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Docetaxel and dasatinib or placebo in men with metastatic castration-resistant prostate cancer (READY): a randomised, double-blind phase 3 trial

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Contributors

Bristol-Myers Squibb employees (including GCT, PP, SD, and SC) and senior academic investigators (JCA, FS, AJA, EYY, GW, JSdB, and CJL) contributed to trial design, study conduct, patient recruitment, and data collection, analysis, and interpretation. JB, JM, SVS, VBM, EE, SO, MJM, BS, PJG, AH, JHH, SB, ER, and EG were investigators in the study and contributed to the recruitment and treatment of the patients, and data collection and interpretation. The initial draft of the manuscript was jointly prepared by lead and senior authors (JCA and CJL) and the medical writer. All authors reviewed and contributed to the subsequent drafts and approved the final version. JCA had full access to all of the study data and the final decision to submit for publication.

Conflicts of interest

GCT, PP, SD, and SC are full-time employees of Bristol-Myers Squibb, and own company stocks and stock options. AJA has served as a consultant for Sanofi-Aventis, and has received research funding from Bristol-Myers Squibb and Sanofi-Aventis. FS has received research funding from Bristol-Myers Squibb. GW has received honoraria from Bristol-Myers Squibb. EE has received honoraria from Johnson & Johnson, Sanofi-Aventis, and Takeda; has participated on the speakers' bureau for Johnson & Johnson; and has received research funding from Sanofi-Aventis and Astellas/Medivation. SO has received honoraria from Bristol-Myers Squibb. MJM has served as a consultant for Bayer, Janssen, and Takeda and has received research funding from Algeta, Bayer, Sanofi-Aventis, and Takeda. BS has received honoraria and travel support from Bristol-Myers Squibb. All other authors declare that they have no conflicts of interest.

See Online for appendix

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Summary

Background—Src kinase-mediated interactions between prostate cancer cells and osteoclasts might promote bone metastasis. Dasatinib inhibits tyrosine kinases, including Src kinases. Data suggests that dasatinib kinase inhibition leads to antitumour activity, affects osteoclasts, and has synergy with docetaxel, a first-line chemotherapy for metastatic castration-resistant prostate cancer. We assessed whether dasatinib plus docetaxel in chemotherapy-naive men with metastatic castration-resistant prostate cancer led to greater efficacy than with docetaxel alone.

Methods—In this double-blind, randomised, placebo-controlled phase 3 study, we enrolled men of 18 years or older with chemotherapy-naive, metastatic, castration-resistant prostate cancer, and adequate organ function from 186 centres across 25 countries. Eligible patients were randomly assigned (1:1) via an interactive voice response system to receive docetaxel (75 mg/m^2 intravenously every 3 weeks, plus oral prednisone 5 mg twice daily), plus either dasatinib (100 mg orally once daily) or placebo until disease progression or unacceptable toxicity. Randomisation was stratified by Eastern Cooperative Oncology Group performance status (0–1 *vs* 2), bisphosphonate use (yes *vs* no), and urinary N-telopeptide (uNTx) value (<60 μmol/mol creatinine *vs* ≥60 μmol/mol creatinine). All patients, investigators, and personnel involved in study conduct and data analyses were blinded to treatment allocation. The primary endpoint was overall survival, analysed by intention to treat. The trial is registered with ClinicalTrials.gov, number NCT00744497.

Findings—Between Oct 30, 2008, and April 11, 2011, 1522 eligible patients were randomly assigned to treatment; 762 patients were assigned to dasatinib and 760 to placebo. At final analysis, median follow-up was 19.0 months (IQR 11.2–25.1) and 914 patients had died. Median overall survival was 21.5 months (95% CI 20.3–22.8) in the dasatinib group and 21.2 months (20.0–23.4) in the placebo group (stratified hazard ratio [HR] 0.99, 95.5% CI 0.87–1.13; p=0.90). The most common grade 3–4 adverse events included diarrhoea (58 [8%] patients in the dasatinib group *vs* 27 [4%] patients in the placebo group), fatigue (62 [8%] *vs* 42 [6%]), and asthenia (40 [5%] *vs* 23 [3%]); grade 3–4 pleural effusions were uncommon (ten [1%] *vs* three [<1%]).

Interpretation—The addition of dasatinib to docetaxel did not improve overall survival for chemotherapy-naive men with metastatic castration-resistant prostate cancer. This study does not support the combination of dasatinib and docetaxel in this population of patients.

Funding—Bristol-Myers Squibb.

Introduction

Docetaxel, a cytotoxic microtubule stabilising agent, is approved for front-line therapy for patients with metastatic, castration-resistant prostate cancer after failure of castrating hormonal therapies.[1,2] However, docetaxel and other more recently introduced therapies, including another microtubule stabiliser (cabazitaxel), androgen modulators (abiraterone and enzalutamide), immunotherapy (sipuleucel-T), and radiotherapy (radium-223), only provide incremental survival benefits,[3–8] emphasising the need for additional options for these patients.

Bone-forming metastases dominate the clinical phenotype of metastatic castration-resistant prostate cancer. They account for much of the morbidity in men with metastases, and their presence is linked to decreased survival.[9] Evidence suggests that crosstalk in the bone

microenvironment between prostate cancer cells and host cells (eg, osteoblasts and osteoclasts) occurs via paracrine and autocrine factor induced signalling.[10] The Src family of kinases (SFKs) mediate signalling pathways which have been implicated in prostate cancer cell growth, invasion, and metastasis in preclinical model systems.[11,12] SFKs also regulate osteoclast functions, including bone resorption, and might be implicated in the development of bone metastases.[13] Preclinical observations suggest that raised SFK activity in tumours of patients with prostate cancer is associated with decreased sensitivity to androgen ablation, metastasis to the bone, and shorter survival.[14,15] These findings implicate SFKs in the lethal progression of prostate cancer, and in resistance to therapies.

Dasatinib (Bristol-Myers Squibb, Princeton, NJ, USA) is a tyrosine-kinase inhibitor that inhibits several kinases including SFK members and BCR-ABL.[16] In preclinical models, dasatinib inhibited prostate cancer growth and metastasis, and suppressed prostate cancer cell-induced osteoclastic activity in the bone micro environment.[17,18] Additionally, the combination of dasatinib and docetaxel had greater activity than either agent alone in a mouse xenograft model of prostate cancer.[18] SFK inhibition by dasatinib, as measured by ex-vivo phospho-Src inhibition in peripheral blood mononuclear cells, correlated with tumour growth inhibition in a mouse xenograft model of prostate cancer.[19] Phospho-Src inhibition in human peripheral blood mononuclear cells lasted for at least 6 h after one dasatinib dose of 70 mg or more.[20] In a phase 2 trial of patients with metastatic castration-resistant prostate cancer, treatment with dasatinib 100 mg once daily reduced serum prostate-specific antigen (PSA) concentrations, led to tumour responses as defined by modified Response Evaluation Criteria in Solid Tumors (mRECIST), and decreased levels of the bone turnover markers urinary N-telopeptide (uNTx) and bone-specific alkaline phosphatase (BAP).[21] Furthermore, results of a phase 1/2 trial showed that the combination of dasatinib and docetaxel in patients with metastatic castration-resistant prostate cancer was safe and well tolerated.[22]

On the basis of these findings, we postulated that the addition of dasatinib to docetaxel might increase the efficacy of docetaxel, and so increase survival of patients with metastatic castration-resistant cancer. We undertook the phase 3 READY trial to compare the effects of dasatinib plus docetaxel with docetaxel alone on survival in chemotherapy-naive patients with metastatic castration-resistant prostate cancer.

Methods

Study design and patients

In this multicentre, double-blind, randomised, placebo-controlled, phase 3 study, participants were recruited from 186 academic hospitals and community clinics across 25 countries. Men aged 18 years or older were eligible if they had histologically confirmed metastatic prostate cancer that had progressed despite castrate concentrations of serum testosterone (≤1.74 nmol/L [≤50 ng/dL]), and received no previous cytotoxic chemotherapy (except for estra mustine). Progression was defined as increased size, or appearance of, measurable nodal or visceral lesions, two or more new lesions on bone scan, or rising serum PSA concentrations (≥2 μg/L) at least 1 week apart. Eligible patients had to have an Eastern Cooperative Oncology Group performance status (ECOGPS) of between 0 and 2, and adequate organ

function. Key exclusion criteria included pleural or pericardial effusion of any grade, peripheral neuropathy of grade two or worse, and clinically significant cardiovascular disease. Antiandrogens had to be discontinued 4 weeks before starting study therapy. Bisphosphonates could be continued, but could not be initiated within 28 days of the start of the study. Further details of the eligibility criteria are detailed in the appendix.

The study was approved by the ethics committee or institutional review board at each site, and was done in accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Conference on Harmonization. All patients provided written informed consent.

Randomisation and masking

Eligible patients were enrolled and randomly assigned to a treatment centrally via an interactive voice response system. Patients were assigned in a 1:1 ratio to docetaxel plus dasatinib, or docetaxel plus placebo, using a computer-generated randomisation schedule. Randomisation was stratified by ECOGPS (0–1 *vs* 2), baseline bisphosphonate use (yes *vs* no), and uNTx value (<60 μmol/mol creatinine *vs* ≥60 μmol/mol creatinine), and was balanced for stratification factors using the Pocock and Simon dynamic balancing procedure.[23] To maintain blinding, dasatinib and matching placebo were supplied as film-coated tablets packaged in identical boxes. Patients, investigators, study site staff, and personnel involved in study monitoring and coordination and data analyses were masked to treatment allocation. The treatment code was broken only after the database was locked for the primary analysis. However, according to a provision in the protocol, the treating physicians broke the treatment code for four patients, because knowledge of study treatment was regarded as essential for further treatment of these patients. The treatment code also was partially broken so that an independent statistician (not an employee of the sponsor) could undertake safety and efficacy analyses for the independent data monitoring committee reviews. Access to these analyses was restricted to the committee members. The data monitoring committee met five times throughout the trial. All meetings (including the one that reviewed the preplanned interim analysis after 632 deaths had occurred) resulted in a recommendation that the trial continue as planned without modification. No formal assessment for the adequacy of the masking was done.

Procedures

All patients received docetaxel 75 mg/m^2 intravenously once every 3 weeks (docetaxel cycle), with oral prednisone 5 mg twice daily. Both dasatinib (100 mg), or placebo were taken orally once daily according to treatment allocation. We did not prespecify a limit to the number of docetaxel cycles that could be received. Patients received treatment (placebo or dasatinib) until disease progression or unacceptable toxicity. Patients who discontinued docetaxel before disease progression could continue their blinded monotherapy until progression. Dose modifications were allowed in cases of toxicity. Docetaxel could be reduced to 60 mg/m^2 in the event of grade 3 or 4 haematological toxicities (neutropenia, or thrombo cytopenia), or grade 3 non-haematological toxicities. Dasatinib or placebo could be reduced to 70 mg once daily in the case of grade 3 non-haematological toxicities recurring at a reduced docetaxel dose of 60 mg/m^2 or grade 4 neutropenia or thrombocytopenia.

Docetaxel, dasatinib, or both, were withheld until recovery of toxicities to grade 1 or better, at which point the dosing was resumed. Study drugs were discontinued in case of delays due to toxicity lasting longer than 21 days (unless otherwise agreed by the sponsor), grade 4 non-haematological toxicities, or grade 3 non-haematological toxicities recurring while receiving dasatinib 70 mg and docetaxel 60 mg/m^2. Once a dose reduction had been implemented, the patient's dose could not be re-escalated, unless the treating physician thought that it was in the best interest of the patient. The criteria for dose modifications are detailed in the appendix.

The primary endpoint was overall survival. Secondary endpoints were the proportion of patients who achieved an objective response (defined as the sum total of complete response and partial response), time to first skeletal-related event (TFSRE), the proportion of patients with reduction in uNTx from baseline of 35% or more or to normalisation, patients' progression-free survival (PFS), time to PSA progression, and the proportion of patients with reduction in pain intensity from baseline of 30% or more (appendix). Tumour assessments with MRI, CT, or spiral CT and bone scans and imaging were done at baseline, every 12 weeks on treatment, at the end of treatment, and about every 12 weeks thereafter until disease progression. All scans, except for bone scans and imaging, were assessed by using mRECIST (version 1.0) modified according to the recommendations by Prostate Cancer Working Group 2.[24] Bone scans and images were assessed for the presence of new lesions by investigators and an independent radiological review committee. Serum samples for PSA measurements and urine samples for uNTx measurements were obtained at baseline, before each 3 week cycle, at the end of treatment, and about every 12 weeks thereafter until disease progression. Assessment of skeletal-related events was made every 12 weeks on treatment, at the end of treatment, and about every 12 weeks thereafter until disease progression. Pain intensity was assessed using question 3 of the Brief Pain Inventory (Short Form).[25,26] Patients were asked to fill out the form within 14 days before the start of study medication, before each cycle, at end of treatment, and at every follow-up visit for toxicity. Study drug toxicities were monitored continuously. Adverse events and laboratory abnormalities were graded according to the Common Terminology Criteria for Adverse Events (version 3.0). Serious adverse events were defined as those that resulted in death, were life threatening, required admission to hospital (or prolongation of existing hospital stay), resulted in a persistent or substantial disability or incapacity, were a congenital abnormality or birth defect, or were important medical events (eg, those necessitating medical or surgical intervention). For reporting purposes, the pregnancy, overdose, and cancer were also regarded as important medical events.

Statistical analysis

Analyses for overall survival, TFSRE, PFS, and time to PSA progression were based on the intention-to-treat population, whereas those for objective response, uNTx reduction, and pain reduction were based on evaluable patients (for the definition of evaluable patients according to each of these endpoints, see appendix). All safety analyses were based on data from randomly assigned patients who received at least one dose of any study therapy.

The sample size was initially calculated to be 1380 patients assuming an exponential survival distribution and a median overall survival for the placebo group of 19.2 months on the basis of the registrational trial of docetaxel.[2] The assumption for median overall survival was later updated to 21.5 months according to data from the more recent Cancer and Leukemia Group B (CALGB) trial (bevacizumab with or without docetaxel).[27] We estimated, on the basis of the updated assumption, that at least 858 deaths (at least 1500 randomly assigned patients) would be required for 90% power, and a two-sided α of 0.05 in a log-rank test to detect a hazard ratio (HR) of 0.8 (dasatinib *vs* placebo).

The primary analysis of overall survival was a comparison between the groups using a log-rank test at two-sided α of 0.045 (adjusting for the preplanned interim analysis using the O'Brien-Fleming spending function). We compared other time-to-event endpoints (TFSRE, PFS, and time to PSA progression) between treatment groups using a stratified log-rank test at two-sided α of 0.05. We computed HRs of dasatinib versus placebo and associated 95% CIs (95.5% for overall survival) using a Cox proportional hazards model. We estimated medians and associated 95% CIs using the Kaplan-Meier product limit method. We compared objective response, uNTx reduction, and pain reduction between treatment groups using stratified Cochran-Mantel-Haenszel test, and estimated associated odds ratios and 95% CIs. We used a Cox proportional hazards model to analyse overall survival for subgroups based on prespecified baseline factors (age, ethnic origin, region, bisphosphonate use, uNTx, ECOGPS, presence of bone metastasis, type of progression, and pain intensity). The log-rank test, proportional hazards model, and Cochran-Mantel-Haenszel test were all stratified by baseline bisphosphonate use and uNTx value at randomisation. All CIs are two-sided. We did all statistical analyses with SAS (version 8.2) and East (version 5.4).

This study is registered with ClinicalTrials.gov, number NCT00744497.

Role of the funding source

The employees of the sponsor (including GCT, PP, SD, and SC) collaborated with academic investigators (FS, AJA, EYY, GW, and CL) for trial design. During the study, data from study sites were obtained and managed by the sponsor. After database lock, raw data were analysed by statisticians employed by the sponsor (including PP), and reviewed and interpreted through collaboration between employees of the sponsor (including GCT, PP, and SC) and academic investigators (JCA, FS, AJA, EYY, GW, and CL). A detailed clinical study report drafted by employees of the sponsor (including GCT and PP) was reviewed, commented on, and approved by JCA. GCT, PP, and SC had full access to the raw data. All authors had access to pertinent trial data listings and tables. A medical writer employed by Bristol-Myers Squibb assisted investigators in the drafting and finalising of the report. All authors reviewed the initial draft and approved the final version of the report. The corresponding author (JCA) had full access to all the study data, and had final responsibility for the decision to submit for publication.

Results

Between Oct 30, 2008, and Jan 10, 2011, 1930 patients were enrolled and assessed for eligibility (appendix). Between Oct 30, 2008, and April 11, 2011, 1522 eligible patients

from 183 of the 186 centres (three centres did not randomise any participants) across 25 countries (appendix) were randomly assigned to treatment with either dasatinib (n=762), or placebo (n=760; figure 1). 761 of 762 patients in the dasatinib group and 757 of 760 patients in the placebo group received at least one dose of any study therapy. The patient in the dasatinib group who did not receive treatment no longer met inclusion criteria (presented thrombocytopenia). Of the three patients in the placebo group who did not receive treatment, one no longer met inclusion criteria (presented multiple comorbidities) and two withdrew consent before receiving the first dose (figure 1). Patient characteristics at baseline were balanced between the groups (table 1). Most patients (680 [89%] of 762 in the dasatinib group and 685 [90%] of 760 patients in the placebo group) had bone disease. At the database lock on Oct 24, 2012, subsequent to reaching the prespecified minimum of 858 events, 911 deaths had been reported. At the database lock, 721 (95%) patients in the dasatinib group and 713 (94%) patients in the placebo group had discontinued treatment (figure 1). The primary reasons for treatment discontinuation were disease progression (208 [27%] patients in the dasatinib group and 307 [40%] patients in the placebo group) and drug-related toxicity (140 [18%] and 68 [9%], respectively).

The median treatment duration was 8.1 months (IQR 3.3–13.4) in the dasatinib group and 8.4 months (4.9–13.3) in the placebo group. 177 patients (23%) of 762 assigned to dasatinib and 108 (14%) of 760 assigned to placebo received treatment for 3 months or less. 715 (94%) patients received 70% or more of the expected dasatinib dose, a dose that has been shown to be biologically active in metastatic castration-resistant prostate cancer.[19] Patients in the dasatinib group received a median of eight cycles of docetaxel (IQR four to 12), and those in the placebo group received nine (six to 12). 211 (28%) patients in the dasatinib group and 220 (29%) patients in the placebo group received more than ten cycles of docetaxel. 98% of patients in both groups (744 patients in the dasatanib group and 743 in the placebo group) received 60 mg/m^2 of docetaxel (70% of the expected dose), which has been shown to be an efficacious dose in patients with metastatic castration-resistant prostate cancer.[2] 111 (15%) patients in the dasatinib group and 75 (10%) in the placebo group had at least one dose reduction for dasatinib and placebo. 348 (46%) and 302 (40%) patients had at least one dose interruption in the dasatinib and placebo groups, respectively. 192 (25%) of patients in the dasatinib group had at least one cycle of docetaxel at a reduced dose, as did 155 (20%) of patients in the placebo group; 49 (6%) and 45 (6%), respectively, had docetaxel dose interruptions.

After a median follow-up of 19.0 months (IQR 11.2–25.1), 914 patients had died; 452 (59%) of 762 patients assigned to dasatinib, and 462 (61%) of 760 patients assigned to placebo. Dasatinib did not improve overall survival compared with placebo (stratified HR 0.99, 95.5% CI 0.87–1.13; p=0.90). Median overall survival was 21.5 months (95% CI 20.3–22.8) in the dasatinib group, and 21.2 months (20.0–23.4) in the placebo group (figure 2). Prespecified subgroup analysis of overall survival generally showed no significant difference between patients assigned to dasatinib and placebo, although patients in the dasatinib group with an ECOGPS of 2 seemed to have poorer overall survival than those assigned to placebo (figure 3).

Prespecified secondary endpoints are summarised in table 2. Median TFSRE was 31.1 months (95% CI 31.1–not reached) in the placebo group, and was not reached in the dasatinib group (table 2, figure 4). We noted similar TFSRE results in an exploratory analysis that included skeletal-related events on subsequent treatments (appendix). The distribution of skeletal-related events by event type is also presented in the appendix. Median PFS and median time to PSA progression were similar between the placebo and dasatinib groups (table 2), as were the other secondary endpoints presented in table 2. Waterfall plots showing changes in PSA, tumour lesion, uNTx, or BAP were similar between the groups (appendix).

The TFSRE results prompted us to do a post-hoc analysis to assess if bisphosphonate use and raised uNTx concentrations at baseline could predict outcomes. In this analysis, HRs of dasatinib to placebo for TFSRE were 0.69 (95% CI 0.46–1.05) in patients with bisphosphonate use and normal uNTx, 0.59 (0.24–1.44) in patients with bisphosphonate use and abnormal uNTx, 0.80 (0.44–1.45) in patients with no bisphosphonate use and normal uNTx, and 0.90 (0.63–1.30) in patients with no bisphosphonate use and abnormal uNTx (appendix). The corresponding HRs for overall survival were 0.91 (95% CI 0.70–1.18), 1.56 (1.04–2.35), 1.19 (0.90–1.58), and 0.84 (0.69–1.04), respectively (appendix). The results point to potential interactions between bone (as measured by baseline uNTx) and bisphosphonate use and SFKs, which might have affected the results.

Post-study cancer therapy was received by 327 (43%) of 762 patients in the dasatinib group, and 341 (45%) of 760 patients in the placebo group. Therapies included radiotherapy (184 [24%] in the dasatinib group *vs* 197 [26%] in the placebo group) and systemic therapies (305 [40%] *vs* 326 [43%], respectively), of which the most common systemic agents were abiraterone (119 [16%] *vs* 127 [17%]), docetaxel (94 [12%] *vs* 93 [12%]), and cabazitaxel (53 [7%] *vs* 65 [9%]).

Grade 3–4 adverse events were reported in 454 (60%) of 761 patients assigned to dasatinib and 415 (55%) of 757 patients assigned to placebo (table 3). The most common (occurring in 5% or more of patients) grade 3–4 adverse events that occurred more frequently with dasatinib than with placebo were diarrhoea, fatigue, and asthenia. Grade 3–4 peripheral neuropathy occurred at similar frequencies between the groups (table 3). Gastrointestinal bleeding was more frequent with dasatinib than with placebo (all grades, 72 [9%] *vs* 39 [5%]; grade 3–4, 20 [3%] *vs* eight [1%]). Fluid retention was reported in 39% of patients in each group (295 in the dasatinib group and 296 in the placebo group), including pleural effusion (all grades, 118 [16%] *vs* 30 [4%]; grade 3–4, ten [1%] *vs* three [<1%]). Grade 3–4 laboratory abnormalities including neutropenia were generally similar between the groups, except for hypophosphataemia, which was more frequent with dasatinib (table 3).

Adverse events leading to treatment discontinuation were reported in 293 (38%) patients on dasatinib and 186 (25%) patients in the placebo group. The most frequent adverse events leading to discontinuation were fatigue (27 [4%] in the dasatinib group *vs* 20 [3%] in the placebo group), diarrhoea (22 [3%] *vs* ten [1%]), and pleural effusion (24 [3%] *vs* two [<1%]). Drug-related adverse events leading to discontinuation were reported for 143 (19%) patients in the dasatinib group and 75 (10%) in the placebo group. Pleural effusion was the

only drug-related event that led to discontinuation for more than 1% of patients in the dasatinib group (18 [2%] *vs* one [<1%] patient in the placebo group).

376 (49%) of 762 patients in the dasatinib group had one or more serious adverse events during treatment, as did 317 (42%) of 760 patients in the placebo group. The most frequent serious adverse events in the dasatinib group were diarrhoea (44 [6%]), febrile neutropenia (31 [4%]), pneumonia (32 [4%]), and pyrexia (29 [4%]). The corresponding numbers in the placebo group were ten (1%), 27 (4%), 22 (3%), and 14 (12%), respectively.

At the time of database lock, 452 (59%) of 762 patients in the dasatinib group and 462 (61%) of 760 patients in the placebo group had died. The main reason for death was disease progression (340 [45%] in the dasatinib group *vs* 376 [50%] in the placebo group). 77 (10%) patients in the dasatinib group and 49 (6%) patients in the placebo group died within 30 days of the last dose. Six (1%) deaths in the dasatinib group were regarded by investigators to be treatment-related and were ascribed to febrile neutropenia, septic shock, pulmonary insufficiency, cerebral haematoma, cardio-respiratory failure, and progressive disease or haemorrhage. Four (1%) patients' deaths in the placebo group were regarded by investigators to be treatment-related, and were attributed to irreversible cardiogenic shock, acute renal failure, septicaemia, and pneumonia.

Discussion

This randomised phase 3 study of patients with metastatic castration-resistant prostate cancer previously unexposed to chemotherapy showed no overall survival improvement with dasatinib plus docetaxel compared with docetaxel alone. Since treatment groups were balanced in terms of baseline characteristics, treatment duration, docetaxel dose intensity, and post-study therapies, these factors were unlikely to have contributed to the reported outcome. Efforts to measure inhibition of phospho-Src in this trial, and two other phase 2 trials[21,22] did not succeed. Thus, it is not known whether Src kinases were optimally inhibited by the dasatinib dose and schedule used. Prespecified subgroup analyses showed no significant differences between treatment groups except for patients with an ECOG status of 2, who had worse overall survival when treated with dasatinib, suggesting that ECOG status should be taken into account when planning future trials in this patient population.

Our overall survival results underscore the limitations of uncontrolled phase 2 trials, and the challenges of clinical translation of preclinical observations. Promising randomised phase 2 trials have not translated into successful phase 3 trials of targeted therapy in combination with docetaxel. Trials of both bevacizumab and atrasentan (an endothelin A antagonist) did not prove successful in increasing overall survival in a population of chemotherapy-naive patients with metastatic castration-resistant prostate cancer.[27,28] Our phase 3 study emphasises the need for more extensive preclinical assessment, and initial clinical confirmation before proceeding to phase 3 trials (panel). Clearly, the complexity lies in either the disease itself or the agents selected. In our experience, prostate cancer—metastatic castration-resistant prostate cancer in particular—presents additional challenges because of the heterogeneity of the disease, and the absence of specific biomarkers to identify responding patients. With a goal to identify patients who might respond to Src kinase

inhibition, we obtained serial serum and plasma samples from 75 patients throughout their treatment in this study. These samples are being analysed for cytokines and other markers believed to be important in the prostate-cancer bone microenvironment.

In this study, secondary efficacy outcomes were generally similar between the groups. Notably, a phase 2 trial of single-agent dasatinib in chemotherapy-naive patients with metastatic castration-resistant prostate cancer suggested that dasatinib could affect both tumour growth and bone turnover.[21] However, since the addition of dasatinib to docetaxel did not improve objective response, PFS, time to PSA progression, uNTx, and BAP, docetaxel seemed to be have been primarily responsible for inhibition of both tumour growth and bone turnover in these patients. Indeed, docetaxel itself has been shown to have favourable effects on bone markers, probably mediated through its antitumour efficacy,[31] which might have confounded interpretation of the uncontrolled phase 2 trial.[22] A slight—although not significant—delay in TFSRE was reported in the dasatinib plus docetaxel group compared with the docetaxel alone group, pointing to the possibility that dasatinib might affect bone in the presence of docetaxel. This theory is consistent with preclinical data suggesting a role for Src kinases in bone-related pathogenesis.[13,17,18] However, in a post-hoc analysis, the delay in TFSRE with dasatinib versus placebo was similar in patients with normal or abnormal uNTx (appendix). This finding, in conjunction with the lack of effect that the addition of dasatinib had on uNTx or BAP, suggests that factors other than osteoclast suppression might have contributed to the slightly delayed TFSRE. These findings suggest that combination bone-directed strategies that include Src kinase inhibitors might be worth pursuing.

We noted no unexpected safety findings in this study. Adverse events, treatment discontinuation, and dose reductions were all slightly higher with dasatinib than with placebo. Pleural effusion, a hallmark of dasatinib safety, occurred in the dasatinib group at a frequency consistent with historical data for dasatinib in patients with leukaemia.[32] However, there was a striking absence of increases in grade 3–4 haematological and neurological side-effects with the addition of dasatinib to docetaxel. Of note, the incidence of peripheral neuropathy or grade 3–4 neutropenia in the placebo group of this study was low relative to historical data for docetaxel therapy in patients with metastatic castration-resistant prostate cancer.[2] This finding might be a result of treating physicians' greater familiarity with docetaxel therapy, and thus better patient management. Of ten treatment-related deaths in the study, six were in the dasatinib group. Overall, the addition of dasatinib to docetaxel was well tolerated with an acceptable safety profile. However, this profile should be interpreted in the context of no apparent clinical benefit.

In conclusion, this sufficiently powered, well controlled study in chemotherapy-naive patients with metastatic castration-resistant prostate cancer showed no clinical benefit of adding dasatinib to docetaxel. The challenge of combining a molecularly targeted agent with docetaxel chemotherapy, despite several phase 3 efforts with various promising agents, has not been overcome.[27,28,33] This consistent finding across many agents suggests that a fundamental conceptual flaw exists in the approach. Possibilities regarding the limitation of the approach include the heterogeneous study population, unique interactions between chemotherapy and molecularly targeted therapies that result in a consistent bias against the

targeted agents, paracrine or intracrine androgen signalling as a driver of resistance to therapy, multiple and redundant pathways as drivers of disease progression in very advanced stages of metastatic castration-resistant prostate cancer, the fact that the cancers treated so far are not accurately represented by preclinical models, and suboptimal doses and dosing schedules of targeted agents. The consistent failure of phase 3 trials to find a significant benefit when assessing the addition of targeted agents to docetaxel suggests that these drug combinations should undergo more rigorous design and assessment of preclinical, coclinical, and initial human investigation before phase 3 trials. Taken together, our results suggest that there are crucial knowledge gaps that must be overcome by more reliably linking the understanding of drug mechanisms to prostate carcinogenesis. Persistent but low concentrations of androgens present in patients with metastatic castration-resistant prostate cancer might be a dominant driver of the disease[34,35] and might contribute to resistance reported with targeted therapies, including dasatinib. In an ongoing study (NCT01254864), we are exploring the hypothesis that further suppression of androgens through CYP17 inhibition with abiraterone might result in improved efficacy of dasatinib in patients with metastatic castration-resistant prostate cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Panel: Research in context

Systematic review

The phase 3 trial we did was based on three broad principles: the unmet clinical need for patients with metastatic castration-resistant prostate cancer who have a short survival; preclinical and phase 2 results linking Src kinases to therapy resistance and progression; and the clinical benefit with radiopharmaceuticals that target bone as an organ site. Our trial design attempted to account for the central role of bone by including a bone turnover marker to stratify patients and built on the knowledge that bone turnover markers are modulated by dasatinib in prostate cancer and in other malignancies. To assess the current status of clinical research in this area, we did a PubMed search with the terms "Src kinase inhibitors AND prostate cancer", "Src kinases AND docetaxel", and "dasatinib AND prostate cancer" on June 13, 2013. The search found phase 2 trials that assessed two additional Src kinase inhibitors (AZD0530 and KX2-391) in patients with metastatic castration-resistant prostate cancer who had received no previous chemotherapy,[29,30] but revealed no report of phase 3 trials of Src kinase inhibitors.

Interpretation

The results of this phase 3 randomised trial do not support the use of dasatinib in unselected men with castration-resistant prostate cancer. More broadly, it shows the need to undertake future studies on the basis of an improved understanding of the biological heterogeneity of prostate cancer as informed by predictive and companion biomarkers.

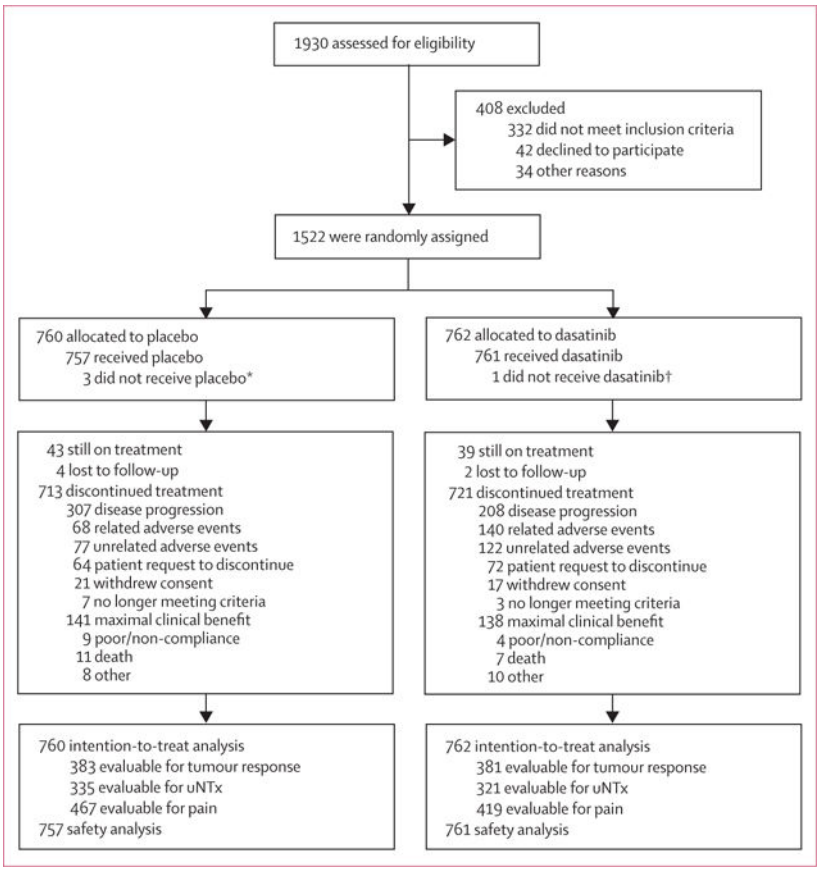

Figure 1. Trial profile

Immediately after the completion of the primary analysis, patients in the placebo group still on treatment (n=43) at the database lock were taken off the placebo medication. Patients still on treatment (n=39) in the dasatinib group were allowed to remain on dasatinib therapy, provided they signed an updated informed consent form with the knowledge that no survival benefit for docetaxel plus dasatinib had been observed in the trial. uNTx=urinary N-telopeptide. *Two patients declined to participate and one patient no longer met inclusion criteria. †No longer met inclusion criteria.

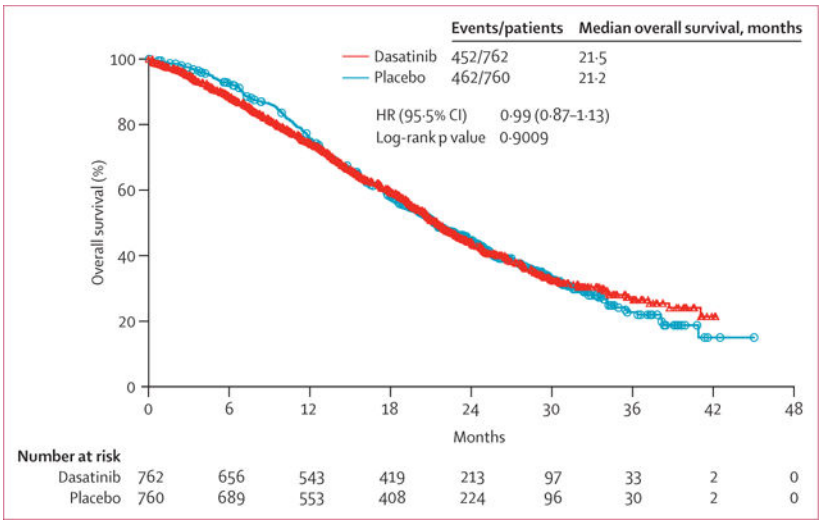

Figure 2. Kaplan-Meier estimate of overall survival in the intention-to-treat population

Patients who had not died or who were lost to follow-up were censored on the last date on which they were known to have been alive. The circles and triangles along each curve represent censored patients. HR=hazard ratio.

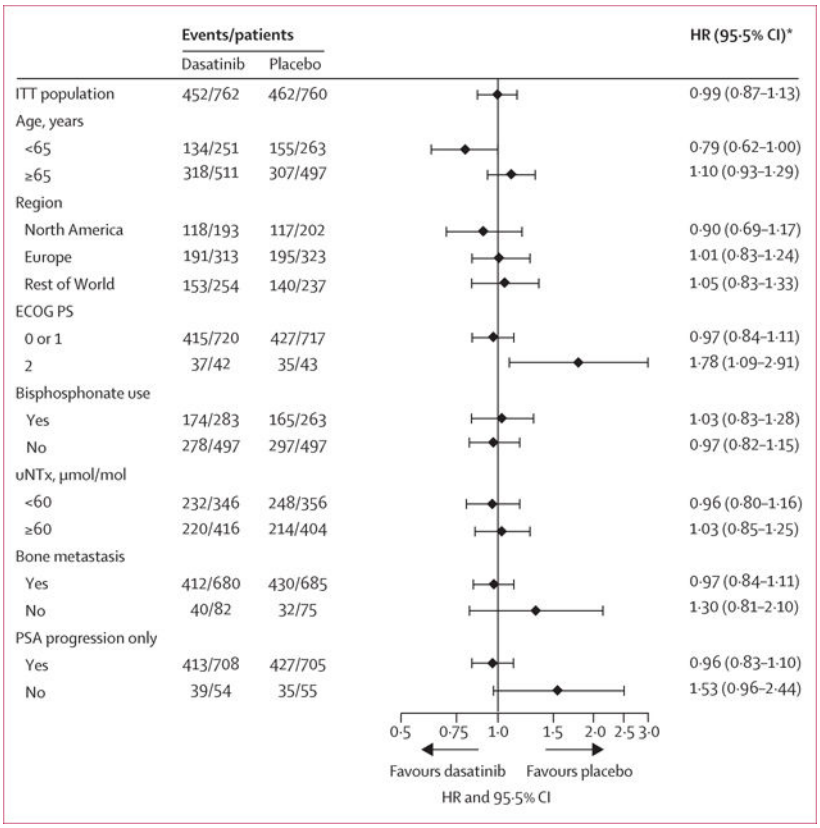

Figure 3. Overall survival in selected subgroups

ECOGPS=Eastern Cooperative Oncology Group performance status. HR=hazard ratio. ITT=intention-to-treat. PSA=prostate-specific antigen. uNTx=urinary N-telopeptide. *Ratio of dasatinib to placebo.

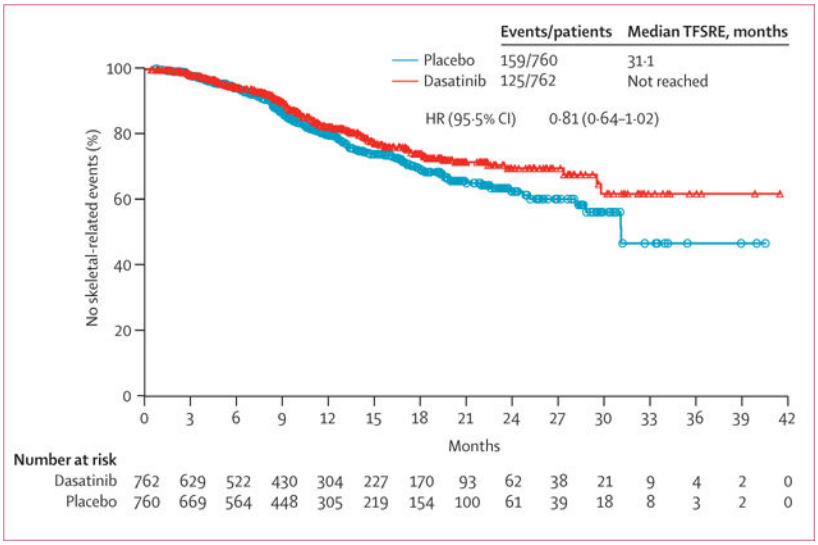

Figure 4. Kaplan-Meier estimate of TFSRE in the intention-to-treat population

Patients who died without a skeletal-related event (SRE) or who had a first SRE while on subsequent cancer therapy were censored on the date of last SRE assessment before the start date of subsequent therapy. Patients who had no SRE assessment were censored on the date of randomisation. The circles and triangles along each curve represent censored patients. SREs consisted of: pathological bone fracture (vertebral or non-vertebral) in the region of cancer involvement that occurred spontaneously or as a result of trivial trauma; radiation therapy to bone, including administration of a radioisotope such as strontium 89; cancer-related surgery to bone; and spinal cord or nerve root compression confirmed by MRI or CT (if MRI was not available). HR=hazard ratio. TFSRE=time to first skeletal-related event.

Table 1

Baseline patient characteristics

	Dasatinib (N=762)	Placebo (N=760)
Age, years	69 (45–92)	68 (40–90)
≥65 years	511 (67%)	497 (65%)
Ethnic origin		
White	656 (86%)	645 (85%)
Other	106 (14%)	115 (15%)
Eastern Cooperative Oncology Group performance status		
0	367 (48%)	370 (49%)
1	353 (46%)	347 (46%)
2	42 (6%)	43 (6%)
Urinary N-telopeptide, μmol/mol creatinine		
<60	346 (45%)	356 (47%)
≥60	416 (55%)	404 (53%)
Previous and current bisphosphonate use		
Yes	283 (37%)	263 (35%)
No	479 (63%)	497 (65%)
Time from diagnosis of metastatic disease to randomisation, months	13.1 (0.1–139.6)	12.1 (0.1–195.2)
Serum prostate-specific antigen, ng/mL	77.0 (0–6818)	87.0 (0–8318)
Abnormal LDH concentration	298 (39%)	307 (41%)
Evidence of disease progression		
Nodal/visceral progression	284 (37%)	263 (35%)
Bone scan/bone image	471 (62%)	481 (63%)
Rising PSA only	153 (20%)	168 (22%)
Local recurrence only	1 (<1%)	3 (<1%)
More than one type	569 (75%)	552 (73%)
Type of metastatic disease		
Bone disease only	307 (40%)	286 (38%)
Visceral/nodal disease only	80 (11%)	73 (10%)
Both bone and visceral/nodal disease	373 (49%)	399 (53%)
No evidence of metastatic disease	2 (<1%)	2 (<1%)
Number of disease sites		
1	283 (37%)	299 (39%)
≥2	98 (13%)	84 (11%)
Bone pain intensity		
0–1	309 (41%)	267 (35%)

	Dasatinib (N=762)	Placebo (N=760)
2–4	204 (27%)	220 (29%)
>4	212 (28%)	245 (32%)
Previous (discontinued) cancer treatment		
Surgery	468 (61%)	456 (60%)
Radiotherapy	387 (51%)	371 (49%)
Systemic therapy (metastatic setting)	515 (68%)	516 (68%)
1	260 (34%)	255 (34%)
≥2	255 (33%)	261 (34%)
Systemic therapy (non-metastatic setting)	296 (39%)	273 (36%)
1	143 (19%)	117 (15%)
≥2	153 (20%)	156 (21%)
Regional distribution		
North America	202 (26%)	193 (25%)
Europe	323 (42%)	313 (41%)
Rest of world *	237 (31%)	254 (33%)

Data are median (range) or number (%). LDH=lactate dehydrogenase. PSA=prostate-specific antigen.

* Includes Australia, India, Mexico, South Africa, South America, and South Korea.

Table 2

Summary of secondary efficacy endpoints

	Dasatinib (N=762)				Placebo (N=760)				OR or HR (95% CI)	p value
	Number of events	Proportion of patients or median time to event (95% CI)	At 1 year	At 2 years	Number of events	Proportion of patients or median time to event (95% CI)	At 1 year	At 2 years		
Objective response	116/381	30.5% (25.9–35.8)	..	..	122/383	31.9% (27.2–36.8)	..	..	OR 0.94 (0.69–1.27)	0.67
Time to first skeletal-related event	125	Not reached	82% (79–86)	70% (65–75)	159	31.1 months (28.8–not reached)	80% (77–83)	63% (57–69)	HR 0.81 (0.64–1.02)	0.08
Reduction in urinary N-telopeptide*	212/321	66.0% (60.6–71.2)	..	..	203/335	60.6% (55.1–65.9)	..	..	OR 1.28 (0.93–1.76)	0.13
Progression-free survival	484	11.8 months (11.1–13.4)	49% (46–53)	20% (16–24)	515	11.1 months (10.8–11.7)	45% (41–49)	20% (16–23)	HR 0.92 (0.82–1.05)	0.22
Time to prostate-specific antigen progression	473	7.2 months (6.6–7.9)	21% (17–24)	2% (0.3–3.8)	516	6.9 months (6.5–7.4)	16% (12–19)	1% (0.0–1.7)	HR 0.89 (0.79–1.01)	0.08
Reduction in pain intensity†	279/419	66.6% (61.9–71.1)	..	..	334/467	71.5% (67.2–75.6)	..	..	OR 0.79 (0.59–1.05)	0.11

Endpoints are listed in a hierarchical testing order as stipulated in the protocol. Data for time-to-event endpoints (TFSRE, PFS, and time to PSA progression) are based on intention-to-treat patients with comparisions of dasatinib to placebo using a stratified log-rank test. Data for objective response, reduction in uNTx, and reduction in pain intensity are based on evaluable patients (as defined in the appendix) with comparisions of dasatinib to placebo using stratified Cochran-Mantel-Haenszel test. All p values are for descriptive purposes only. OR=odds ratio. HR=hazard ratio.

*Reduction of 35% or more from baseline, or to normalisation (<60 μmol/mol creatinine).

†Reduction of 30% or more from baseline.

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Table 3

Adverse events and laboratory abnormalities

	Dasatinib (N=761)					Placebo (N=757)				
	Any grade	**Grade 1–2**	**Grade 3**	**Grade 4**	**Grade 5**	**Any grade**	**Grade 1–2**	**Grade 3**	**Grade 4**	**Grade 5**
Adverse events										
Any	745 (98%)	241 (32%)	323 (42%)	131 (17%)	50 (7%)	732 (97%)	277 (37%)	305 (40%)	110 (15%)	40 (5%)
Diarrhoea	426 (56%)	366 (48%)	57 (7%)	1 (<1%)	2 (<1%)	314 (41%)	287 (38%)	25 (3%)	2 (<1%)	0
Fatigue	338 (44%)	276 (36%)	59 (8%)	3 (<1%)	0	330 (44%)	288 (38%)	41 (5%)	1 (<1%)	0
Alopecia	311 (41%)	..	..	..	..	325 (43%)	..	..	..	..
Nausea	288 (38%)	271 (36%)	17 (2%)	0	0	229 (30%)	218 (29%)	11 (1%)	0	0
Superficial oedema	184 (24%)	173 (23%)	11 (1%)	0	0	237 (31%)	226 (30%)	11 (1%)	0	0
Peripheral oedema	170 (22%)	162 (21%)	8 (1%)	0	0	217 (29%)	208 (27%)	9 (1%)	0	0
Decreased appetite	206 (27%)	192 (25%)	14 (2%)	0	0	152 (20%)	143 (19%)	9 (1%)	0	0
Back pain	146 (19%)	124 (16%)	20 (3%)	2 (<1%)	0	193 (25%)	163 (22%)	27 (4%)	3 (<1%)	0
Constipation	156 (20%)	150 (20%)	6 (1%)	0	0	192 (25%)	187 (25%)	4 (1%)	1 (<1%)	0
Asthenia	167 (22%)	127 (17%)	36 (5%)	4 (1%)	0	144 (19%)	121 (16%)	22 (3%)	1 (<1%)	0
Dyspnoea	164 (22%)	142 (19%)	19 (2%)	3 (<1%)	0	130 (17%)	109 (14%)	15 (2%)	3 (<1%)	3 (<1%)
Dysgeusia	165 (22%)	165 (22%)	0	0	0	147 (19%)	147 (19%)	0	0	0
Vomiting	170 (22%)	161 (21%)	8 (1%)	1 (<1%)	0	122 (16%)	113 (15%)	8 (1%)	1 (<1%)	0
Peripheral neuropathy	83 (11%)	74 (10%)	9 (1%)	0	0	110 (15%)	92 (12%)	17 (2%)	1 (<1%)	0
Pyrexia	148 (19%)	141 (19%)	6 (1%)	1 (<1%)	0	80 (11%)	79 (10%)	0	1 (<1%)	0
Cough	136 (18%)	134 (18%)	2 (<1%)	0	0	113 (15%)	111 (15%)	2 (<1%)	0	0
Pain in extremity	114 (15%)	106 (14%)	7 (1%)	1 (<1%)	0	129 (17%)	118 (16%)	10 (1%)	1 (<1%)	0
Arthralgia	102 (13%)	93 (12%)	8 (1%)	1 (<1%)	0	123 (16%)	113 (15%)	10 (1%)	0	0
Nail disorder	79 (10%)	79 (10%)	0	0	0	119 (16%)	115 (15%)	4 (1%)	0	0
Weight decreased	120 (16%)	113 (15%)	7 (1%)	0	0	76 (10%)	74 (10%)	2 (<1%)	0	0
Pleural effusion	118 (16%)	106 (14%)	10 (1%)	0	1 (<1%)	30 (4%)	26 (3%)	3 (<1%)	0	0
Peripheral sensory neuropathy	98 (13%)	92 (12%)	5 (1%)	1 (<1%)	0	105 (14%)	98 (13%)	6 (1%)	1 (<1%)	0
Rash	105 (14%)	105 (14%)	0	0	0	75 (10%)	75 (10%)	0	0	0
Insomnia	75 (10%)	73 (10%)	2 (<1%)	0	0	94 (12%)	92 (12%)	2 (<1%)	0	0
Lacrimation increased	48 (6%)	48 (6%)	0	0	0	86 (11%)	86 (11%)	0	0	0

	Dasatinib (N=761)					Placebo (N=757)				
	Any grade	**Grade 1–2**	**Grade 3**	**Grade 4**	**Grade 5**	**Any grade**	**Grade 1–2**	**Grade 3**	**Grade 4**	**Grade 5**
Headache	84 (11%)	77 (10%)	7 (1%)	0	0	65 (9%)	63 (8%)	2 (<1%)	0	0
Urinary tract infection	77 (10%)	69 (9%)	7 (1%)	1 (<1%)	0	69 (9%)	60 (8%)	9 (1%)	0	0
Laboratory abnormalities										
Anaemia	720 (97%)	661 (89%)	46 (6%)	13 (2%)	..	712 (95%)	668 (90%)	31 (4%)	13 (2%)	..
Neutropenia	161 (22%)	115 (16%)	19 (3%)	27 (4%)	..	84 (11%)	43 (6%)	19 (3%)	22 (3%)	..
Leukopenia	149 (20%)	119 (16%)	21 (3%)	9 (1%)	..	128 (17%)	96 (13%)	28 (4%)	4 (1%)	..
Thrombocytopenia	100 (14%)	97 (13%)	3 (<1%)	0	..	108 (14%)	102 (14%)	5 (1%)	1 (<1%)	..
Hypocalcaemia	377 (52%)	352 (49%)	14 (2%)	11 (2%)	..	308 (41%)	285 (39%)	15 (2%)	8 (1%)	..
Hypophosphataemia	257 (36%)	164 (23%)	89 (12%)	4 (1%)	..	189 (26%)	146 (20%)	36 (5%)	7 (1%)	..
Hypomagnesaemia	98 (14%)	89 (12%)	9 (1%)	0	..	108 (14%)	104 (14%)	3 (<1%)	1 (<1%)	..

Data are number of patients who had an event (% of patients). Events listed are those occurring at any grade in at least 10% of randomly assigned patients who received at least one dose of any study therapy in either treatment group. Data for laboratory abnormalities were based on laboratory assessments.