (70 mg and 100 mg; n = 47)
All deaths	2 (4.2)	2 (4.3)
Subjects with 1 dose interruption (n)	15 (31.3)	30 (63.8)
Dose interruptions (n)		
1	12 (25.0)	19 (40.4)
2	2 (4.2)	4 (8.5)
3	0	4 (8.5)
>3	1 (2.1)	3 (6.4)
Interval to first dose interruption for toxicity (d)		
Median	50	39
Range	4–172	2–127
Drug-related serious AEs	3 (6.3)	6 (12.8)
Drug-related AEs leading to discontinuation	6 (12.5)	7 (14.9)
All AEs	48 (100.0)	47 (100.0)
Drug-related AEs	43 (89.6)	47 (100.0)
Drug-related grade 3 or 4 AEs	6 (12.5)	15 (31.9)

QD, once daily; BID, twice daily; AEs, adverse events.

Data in parentheses are percentages.

Table 3

Adverse events of special interest *

Adverse Event	QD (100 mg; n = 48)		Pooled BID (70 mg and 100 mg; n = 47)	
	Grade 3–4 (n) [†]	All Grades (n) [†]	Grade 3–4 (n)	All Grades (n)
Diarrhea	0	13 (27.1)	2 (4.2)	29 (61.7)
Pleural effusion	1 (2.1)	9 (18.8)	1 (2.1)	24 (51.1)
Nausea	0	13 (27.1)	1 (2.1)	22 (46.8)
Anorexia	0	10 (20.8)	0	17 (36.2)
Fatigue	0	21 (43.8)	5 (10.6)	21 (44.7)
Dyspnea	1 (2.1)	11 (22.9)	4 (8.5)	19 (40.4)
Rash	0	8 (16.7)	1 (2.1)	19 (40.4)
Headache	0	13 (27.1)	0	18 (38.3)
Asthenia	1 (2.1)	9 (18.8)	2 (4.2)	13 (27.6)
Superficial edema	0	5 (10.4)	0	12 (25.5)
Pericardial effusion	0	1 (2.1)	0	11 (23.4)
Flushing	0	3 (6.3)	0	10 (21.3)
Musculoskeletal pain	0	10 (20.8)	0	9 (19.1)

Abbreviations as in Table 2.

Data in parentheses are percentages.

* AEs of special interest (drug-related AEs) as defined by medical monitor summarized by grouped preferred term (MedDRA version 11.1; AEs of special interest listed defined as AEs reported in 20% of population for either the QD or the BID doses.

[†]No grade 4 or 5 AEs observed in 10% of subjects for 100 mg QD dose.