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Bosutinib plus capecitabine for selected advanced solid tumours: results of a phase 1 dose-escalation study

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Background: This phase 1 study evaluated the maximum tolerated dose (MTD), safety, and efficacy of bosutinib (competitive Src/Abl tyrosine kinase inhibitor) plus capecitabine.

Methods: Patients with locally advanced/metastatic breast, pancreatic, or colorectal cancers; cholangiocarcinoma; or glioblastoma received bosutinib plus capecitabine at eight of nine possible dose combinations using an 'up-down' design to determine the toxicity contour of the combination.

Results: Among 32 enrolled patients, none of the 9 patients receiving MTD (bosutinib 300 mg once daily plus capecitabine 1000 mg m⁻² twice daily) experienced dose-limiting toxicities (DLTs). Overall, 2 out of 31 (6%) evaluable patients experienced DLTs (grade 3 neurologic pain ($n=1$); grade 3 pruritus/rash and increased alanine aminotransferase ($n=1$)). Most common treatment-related adverse events (AEs) were diarrhoea, nausea, vomiting, palmar-plantar erythrodysesthesia (PPE), fatigue; most frequent grade 3/4 AEs: PPE, fatigue, and increased alanine/aspartate aminotransferase. Although diarrhoea was common, 91% of affected patients experienced maximum grade 1/2 events that resolved. Best overall confirmed partial response or stable disease >24 weeks (all tumour types) was observed in 6 and 13% of patients.

Conclusions: In this population of patients with advanced solid tumours, bosutinib plus capecitabine demonstrated a safety profile similar to that previously reported for bosutinib or capecitabine monotherapy; limited efficacy was observed.

Advanced solid tumours are commonly treated with chemotherapeutic agents, including capecitabine, an oral 5-fluorouracil (5-FU) prodrug that induces cell death by inhibiting thymidylate synthase (TS; Koukourakis *et al*, 2008; XELODA Full Prescribing Information, 2013). Capecitabine monotherapy has shown efficacy in metastatic colorectal cancer (overall response rate (ORR): 19%;

Van Cutsem *et al*, 2001) and in metastatic breast cancer (ORR: 15–28%; Blum *et al*, 1999, 2001; Reichardt *et al*, 2003; Fumoleau *et al*, 2004; Amari *et al*, 2010; Blum *et al*, 2012). However, resistance to 5-FU, which is mediated primarily by TS upregulation, has been observed in several solid tumour models (Beck *et al*, 1994; Johnston *et al*, 1995; Peters *et al*, 2002).

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Preclinical findings show that inhibition of the proto-oncogene, nonreceptor tyrosine kinase Src (Summy and Gallick, 2003; Parsons and Parsons, 2004), synergises with 5-FU to restore chemosensitivity in pancreatic cancer cells (Ischenko *et al*, 2008) and to increase cytotoxicity in breast cancer models (Somlo *et al*, 2013). In addition, a study in non-small-cell lung cancer cells showed synergistic cytotoxic effects with the combination of the Src inhibitor dasatinib and the TS-inhibitor pemetrexed and demonstrated that pemetrexed-induced TS upregulation is blocked via Src inhibition; notably, in that study, pretreatment TS levels were positively correlated with Src levels, and increased Src and TS levels were significantly correlated with poorer survival in the donor patients (Ceppi *et al*, 2012). These findings suggest a potential role for the combination of a TS inhibitor and a Src inhibitor in countering 5-FU resistance.

Src has been recognised as a potential therapeutic target in a number of solid tumour settings, as Src dysregulation promotes tumour progression, metastasis, invasion, and angiogenesis (Talamonti *et al*, 1993; Verbeek *et al*, 1996; Summy and Gallick, 2003; Trevino *et al*, 2006; Park *et al*, 2007; Finn, 2008; Guarino, 2010; Gleixner *et al*, 2011). Src inhibition has been shown to exert antitumour activity in cellular and xenograft models of breast cancer (Finn *et al*, 2007; Huang *et al*, 2007; Jallal *et al*, 2007) and to exert antitumour and anti-invasive activity in colon (Golas *et al*, 2005; Serrels *et al*, 2006), head and neck (Johnson *et al*, 2005; Song *et al*, 2013), prostate (Nam *et al*, 2005), non-small-cell lung (Johnson *et al*, 2005), glioblastoma (Du *et al*, 2009), and sarcoma (Shor *et al*, 2007) cancers in preclinical studies.

Dasatinib and bosutinib are dual inhibitors of the Src and Abl tyrosine kinases (Mayer and Krop, 2010). An initial phase 1 study has evaluated the combination of dasatinib (100–140 mg daily) with capecitabine (800–1000 mg m⁻² twice daily) in advanced breast cancer (*n* = 52), resulting in an ORR of 22% and manageable tolerability (Somlo *et al*, 2013). Although the ORR was similar to that reported with capecitabine monotherapy in other studies (Blum *et al*, 1999, 2001; Reichardt *et al*, 2003; Fumoleau *et al*, 2004; Amari *et al*, 2010), the phase 1 study was not powered sufficiently to assess the efficacy contributions of dasatinib to the combination (Somlo *et al*, 2013), suggesting that further evaluation of Src inhibitors in combination with capecitabine is needed.

Bosutinib (SKI-606), which is approved in the United States (Bosulif Full Prescribing Information, 2013) and Europe (Bosulif Summary of Product Characteristics, 2013) for use in Philadelphia chromosome-positive chronic myeloid leukaemia, has been shown to inhibit Src and the growth of pancreatic tumour xenografts (Messersmith *et al*, 2009), the migration and invasion of breast cancer cells (Vultur *et al*, 2008), and the growth and invasion of prostate cancer cells and xenografts (Rabbani *et al*, 2010) in preclinical models. In addition, bosutinib at a dose of 400 mg per day has shown limited activity (ORR: 5.5%; median progression-free survival (PFS): 9.9 weeks) and a manageable tolerability profile in a phase 2 study of patients (*n* = 73) with unselected, heavily pretreated advanced breast cancer (67% hormone receptor-positive; Campone *et al*, 2012). Together, these preclinical and preliminary clinical findings support the feasibility of evaluating the combination of bosutinib and capecitabine in patients with select locally advanced or metastatic solid tumours. In the present study, the maximum tolerated dose (MTD) and the safety, tolerability, and antitumour activity of this combination are assessed in patients with advanced solid tumours.

MATERIALS AND METHODS

Study design. This study was originally planned as a phase 1/2, multicentre, open-label study (ClinicalTrials.gov; Unique ID:

NCT00959946); the phase 1 portion was completed and the results are reported here. The phase 1 study used an ‘up-down’ dose-escalation design (Ivanova and Wang, 2004) to determine the MTD of bosutinib plus capecitabine combination therapy in patients with selected solid tumours. The results of a simulation study showed that, compared with a specific 3 + 3 design, this ‘up-down’ dose-escalation design allows more patients to be evaluated closer to the MTD and fewer at toxic dose levels (see Supplementary Materials). Bosutinib was administered orally once daily continuously, and capecitabine was administered orally twice daily on days 1 to 14 of each 21-day treatment cycle. Up to nine dose combinations, including three dose levels of bosutinib (200, 300, and 400 mg) and three dose levels of capecitabine (625, 750, and 1000 mg m⁻²), were selected as possible dose levels. The initial dose cohorts with two patients each were (i) bosutinib 200 mg per day plus capecitabine 750 mg m⁻² twice daily and (ii) bosutinib 300 mg per day plus capecitabine 625 mg m⁻² twice daily.

Additional cohorts could be enrolled at higher or lower dose levels based on the number of dose-limiting toxicities (DLTs; described below) observed during the first 21 days in the current cohort of two patients, the cumulative toxicity rate at that dose combination, and the current doses of bosutinib and capecitabine. Cohort enrollment was based on the rules presented in Table 1 (see Supplementary Materials for additional information). The ‘up-down’ dose-escalation design allowed up to nine dose combinations across the two drugs studied (Table 2). This design would also allow the possibility of achieving two concurrent MTD levels, one that would maximise bosutinib and the other that would maximise capecitabine, in the event that increasing both concurrently proved untenable. Patients were enrolled at the next dose level when two evaluable patients at the same dose level had been evaluated for the first 21-day treatment cycle and had received at least 14 doses of bosutinib and at least 10 doses of capecitabine or experienced a DLT, whichever occurred first, until a total of 24 evaluable patients were assessed. If a patient withdrew from the study before completing the 21-day period without experiencing a DLT, another patient was enrolled to replace that patient at the current dose combination.

DLTs were defined as any of the following treatment-related events that occurred during the first 21-day cycle: grade 3/4 non-haematologic adverse event (AE), including nausea, vomiting, or diarrhoea despite optimal medical therapy, and asthenia lasting more than 3 days; grade 4 haematologic AE; or delayed recovery from one of the above AEs, causing delay of treatment by at least 3 weeks.

Table 1. Cohort enrollment rules

Number of DLTs in current cohort ^a	Cumulative toxicity rate	Next enrollees
0	<33%	2 Patients at 1 level higher for bosutinib (capecitabine unchanged) 2 patients at 1 level higher for capecitabine (bosutinib unchanged)
0	≥33%	2 Patients at 1 level lower for bosutinib and 1 level higher for capecitabine
1 or 2	<33%	2 Patients at 1 level higher for bosutinib and 1 level lower for capecitabine
1 or 2	≥33%	If the current bosutinib level > capecitabine, 2 subjects at 1 level lower bosutinib (capecitabine unchanged). Otherwise, 2 subjects at 1 level lower capecitabine (bosutinib unchanged)

Abbreviation: DLT = dose-limiting toxicity.
^aOut of two patients.

The MTD for bosutinib plus capecitabine was defined as the highest dose level at which less than 33% of patients experienced a DLT.

Written informed consent was obtained from all patients before enrollment. The protocol was reviewed and approved by the Ethics Committees/Institutional Review Boards of the participating institutions, and the study was conducted according to the Declaration of Helsinki and European Good Clinical Practice requirements.

Eligibility criteria. Eligible patients were men and women aged ≥ 18 years with a confirmed pathologic diagnosis of locally advanced or metastatic breast cancer, pancreatic cancer, colorectal cancer, cholangiocarcinoma, or glioblastoma that was not curable with approved regimens. Patients were also required to have at least one radiologically measurable lesion as defined by the Response Evaluation Criteria In Solid Tumors (RECIST), version 1.0, and an Eastern Cooperative Oncology Group Performance Status score of 0 to 2. Bone or skin could not be the only site of disease, and patients with clinically unstable primary or metastatic central nervous system tumours were ineligible. No prior treatment with Src inhibitors was permitted; however, prior treatment with capecitabine or 5-FU was allowed unless stopped for toxicity. No chemotherapy, investigational therapy, major surgery, or radiation therapy within 14 days of study treatment initiation was allowed. Patients with any other major illness, including a history of clinically significant or uncontrolled cardiac disease, serious active infection, uncontrolled major seizure disorder, or significant pulmonary disorder, were ineligible.

Safety and efficacy assessments. The primary safety objective was to determine the MTD of bosutinib plus capecitabine in patients with solid tumours by examining the DLT rates within the dose cohorts. All patients who received at least one dose of study treatment were included in the safety evaluation, which included the incidence of AEs, physical examination, laboratory evaluations, 12-lead electrocardiogram, and left ventricular ejection fraction measurement. Safety events were graded for severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Tumour assessments were performed for all patients at screening, and response was assessed every 6 weeks until disease progression or treatment discontinuation. No primary efficacy end point was specified; the secondary objective of antitumour activity was assessed based on best confirmed overall response according to

RECIST version 1.0 (Therasse *et al*, 2000) and ORR (confirmed complete response (CR) or partial response (PR)).

RESULTS

Patients. A total of 32 patients were enrolled in this phase 1 study between October 2009 and March 2011, among whom, the median age was 62 (range, 42–82) years (Table 3). The majority of patients had a diagnosis of colorectal cancer (44%), breast cancer (34%), or pancreatic cancer (16%); cholangiocarcinoma and glioblastoma were each present in one patient. Most (69%) patients had previously received at least five antitumour treatment regimens for locally advanced or metastatic disease; 22% of patients had previously received capecitabine treatment.

The median study duration was 81.0 days (range, 22–420 days), with a median duration of treatment of 63.5 days (range, 19–419 days). All patients discontinued the study, the primary reasons for which included disease progression (*n* = 26 (81%)), AEs (*n* = 4 (13%)), death (*n* = 1 (3%)), and patient withdrawal (*n* = 1 (3%)).

Determination of the MTD. Because of the adaptive nature of the study design, all possible dose combinations shown in Table 2 were explored at least once, with the exception of bosutinib 400 mg per day plus capecitabine 625 mg m⁻² twice daily. The sequence of patient enrollment in each dose-escalation cohort is shown in Table 4. Based on the observed toxicity, the MTD was determined to be bosutinib 300 mg per day plus capecitabine 1000 mg m⁻² twice daily on days 1–14 of each 21-day treatment cycle, with no DLTs observed for the two patients treated at the MTD during the dose-escalation phase. An additional seven patients were subsequently

Table 2. Dose combinations for determination of the MTD

Capecitabine, mg m ⁻² twice daily	Bosutinib, mg per day		
	200, <i>n</i>	300, <i>n</i>	400, <i>n</i>
1000	4	9 ^{a,b}	2 ^c
750	4 ^d	4	2 ^c
625	2	5 ^{d,e}	

Abbreviations: DLT = dose-limiting toxicity in patients who experienced a DLT within the first 21 days of treatment, regardless of the number of treatment doses received, or in patients who received ≥ 14 doses of bosutinib and ≥ 10 days of capecitabine in the first 21 days of treatment; MTD = maximum tolerated dose (shaded in table); *n* = total number of patients enrolled at each dose combination.

^aBased on the DLTs, the MTD was determined to be bosutinib 300 mg per day plus capecitabine 1000 mg m⁻² (which is shaded in the table). No DLTs were observed at the MTD dose level.

^bTwo patients were initially enrolled at the MTD level, for a total of 24 patients included in the initial DLT evaluation; an additional seven patients were subsequently enrolled at this dose level to allow further evaluation and confirmation of the MTD.

^cDLTs were observed in 1 (50%) patient in the bosutinib 400 mg per day plus capecitabine 1000 mg m⁻² group (grade 3 alanine aminotransferase and pruritus/rash) and 1 (50%) patient in the bosutinib 400 mg per day plus capecitabine 750 mg m⁻² group (grade 3 neurologic pain).

^dInitial dose cohorts investigated.

^eOne of the five patients treated at this dose level was excluded from the DLT evaluation because of no DLT and failure to receive ≥ 14 doses of bosutinib or ≥ 10 doses of capecitabine.

Table 3. Patient demographic and baseline disease characteristics

Characteristic	N = 32
Age (years)	
Median (range)	62 (42–82)
Sex, <i>n</i> (%)	
Women	18 (56)
Men	14 (44)
Race, <i>n</i> (%)	
White	24 (75)
Asian	7 (22)
Black/African American	1 (3)
ECOG performance status,^a <i>n</i> (%)	
0	20 (63)
1	12 (38)
Tumour type, <i>n</i> (%)	
Colorectal cancer	14 (44)
Breast cancer	11 (34)
Pancreatic cancer	5 (16)
Cholangiocarcinoma	1 (3)
Glioblastoma	1 (3)
No. of prior regimens in the locally advanced or metastatic setting	
0	1 (3)
1	4 (13)
2	1 (3)
3	1 (3)
4	3 (9)
≥ 5	22 (69)
Prior capecitabine treatment	
<i>n</i> (%)	7 (22)

Abbreviation: ECOG = Eastern Cooperative Oncology Group.

^aPercentages may not total 100% because of rounding.

Table 4. The sequence of patient enrollment in each dose-escalation cohort^a

Sequence of cohort enrollment	Cohort					Next dose cohort
	Dose level (CAPE (mg m ⁻²)/ BOS (mg))	Number	Patients enrolled, n	Patients evaluable for DLT, n	DLT	
1	750/200	C1	2	2	None	C3/C4
2	625/300	C2	3 ^b	2	None ^c	C7
3	750/300	C3	2	2	None	C5/C6
4	1000/200	C4	2	2	None	C8 ^d
5	750/400	C5	2	2	1 DLT: Grade 3 neurologic pain	C9
6	1000/300	C6	2	2	None	C10
7	625/200	C7	2	2	None	C11/C12
8	750/300	C9	2	2	None	NA ^e
9	1000/200	C8	2	2	None ^f	NA
10	1000/400	C10	2	2	1 DLT in 1 patient: Grade 3 ALT increased Grade 3 itchy skin Grade 3 skin rash	
11	750/200	C11	2	2	None	NA ^e
12	625/300	C12	2	2	None	NA ^e

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; BOS = bosutinib; C = cohort; CAPE = capecitabine; DLT = dose-limiting toxicity; NA, not applicable.

^aData snapshot date: 06 July 2011.

^bOne patient was not evaluable for DLTs and was replaced.

^cA DLT occurred in Cohort 2 at the time enrollment in Cohort 7 was initiated; however, during subsequent review, the corresponding AE (grade 3 ALT increased) was not deemed to be a DLT.

^dAfter completion of Cohort 4, two additional patients were enrolled in Cohort 8 (same dose level) per protocol because Cohort 6 was already enrolling.

^eEnrollment in subsequent cohorts after Cohort 8 was not required because enrollment of 24 evaluable patients had been completed as the last patient finished Cohort 8.

^fA DLT occurred in Cohort 8; however, during subsequent review, the corresponding AE (grade 4 fatigue) was deemed not a DLT during a subsequent review. This DLT did not affect cohort enrollment as 24 subjects had already been enrolled when C8 was finished.

enrolled at the MTD to confirm the selected dose, and again no DLTs were observed. Only one MTD was identified for this combination.

Overall, 2 out of 31 (6%) evaluable patients experienced DLTs. The first patient was a 56-year-old woman with metastatic breast cancer who was receiving bosutinib 400 mg per day plus capecitabine 750 mg m⁻² twice daily and experienced grade 3 neurologic pain on study day 5. Bosutinib 400 mg per day was stopped on study day 8 and bosutinib 300 mg per day was started on study day 14, after the neurologic pain resolved to grade 1. The second patient was a 58-year-old woman with metastatic breast cancer who was receiving bosutinib 400 mg per day plus capecitabine 1000 mg m⁻² twice daily who experienced grade 3 increased alanine aminotransferase (ALT) and pruritus/rash, both of which resolved following temporary discontinuation of bosutinib. These DLTs were considered to be treatment related; association with either bosutinib or capecitabine treatment was not determined. One additional patient receiving bosutinib 200 mg per day plus capecitabine 1000 mg m⁻² twice daily experienced grade 2 fatigue, which later progressed to grade 4 severity one day after the 21-day DLT assessment period; because of this timing the event did not meet the DLT criteria. The recommended MTD of the combination would not have changed if this subject met the DLT criteria. Notably, DLTs resolved after temporarily stopping treatment and none of these events were considered by the investigators to be serious AEs.

Safety and tolerability. All 32 (100%) patients experienced at least one treatment-emergent AE among whom 29 (91%) experienced at least one treatment-related (bosutinib and/or capecitabine) AE. The most common treatment-related AEs, overall as well as within the MTD cohort, were diarrhoea, nausea, palmar-plantar erythrodysesthesia (PPE), fatigue, and vomiting (Table 5). A total of 15 (47%) patients experienced at least one grade 3/4 treatment-related AE, most frequently PPE, increased ALT, and increased aspartate aminotransferase (AST; Table 5). Ten (31%) patients experienced

at least one serious AE, including anaemia, atrial fibrillation, constipation, gastrointestinal obstruction, asthenia, chest pain, hemiparesis, renal impairment, acute respiratory distress syndrome, dyspnoea (*n* = 1 each); bronchitis (*n* = 2), and disease progression (glioblastoma multiforme (*n* = 1), malignant neoplasm (*n* = 2); pancreatic cancer (*n* = 1)).

Although diarrhoea was common (*n* = 23 (72%)), 91% (21 out of 23) of patients with diarrhoea experienced only maximum grade 1 or 2 events, all patients had their diarrhoea resolved (median (range) cumulative duration of 10 (1–267) days), and no patient discontinued treatment because of diarrhoea, suggesting that events were manageable. Two (9%) patients required dose interruption, and one (4%) patient had dose reduction in order to manage their diarrhoea events. Treatment-emergent AEs of grade 3/4 ALT or AST elevations were reported in three (9%) and three (9%) patients, respectively; these events were managed by dose interruption in two and two patients, respectively, and all resolved with no patient discontinuing treatment. Treatment-related haematologic AEs were relatively uncommon, with one patient each experiencing maximum grade 1 or 2 leukopenia, lymphopenia, neutropenia, and thrombocytopenia. Cardiac events were reported in five (16%) patients; four of these subjects with events considered drug related, one of which was a serious AE of atrial fibrillation observed in a patient with a history of peripheral arterial occlusive disease and hypertension, who was receiving Warfarin. Prolonged QT (grade 2) was reported in two patients, and decreased ejection fraction (grade 3) was reported in one patient; all had a prior history of cardiac disease. Most of the resolved cardiac events were transient, with cumulative median (range) duration of 16 (10–22) days, and all but one of the patients (grade 3 decreased ejection fraction) had their cardiac events resolve. Cumulative duration for this patient is unknown.

Grade 3/4 laboratory values were reported in nine (28%) patients on treatment, and included abnormal sodium values

Table 5. Treatment-related AEs and treatment modifications and discontinuations due to AEs

Treatment-related AEs	MTD cohort (n = 9)		All patients (N = 32)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any AE, ^a n (%)	9 (100)	4 (44)	29 (91)	15 (47)
Diarrhoea	8 (89)	0	21 (66)	2 (6)
Nausea	4 (44)	0	13 (41)	0
PPE	3 (33)	1 (11)	10 (31)	3 (9)
Fatigue	4 (44)	0	9 (28)	2 (6)
Vomiting	2 (22)	0	8 (25)	0
Decreased appetite	2 (22)	0	5 (16)	0
Increased ALT	2 (22)	1 (11)	4 (13)	3 (9)
Mucosal inflammation	2 (22)	0	4 (13)	0
Increased AST	2 (22)	2 (22)	3 (9)	3 (9)
Rash	1 (11)	0	3 (9)	1 (3)
Constipation	1 (11)	0	3 (9)	0
Gastroesophageal reflux disease	0	0	3 (9)	0
Pain in extremity	0	0	2 (6)	0
Peripheral sensory neuropathy	0	0	3 (9)	0
Dyspnoea	0	0	2 (6)	1 (3)
Abdominal pain	1 (11)	0	4 (13)	0
Dry skin	0	0	2 (6)	0
Headache	1 (11)	0	2 (6)	0
Flatulence	1 (11)	0	2 (6)	0
Electrocardiogram QT prolonged	0	0	2 (6)	0
Decreased ejection fraction	1 (11)	1 (11)	1 (3)	1 (3)
Hypophosphatemia	1 (11)	1 (11)	1 (3)	1 (3)
Atrial fibrillation	0	0	1 (3)	1 (3)
Chest pain	0	0	1 (3)	1 (3)
Hypersensitivity	0	0	1 (3)	1 (3)
Neuralgia	0	0	1 (3)	1 (3)
Pruritus	0	0	1 (3)	1 (3)
Treatment modifications and discontinuations due to AEs, n (%)	MTD cohort (n = 9)		All patients (N = 32)	
Dose reduction				
Bosutinib	1 (11)		3 (9)	
Capecitabine	1 (11)		4 (13)	
Dose interruption				
Bosutinib	3 (33)		11 (34)	
Capecitabine	4 (44)		16 (50)	
Discontinuation				
Discontinued treatment ^b	1 (11)		4 (13)	

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; MTD = maximum tolerated dose; PPE = palmar-plantar erythrodysesthesia.
^aIncludes all treatment-related grade 3/4 AEs as well as all treatment-related AEs of any grade reported for ≥ 2 patients or for which at least one report was a grade 3/4 AE.
^bAEs leading to treatment discontinuation include right hemiparesis (due to disease progression that led to death) and asthenia (n = 1), fatigue (n = 1), bronchitis (that led to death) and acute respiratory distress syndrome (n = 1), and PPE (n = 1). In addition, three other patients had AEs related to disease progression that led to treatment discontinuation, reported as malignant neoplasm (n = 2) and glioblastoma multiforme (n = 1).

(n = 3); international normalised ratio, partial thromboplastin time, phosphorous, calcium, ALT, and prothrombin time (n = 2 each); and glucose, AST, and haemoglobin (n = 1 each). Grade 3/4 partial thromboplastin time and prothrombin time increases were reported in one patient both at baseline and on treatment. Based on electrocardiogram laboratory data, no patient had a QT or corrected QT (QTc) interval greater than 500 ms.

Bosutinib and capecitabine dose modifications due to AEs are shown in Table 5. Bosutinib dose reduction and interruption due to an AE occurred in 9% and 34% of patients, respectively. Capecitabine dose reduction and interruption due to an AE occurred in 13% and 50% of patients, respectively. Four (13%) patients experienced AEs that led to treatment discontinuation; AEs included right hemiparesis (due to disease progression that led to death) and asthenia (n = 1), fatigue (n = 1), bronchitis (that led to death) and acute respiratory distress syndrome (n = 1), and PPE syndrome

(n = 1). In addition, three other patients had AEs related to disease progression that led to treatment discontinuation, reported as malignant neoplasm (n = 2) and glioblastoma multiforme (n = 1). Of the AEs that led to treatment discontinuation, only PPE and fatigue were considered treatment related.

Overall, six (19%) deaths occurred during the study, with five deaths occurring within 28 days of the last study dose. Five of the six deaths were due to disease progression (primary diagnoses of pancreatic cancer (n = 2); breast cancer, glioblastoma multiforme, and colorectal cancer (n = 1 each)), whereas the other was due to an unrelated AE of bronchial infection (n = 1). None of the deaths were considered drug related.

Antitumour activity. Among the intent-to-treat population (n = 32), one patient with breast cancer and one patient with colorectal cancer achieved a confirmed PR; no patient achieved a

CR (ORR: 6% (95% CI: 1–21%)). Stable disease (SD) lasting ≤ 24 weeks was observed in 10 patients (breast cancer ($n=3$); colorectal cancer ($n=7$)); SD lasting >24 weeks was observed in an additional 4 patients (breast cancer ($n=2$); colorectal cancer ($n=2$)). None of the patients with pancreatic cancer, cholangiocarcinoma, or glioblastoma achieved a response or SD. A total of 15 patients (cholangiocarcinoma ($n=1$); colorectal cancer ($n=4$); breast cancer ($n=5$); and pancreatic cancer ($n=5$)) had a best response of progressive disease. The response status of the patient with glioblastoma was indeterminate because the patient did not have any post-baseline tumour assessments and discontinued treatment before their week 6 assessment because of an AE.

DISCUSSION

The primary purpose of this study was to determine the MTD of bosutinib plus capecitabine in patients with select locally advanced or metastatic solid tumours. The MTD of this treatment combination was bosutinib 300 mg per day plus capecitabine 1000 mg m^{-2} twice daily on days 1–14 of each 21-day cycle.

A challenge in developing combination regimens incorporating a novel agent is whether the chemotherapy dose should be maximised with increasing doses of the novel agent, or whether the novel agent should be maximised with increasing doses of chemotherapy. The ‘up-down’ design allows for both possibilities to be explored, with the possibility of achieving up to three MTD levels for the combination. A similar ‘up-down’ design was used in a recent phase 1 study to evaluate the MTD of neratinib in combination with temsirolimus in patients with solid tumours (Gandhi *et al*, 2014).

The 3+3 design is the most common method for dose evaluation in phase 1 studies and has the advantages of ease of implementation and interpretation, together with the requirement for smaller numbers of patients (Le Tourneau *et al*, 2009; Liu *et al*, 2013). However, drawbacks of this method include the need for a large number of dose escalation steps (e.g., ≥ 6 dose levels) and treatment of many patients at subtherapeutic doses, as well as uncertainty surrounding the recommended phase 2 dose identified (Le Tourneau *et al*, 2009). In contrast, the ‘up-down’ design used in the present study allows for exploration of more dose combinations. Although the ‘up-down’ design allows for a more definitive identification of the MTD, the additional dose combinations evaluated require enrollment of additional patients. The simulation study also demonstrated that, compared with a specific 3+3 design, more patients are evaluated closer to the MTD and fewer patients at toxic dose levels using the ‘up-down’ design. Moreover, the ‘up-down’ design mitigates the underestimation of the MTD that is associated with the 3+3 design.

Notably, the MTD for bosutinib (300 mg per day) in combination with capecitabine in this study is lower than the therapeutic dose identified for bosutinib monotherapy in previous studies—500 mg per day in patients with chronic/advanced phase CML (Cortes *et al*, 2011, 2012) and 400 mg per day in patients with advanced solid tumours (Daud *et al*, 2012). In addition, the MTD identified for capecitabine (1000 mg m^{-2} twice daily) in this study is lower than the 1250 mg m^{-2} twice-daily dose recommended by the US Food and Drug Administration for metastatic breast cancer (XELODA Full Prescribing Information, 2013). However, retrospective analysis of medical and pharmacy records from 141 patients with metastatic breast cancer treated with capecitabine 1250 mg m^{-2} twice daily demonstrated greater toxicity at that dose than previously reported in clinical studies, supporting a starting dose of 1000 mg m^{-2} twice daily (Hennessy *et al*, 2005). Thus, the MTD dose of capecitabine identified in the current study (1000 mg m^{-2} twice daily) may be better aligned with clinical

practice than the 1250 mg m^{-2} twice-daily dose, and it is within the range of doses (1000–1250 mg m^{-2} twice daily) recommended by the National Comprehensive Cancer Network (National Comprehensive Cancer Network, 2014).

In the present study, the combination of bosutinib and capecitabine (all dose combinations) was well tolerated, which might reflect the fact that 88% of patients received bosutinib at doses lower than 400 mg per day and 53% received capecitabine at a dose lower than 1000–1250 mg m^{-2} twice daily. Comparing AE incidence between the MTD cohort ($n=9$) and all patients excluding those receiving the MTD ($n=23$), incidence was increased in MTD-treated patients for AEs commonly reported with bosutinib (i.e., diarrhoea, 89% vs 57%; increased ALT, 22% vs 9%; increased AST, 22% vs 4%), suggesting efficient selection of the MTD for bosutinib. In contrast, the most frequent AE reported with capecitabine across clinical trials—PPE (i.e., hand-foot syndrome)—was not elevated in patients receiving the MTD versus all other patients (33% vs 30%); it is unclear whether assessment of a higher dose of capecitabine (e.g., 1250 mg m^{-2} twice daily) in the present study would have yielded different outcomes.

Consistent with the known AE profiles for bosutinib and capecitabine monotherapy, the AE profile of the combination of bosutinib and capecitabine was characterised mostly by mild gastrointestinal events (diarrhoea, nausea, vomiting), PPE, and fatigue. Grade 3/4 ALT and AST elevations were reported in $<10\%$ of patients, and were manageable with no patient discontinuing treatment because of these AEs. The toxicity profile previously observed for bosutinib monotherapy in phase 1 and 2 studies in solid tumours was also generally characterised by mild gastrointestinal events that occurred early during treatment, and manageable ALT and AST elevations (Campone *et al*, 2012; Daud *et al*, 2012). Capecitabine has a well-established toxicity profile that is primarily characterised by high incidences of PPE, diarrhoea, nausea, vomiting, and stomatitis (Hennessy *et al*, 2005). Comparing the incidences of treatment-related AEs in the present study with those previously published for capecitabine monotherapy at a dose of 2510 mg m^{-2} daily in patients with paclitaxel-refractory metastatic breast cancer (Blum *et al*, 1999), certain treatment-related AEs occurred at lower incidence in the present study (all patients), including PPE (31% vs 56%), nausea (41% vs 52%), and vomiting (25% vs 37%), whereas diarrhoea occurred at a higher rate in the present study (66% vs 54%). Notably, PPE events were not observed in studies evaluating bosutinib as monotherapy (Campone *et al*, 2012; Daud *et al*, 2012); thus, the occurrence of PPE events in the current study was likely attributable to capecitabine administration (XELODA Full Prescribing Information, 2013).

The tolerability results in this study are comparable with those seen in a phase 1 study designed to identify DLTs and the recommended phase 2 doses of dasatinib (another dual Abl/Src TKI) plus capecitabine in women with advanced breast cancer (Somlo *et al*, 2013). Consistent with the current study, some of the most common toxicities associated with dasatinib plus capecitabine observed in that study were gastrointestinal events (nausea, vomiting, and diarrhoea), PPE, headache, fatigue, and asthenia (Somlo *et al*, 2013). Moreover, the overall rate of treatment-related grade 3/4 AEs reported here for bosutinib plus capecitabine (47%) is also consistent with those reported for dasatinib plus capecitabine (50%; Somlo *et al*, 2013).

The observed efficacy results should be considered limited, given the lack of a prespecified efficacy end point and the small number of patients evaluated at the MTD ($n=9$). In this study, two patients (breast cancer, $n=1$; colorectal cancer, $n=1$) achieved a confirmed PR while receiving capecitabine at a lower dose than MTD (750 mg m^{-2} twice daily) plus bosutinib 300 mg per day. A phase 1 study of bosutinib monotherapy administered over a range of escalating doses in patients with advanced solid tumours demonstrated a confirmed PR in one patient with breast

cancer, an unconfirmed CR in one patient with pancreatic cancer, and SD in five patients with colorectal or lung cancer lasting 22–50 weeks (Daud *et al*, 2012). In a phase 2 clinical study of single-agent bosutinib 400 mg per day in heavily pretreated patients with advanced breast cancer unselected for hormone receptor status, four patients achieved a confirmed PR; each of these four patients had hormone receptor-positive breast cancer (Campane *et al*, 2012).

Studies of single-agent capecitabine 1250 mg m⁻² twice daily for the treatment of patients with advanced or metastatic breast cancer have reported ORRs ranging from 15 to 28% and SD rates (any duration) ranging from 30 to 46% (Blum *et al*, 1999, 2001; Reichardt *et al*, 2003; Fumoleau *et al*, 2004; Amari *et al*, 2010). Patients with metastatic breast cancer treated with dasatinib plus capecitabine also achieved some clinical benefit in a phase 1 trial, as reflected by an ORR of 22% and an additional 30% experiencing SD lasting more than 24 weeks (Somlo *et al*, 2013). The overall SD rate of 50% observed for dasatinib plus capecitabine is consistent with the overall SD rate with bosutinib plus capecitabine observed here (44%). In contrast, the ORR of 22% reported for the dasatinib plus capecitabine combination (Somlo *et al*, 2013) is higher than the ORR reported for capecitabine plus bosutinib reported here (6%; Somlo *et al*, 2013). The observation that none of the patients with pancreatic cancer in this study achieved a CR or PR with bosutinib plus capecitabine treatment might be expected based on the results of a previous phase 2 study showing that only 3 of 41 patients receiving single-agent capecitabine for pancreatic cancer achieved a PR (ORR, 7%; Cartwright *et al*, 2002). However, comparisons of response rates across these studies are complicated by variations in study design and in patients' baseline characteristics. For example, the current study was a phase 1 study with a limited number of breast cancer patients, most of whom had received substantial amounts of prior therapy, and who had received capecitabine doses lower than those associated with single-agent efficacy (1250 mg m⁻² twice daily; XELODA Full Prescribing Information, 2013).

The identification of patient subgroups most likely to benefit from therapy represents one of the major challenges in the development of novel targeted therapies in breast and other cancers; a number of clinical studies are currently ongoing to assess biomarkers predictive of response to dasatinib and other Src inhibitors in advanced solid tumours (Puls *et al*, 2011). For example, a phase 1 study of dasatinib in combination with capecitabine, oxaliplatin, and bevacizumab in patients with colorectal cancer showed that high expression levels of activated Src are predictive of improved response (Strickler *et al*, 2013). However, these studies are generally limited by the difficulties in assessing correlations between biomarker levels with response, given the small numbers of treatment responders (Strickler *et al*, 2013).

In conclusion, the combination of bosutinib plus capecitabine was associated with a manageable safety profile, which was primarily characterised by mild gastrointestinal events and similar to that previously observed for bosutinib or capecitabine monotherapy. Evidence supporting the efficacy of bosutinib plus capecitabine in patients with advanced solid tumours is limited; rigorous evaluation of the efficacy of bosutinib combined with capecitabine or with other agents for the treatment of advanced solid tumours, including breast cancer, awaits a suitably powered randomised clinical trial recruiting patients selected on the basis of Src inhibitor biomarkers that may optimise their treatment response.

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