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## Phase I study of the combination of crizotinib (as a MET inhibitor) and dasatinib (as a c-SRC inhibitor) in patients with advanced cancer

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### Abstract

**Background**—Both MET and c-SRC are important mediators of cancer progression and there is cross talk between the two molecules. Preclinical studies have demonstrated combination of MET and c-SRC inhibitors is effective in multiple cancer types.

**Methods**—We analyzed the safety and efficacy of administering a c-SRC inhibitor (dasatinib) in combination with a MET inhibitor (crizotinib) in a two-arm concurrent phase I study. Arm A consisted of crizotinib fixed at 250 mg twice per day with escalation of dasatinib. Arm B consisted of dasatinib fixed at 140 mg daily with escalation of crizotinib. Endpoints included dose-limiting toxicities (DLTs), recommended phase II dose (RP2D), and response (RECIST 1.1).

**Results**—We enrolled 61 patients (arm A: 31, arm B: 30). The most common cancers were sarcoma (21%) and prostate cancer (16%). In Arm A, at dose level 2 (DL2), 40% (2/5) experienced DLTs. In the expanded DL1, 21% (4/19) experienced DLTs (all grade 3). In Arm B, at DL2, 50% (2/4) experienced DLTs. In the expanded DL1, 22% (4/18) experienced DLTs (all grade 3). RP2D was determined to be arm A, DL1 (250 mg crizotinib orally twice per day plus 50 mg dasatinib orally daily). Partial response (N=1) and stable disease for 6 months (N=3) were seen.

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**Compliance with Ethical Standards:**

**Conflicts of interest:** The authors have no conflicts of interest to report.

**Ethical approval:** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent:** Informed consent was obtained from all individual participants included in the study.

**Conclusions**—The combination of crizotinib and dasatinib is safe to administer but tolerability is limited given the high rate of adverse events. Responses and durable stable disease were limited. Further precision therapy approach using this specific combination may be difficult given the toxicity.

### Keywords

Crizotinib; dasatinib; phase I; safety; MET; c-Src

## INTRODUCTION

MET is a receptor tyrosine kinase that is activated by binding with its ligand, hepatocyte growth factor/scatter factor (HGF/SF) (1). Various carcinomas overexpress MET, and the surrounding stroma overexpresses HGF/SF (1). MET activation leads to modification of multiple signaling pathways, including c-SRC, RAS-MAPK, and PI3K-AKT, regulating cancer proliferation, invasion, and metastasis (1). Amplification or activation of MET has also been associated with resistance to anti-EGFR therapy in *EGFR*-mutated lung cancer (2) and anti-BRAF therapy in *BRAF*V600-mutated melanoma and colon cancer (3,4). Thus, MET has been an attractive target in cancer therapeutics (1), and multiple small-molecule inhibitors and antibodies against HGF and MET are in clinical development (5).

Although MET has been a target of interest, clinical trials targeting the HGF-MET axis have not been successful even when a combination approach was used (6). One example is a phase III randomized study of erlotinib in combination with onartuzumab (an anti-MET monoclonal antibody) or placebo among patients with previously treated advanced MET-positive non-small cell lung cancer. That study did not demonstrate clinical benefit when onartuzumab was added to erlotinib (for onartuzumab plus erlotinib compared with placebo plus erlotinib, median progression-free survival duration of 2.7 months compared with 2.6 months [ $p = 0.92$ ] and response rate of 8.4% compared with 9.6% [ $p = 0.63$ ]) (7).

The unsuccessful clinical outcomes of MET inhibition could be due to an underlying resistance mechanism. One resistance mechanism from MET inhibition involves interaction with c-SRC. A preclinical study demonstrated that the downstream effects of MET activation by its ligand, HGF, require activation of c-SRC, which leads to interactions among key oncogenic pathways, such as RAS-MAPK and PI3K-AKT (8). In head and neck squamous cell carcinoma (HNSCC) cell lines, sustained MET activation following c-SRC inhibition led to resistance to c-SRC inhibition. The combination of c-SRC and MET inhibitors was synergistic and caused apoptosis in HNSCC cell lines in vitro and decreased tumor size in vivo (9). Another preclinical study using glioblastoma multiforme cell lines showed that among combinations of 12 different tyrosine kinase inhibitors, crizotinib plus dasatinib demonstrated the most cytotoxic combination regimen (10).

Thus, targeting the MET and c-SRC pathways may be effective combination approach to control cancer. Given the supporting preclinical evidence (8,9), we have initiated the first inhuman attempt to determine the safety of administering the combination of crizotinib (multikinase inhibitor including MET) and dasatinib (multikinase inhibitor including c-SRC) in patients with solid tumors (NCT01744652). The primary endpoint of this phase I trial was

to determine dose-limiting toxicities (DLTs) and the recommended phase II dose (RP2D) of this two-drug combination. A secondary endpoint was to investigate the antitumor effects of this combination.

## PATIENTS AND METHODS

### Patients

Patients were eligible for the study when they had a pathologically confirmed solid malignancy that was metastatic or unresectable and for which standard curative or palliative measures that improve survival by at least three months did not exist. Other eligibility criteria were as follows: age  $\geq$  16 years, Eastern Cooperative Oncology Group performance status of 0 to 2, absolute neutrophil count  $\geq$  1,000/ $\mu$ L, platelet count  $\geq$  75,000/ $\mu$ L, total bilirubin  $\leq$  2.0 mg/dL, and aspartate aminotransferase/alanine aminotransferase  $\leq$  2.5 $\times$  upper limit of normal (if liver metastasis was present, then  $\leq$  5.0 $\times$  upper limit of normal). Patients were excluded if they were receiving any concurrent chemotherapy or experiencing any severe or uncontrolled medical disease (e.g., active infection, cardiovascular issues), symptomatic congestive heart failure (New York Heart Association class III or IV) or unstable angina pectoris, known pulmonary hypertension, or inability to swallow oral medication. Patient had been off previous investigational or cytotoxic therapies for at least 3 weeks or within 5 half-lives of biological targeted agents.

This study was approved by the institutional review board at The University of Texas MD Anderson Cancer Center, Houston, TX and written informed consent was obtained from all patients (NCT01744652).

### Study design

This was a two arm Phase I study utilizing modified “3+3” design. One arm (Arm A) received crizotinib 250mg PO twice a day plus an increasing dose of dasatinib. The other arm (Arm B) received dasatinib 140mg PO daily plus an increasing dose of crizotinib. Both arms followed a standard 3+3 phase I dose escalation design. In short, three patients were treated at first dose level and evaluated for toxicity. If none of the patient experience DLT, the next cohort of three patients were treated at the next higher dose level. If one of three patients treated at a dose experiences DLT, then that cohort was expanded to a total of six patients. If the incidence of DLT among those six patients is one in six, then the next cohort was treated at the next higher dose level. If two or more of six patients treated at a dose level experience DLT, then the maximum tolerated dose (MTD) was considered to have been exceeded. In the case that both arms defined the same dose level as the MTD, then the patient enrollment was expanded to further assess the MTD. DLT was defined as having any clinically grade 3 or 4 non-hematologic toxicity and grade 4 neutropenia or thrombocytopenia lasting at least 1 week or longer. The expansion cohort helped further define the RP2D. The arm with the least percentage of DLTs defined the final RP2D of the combination to be used.

## Response assessment

Response and progression was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) guideline version 1.1 every 8 weeks (11). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes were used in the RECIST criteria.

## Statistical analysis

Descriptive statistics were used to summarize demographic information, such as age and sex, as well as toxic effects and treatment outcomes.

## RESULTS

### Patient characteristics

The baseline clinical and demographic characteristics of patients enrolled in the study are summarized in Table 1. Overall, 61 patients with advanced cancer were enrolled, including 31 patients in arm A (250 mg of crizotinib by mouth twice per day with dasatinib dose escalation) and 30 patients in arm B (140 mg of dasatinib by mouth daily with crizotinib dose escalation). Among the 61 patients enrolled, 18 (30%) were female and the median age was 58 years (range 16–76 years). Most patients (49/61; 80%) had an Eastern Cooperative Oncology Group performance status of 1. Patients were heavily treated with prior systemic therapy; the median number of prior therapies was four regimens (range 0–11) in arm A and three (range 1–7) in arm B. Among the 61 patients enrolled, the most common diagnosis was sarcoma (13/61; 21%), followed by prostate cancer (10/61; 16%) and colorectal cancer (5/61; 8%). However, all patients with prostate cancer were enrolled in arm A (Table 1).

### Exposure to study treatment

Among patients enrolled in arm A, all 31 patients received at least one dose of therapy. However, seven patients were considered not evaluable for toxicity because they were not able to receive more than 85% of the prescribed dose during the first treatment cycle. Reasons for not being able to administer the drugs as prescribed without interruptions included grade 2 anorexia, grade 2 nausea, and grade 2 fatigue, among others (Supplementary Table 1). In addition, one patient missed excessive doses owing to hospitalization for possible ureteral obstruction from the underlying cancer, and another patient fell, which led to cerebral hemorrhage and subsequently death not related to the study (Supplementary Table 1).

Among patients enrolled in arm B, all 30 patients received at least one dose of therapy. However, eight patients were not evaluable in the DLT assessment because they were not able to receive more than 85% of the prescribed dose during the first treatment cycle. Reasons for this included tumor progression during the first cycle, development of pneumonia, grade 2 nausea and vomiting, hospitalization for acute renal failure, respiratory failure, and others (Supplementary Table 1).

## Toxicity

All patients who received at least one dose of crizotinib and dasatinib were included in the toxicity analysis. Among the 31 patients enrolled in arm A, 29 (94%) had drug-related adverse events, and 15 (48%) experienced grade 3 adverse events (Table 2). The most common drug-related adverse events of any grade were diarrhea (19/31; 61%) and nausea (18/31; 58%), followed by fatigue (15/31; 48%), vomiting (12/31; 39%), and anorexia (9/31; 29%). Among grade 3 drug-related adverse events, gastrointestinal-related adverse events were commonly seen (diarrhea: 5/31, 16%; vomiting: 4/31, 13%; and nausea: 3/31, 10%; Table 2). There were no grade 4 adverse events.

Among the 30 patients enrolled in arm B, 29 (97%) had drug-related adverse events, and 11 (37%) experienced grade 3 adverse events (Table 2). The most common drug-related adverse event of any grade was fatigue (16/30; 53%), followed by nausea (13/30; 43%) and diarrhea (11/30; 37%). Among grade 3 drug-related adverse events, fatigue and dyspnea each occurred in three patients (10%; Table 2).

## Dose-limiting toxicities

In arm A, 24 patients were enrolled in DL1 (250 mg crizotinib twice per day plus 50 mg dasatinib daily) between both the dose escalation and the expansion cohort and seven patients were enrolled in DL2 (250 mg crizotinib twice per day plus 70 mg dasatinib daily) during the dose escalation. However, as previously mentioned, five patients in DL1 and two patients in DL2 were not evaluable for DLT assessment because they were not able to receive more than 85% of the prescribed dose during the first cycle of intervention (Supplementary Table 1). In arm A, DL1, DLTs were observed in four of the 19 evaluable patients (21%), including grade 3 nausea and grade 3 vomiting in two patients each and esophageal pain, fatigue, diarrhea, and hematemesis (all grade 3) in one patient each. During DL2, DLTs were observed in two of the five evaluable patients (40%), including dehydration, infection, nausea, and vomiting (all grade 3) in one patient each (Table 3).

In arm B, 23 patients were enrolled in DL1 (140 mg dasatinib daily plus 250 mg crizotinib every other day) between both the dose escalation and the expansion cohort and seven patients were enrolled in DL2 (140 mg dasatinib daily plus 200 mg crizotinib daily) during the dose escalation. However, as previously mentioned, five patients in DL1 and three patients in DL2 were not evaluable for DLT assessment because they were not able to receive more than 85% of the prescribed dose during the first cycle of intervention (Supplementary Table 1). In arm B, DL1, DLTs were observed in four of the 18 evaluable patients (22%), including grade 3 fatigue in two patients and creatinine increase, nausea, and hyponatremia (all grade 3) in one patient each. Among patients enrolled in DL2, DLTs were observed in two of the four evaluable patients (50%), including creatinine increase, fatigue, and anorexia (all grade 3) in one patient each (Table 4).

Therefore, the RP2D dose was determined to be 250 mg crizotinib by mouth twice per day plus 50 mg dasatinib by mouth daily.

### Antitumor efficacy

Among the 31 patients enrolled in arm A, one patient with prostate cancer had a partial response (−34%) at DL1; however, owing to grade 2 intolerable drug-related adverse events (fatigue, anorexia, creatinine increase, and transaminitis), the patient was removed from the study 1.1 months after the initiation of therapy. Targeted molecular profiling (46-gene panel) did not reveal an underlying genomic alteration. One patient with lung adenocarcinoma had stable disease (−13%) for 10.1 months (Figure 1a). Genomic profiling through next-generation sequencing did not reveal *MET* alteration; however, the patient harbored other alterations, including *RET*L730I, *EGFR* 3115-1G>T, *TP53* E221\*, *FGFR2* K292M, and *PDGFRB* P123H.

Among the 30 patients enrolled in arm B, no patient experienced a partial response. However, two patients had durable stable disease for more than 6 months (Figure 1b). One patient with clear cell sarcoma had 7.3 months of stable disease (+6%; no molecular profiling done) and another patient with melanoma had prolonged stable disease (−17%, 41.4+ months; molecular profiling negative for alterations).

## DISCUSSION

The primary endpoint of this phase I trial was to determine the RP2D for the combination of crizotinib and dasatinib. Our results indicated that arm A, DL1 (250 mg of crizotinib by mouth twice per day plus 50 mg of dasatinib by mouth daily) had a slightly better toxicity profile (DLTs observed in four of 19 patients [21%]) than arm B, DL1 (250 mg of crizotinib by mouth every other day plus 140 mg of dasatinib by mouth daily), in which DLTs were observed in four of 18 patients (22%). Thus, arm A, DL1 was determined to be the RP2D.

Unfortunately, more than 90% of patients in the study experienced drug-related adverse events and 37–48% of patients experienced grade 3 adverse events (Table 2). Despite maximum supportive measures, the most common drug-related adverse events were gastrointestinal (diarrhea: 37–61%, nausea 43–58%, vomiting: 30–39%, anorexia: 29–30%; Table 2). Moreover, 15 patients (between arms A and B) were not included in DLT assessment because they were not able to receive more than 85% of the prescribed dose during the first cycle of intervention and were thus determined not to be evaluable in the DLT assessment (Supplementary Table 1). The most common reason for not being able to complete the first cycle of therapy was gastrointestinal adverse events, which occurred in 8 of the 15 patients who were not evaluable in the DLT assessment (53%; Supplementary Table 1). DLTs included dehydration, infection, nausea, and vomiting in arm A and creatinine increase, fatigue, nausea, and anorexia in arm B. A recent meta-analysis that evaluated the dosing of two targeted drugs in clinical trials showed that when there is no overlapping target, the combination of targeted drugs could be administered at the full dose in more than half of the trials (12). However, predicting the toxicity may be challenging since dasatinib is known to have broad kinase target (39 proteins) (13). Thus dasatinib most likely had overlapping target(s) with crizotinib which may explain the poor tolerability of the combination seen in current report.

The secondary endpoint of the current study was to investigate the antitumor effects of the combination of crizotinib and dasatinib. As seen in Figure 1, among the 61 patients enrolled in the study (31 in arm A and 30 in arm B), one patient achieved a partial response (−34% in a patient with prostate cancer, although the patient was removed from the study after 1.1 months owing to drug-related adverse events) and three patients achieved stable disease for more than 6 months (−13% in a patient with lung adenocarcinoma for 10.1 months, +6% in a patient with clear cell sarcoma for 7.3 months, and −17% in a patient with melanoma for 41.4+ months). Part of the reason for the low response rate could be that we did not select the patients on the basis of their molecular profiling results such as *MET* alteration that predicts response to crizotinib or kinase-inactivating *BRAF* mutations that confer sensitivity to dasatinib (14,15) (a total of three patients with known *MET* aberrations were enrolled; Table 1). This is consistent with a recent review (evaluation of 346 published clinical trials) showing that the overall response rate from targeted therapy was 5.1% when a biomarker was not used for patient selection, whereas the response rate was 42.0% when patients were selected on the basis of a genomic biomarker (16). Additionally, because c-SRC has been known to be one of the resistance mechanisms from *MET* inhibition (8), the combination of crizotinib and dasatinib may need to be administered in selected patients whose tumor previously progressed after treatment with a *MET* inhibitor. However, we were not able to enroll such patients to test our hypothesis. The other potential reason for the low response rate may be the poor tolerability of the combination (Table 2 and Supplementary Table 1). For future development of this combination regimen or a regimen with a similar mechanism of action, researchers should consider current data when determining the dose.

The current study had a few limitations. First, the patients were heterogeneous; they had multiple tumor types and had received various prior therapies. Second, we did not select the patients who harbored aberrations that could be targeted with crizotinib or dasatinib. Preferably, all patients should undergo next-generation sequencing or proteomics analysis to identify the target of interest. For example, the patient with lung adenocarcinoma who achieved stable disease (−13%) for 10.1 months had a *PDGFRB* P123H alteration, which was potentially targeted with dasatinib (targets *PDGFRB*; Figure 1a).

In summary, the combination of crizotinib and dasatinib among patients with advanced cancer was feasible at the RP2D of 250 mg of crizotinib twice daily and 50 mg of dasatinib daily. However, to our surprise, most patients experienced drug-related adverse events, notably in the form of gastrointestinal adverse events, and the overall tolerability of the combination was limited. Thus, further development of this combination may be limited.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

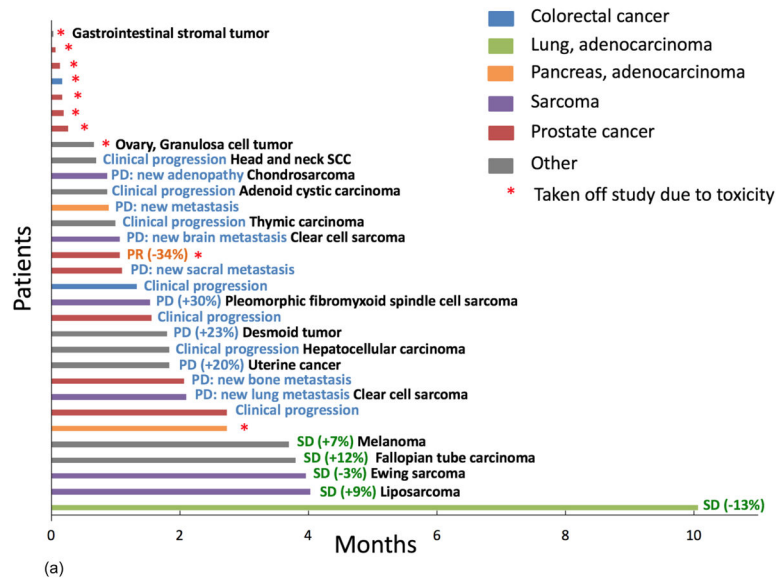
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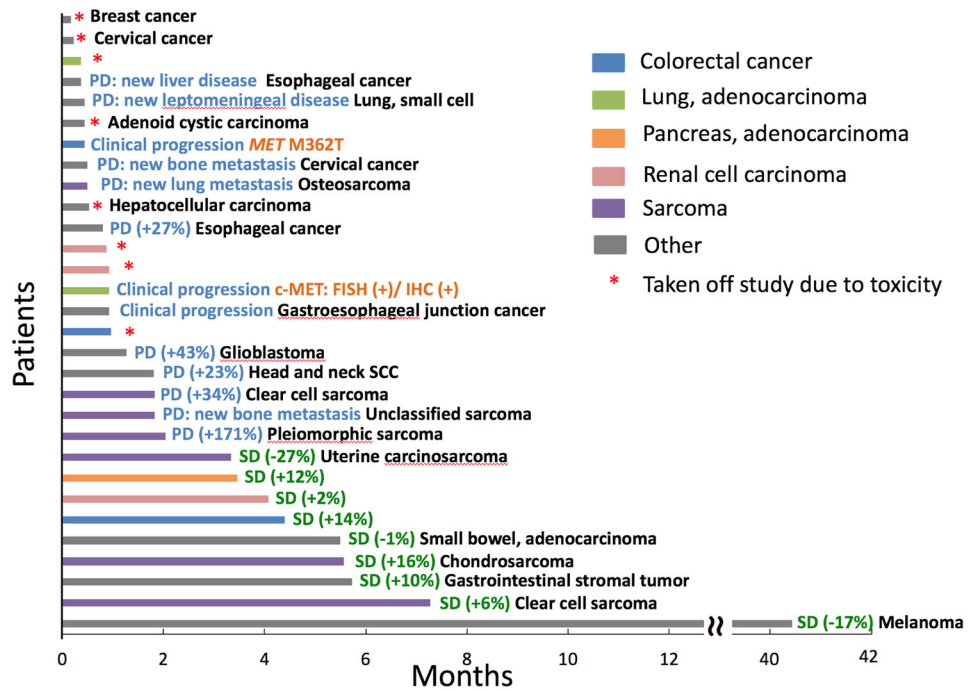
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(b)



**Fig. 1.** Swimmer plots showing clinical outcomes. (a) Clinical outcomes among patients enrolled in arm A (n = 31). One patient with prostate cancer achieved a partial response (PR; -34%); however, the patient was removed from the study after 1.1 months owing to drug-related adverse events. One patient with lung adenocarcinoma achieved stable disease (SD; -13%) for 10.1 months. (b) Clinical outcomes among patients enrolled in arm B (n = 30). Two patients had durable SD, including one patient with melanoma (-17%, 41.4+ months) and one patient with clear cell sarcoma (+6%, 7.3 months). Abbreviations: PD, progressive

disease; SCC, squamous cell carcinoma; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry.

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**Table 1**

Baseline demographic and clinical characteristics.

Characteristic	No. (%)		
	Arm A, n = 31	Arm B, n = 30	Total, n = 61
Median age (range)	59 years (28–76 years)	56 years (16–74 years)	58 years (16–76 years)
Sex			
Female	9 (29)	9 (30)	18 (30)
Male	22 (71)	21 (70)	43 (70)
ECOG <sup>a</sup> performance status			
0	4 (13)	6 (20)	10 (16)
1	26 (84)	23 (77)	49 (80)
2	1 (3)	1 (3)	2 (3)
Diagnosis			
Sarcoma <sup>b</sup>	6 (19)	7 (23)	13 (21)
Prostate cancer	10 (32)	0	10 (16)
Colorectal cancer	2 (6)	3 (10)	5 (8)
Lung adenocarcinoma	1 (3)	2 (7)	3 (5)
Pancreatic adenocarcinoma	2 (6)	1 (3)	3 (5)
Renal cell carcinoma	0	3 (10)	3 (5)
Adenoid cystic carcinoma	1 (3)	1 (3)	2 (3)
Gastrointestinal stromal tumor	1 (3)	1 (3)	2 (3)
Head and neck squamous cell carcinoma	1 (3)	1 (3)	2 (3)
Hepatocellular carcinoma	1 (3)	1 (3)	2 (3)
Melanoma	1 (3)	1 (3)	2 (3)
Esophageal cancer	0 (0)	2 (7)	2 (3)
Cervical cancer	0 (0)	2 (7)	2 (3)
Desmoid tumor	1 (3)	0 (0)	1 (2)
Fallopian tube carcinoma	1 (3)	0 (0)	1 (2)
Ovarian granulosa cell tumor	1 (3)	0 (0)	1 (2)
Thymic carcinoma	1 (3)	0 (0)	1 (2)
Uterine cancer	1 (3)	0 (0)	1 (2)
Breast cancer	0 (0)	1 (3)	1 (2)
Gastroesophageal junction cancer	0 (0)	1 (3)	1 (2)
Glioblastoma	0 (0)	1 (3)	1 (2)
Small cell lung cancer	0 (0)	1 (3)	1 (2)
Small bowel adenocarcinoma	0 (0)	1 (3)	1 (2)
Median no. of prior therapies (range)	4 (0–11)	3 (1–7)	3 (0–11)
<i>MET</i> aberration status			
Tested using FISH or IHC	4 (13)	4 (13)	8 (13)
Positive for <i>MET</i> amplification or overexpression	1 (3), IHC	1 (3), IHC and FISH	2 (3)
Tested for targeted sequencing, including <i>MET</i>	28 (90)	22 (73)	50 (82)
<i>MET</i> M362T	0 (0)	1 (3)	1 (2)

<sup>a</sup>Abbreviations: ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry.

<sup>b</sup>Sarcoma diagnoses included clear cell sarcoma (n = 4), chondrosarcoma (n = 2), and n = 1 each for clear cell sarcoma, uterine carcinosarcoma, pleomorphic sarcoma, osteosarcoma, liposarcoma, Ewing sarcoma, and pleomorphic fibromyxoid spindle cell sarcoma.

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**Table 2**Drug-related adverse events in each arm.<sup>a</sup>

Adverse event	No. (%)	
	Any grade	Grade 3
Arm A, n = 31		
Any drug-related adverse event	29 (94)	15 (48)
Diarrhea	19 (61)	5 (16)
Nausea	18 (58)	3 (10)
Fatigue	15 (48)	2 (6)
Vomiting	12 (39)	4 (13)
Anorexia	9 (29)	2 (6)
Edema in limbs	5 (16)	1 (3)
Transaminitis	5 (16)	0 (0)
Dysgeusia	4 (13)	0 (0)
Anemia	3 (10)	0 (0)
Creatinine increase	3 (10)	2 (6)
Rash	3 (10)	1 (3)
Abdominal pain	2 (6)	2 (6)
Blurred vision	2 (6)	1 (3)
Constipation	2 (6)	0 (0)
Dyspnea	2 (6)	1 (3)
Hypercalcemia	2 (6)	1 (3)
Leukopenia	2 (6)	0 (0)
Light sensitivity	2 (6)	0 (0)
Arm B, n = 30		
Any drug-related adverse event	29 (97)	11 (37)
Fatigue	16 (53)	3 (10)
Nausea	13 (43)	1 (3)
Diarrhea	11 (37)	0 (0)
Anorexia	9 (30)	1 (3)
Vomiting	9 (30)	1 (3)
Dyspnea	6 (20)	3 (10)
Anemia	4 (13)	0 (0)
Constipation	4 (13)	0 (0)
Creatinine increase	4 (13)	2 (7)
Neuropathy	4 (13)	0 (0)
Rash	4 (13)	0 (0)
Thrombocytopenia	3 (10)	0 (0)
Edema in limbs	2 (7)	0 (0)
Headache	2 (7)	0 (0)
Leukopenia	2 (7)	0 (0)

<sup>a</sup>Adverse events of any grade that occurred in more than 5% of the arm. For drug-related adverse events that occurred in less than 5% of patients in each arm, see Supplementary Table 2. There were no grade 4 adverse events in either arm.

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**Table 3**

Dose-limiting toxicities (DLTs) observed in arm A (n = 31).

Dose level	Crizotinib	Dasatinib	Total no. enrolled	Evaluable for DLTs	DLTs	Details
1	250 mg by mouth twice per day	50 mg daily	24	19	4	Grade 3 nausea (n = 2), grade 3 vomiting (n = 2); grade 3 esophageal pain, grade 3 fatigue, grade 3 diarrhea, grade 3 hematemesis (n = 1 each)
2	250 mg by mouth twice per day	70 mg daily	7	5	2	Dehydration, infection, nausea, vomiting (all grade 3, n = 1 each)

**Table 4**

Dose-limiting toxicities (DLTs) in arm B (n = 30).

Dose level	Dasatinib	Crizotinib	Total no. enrolled	Evaluable for DLTs	DLTs	Details
1	140 mg by mouth daily	250 mg every other day	23	18	4	Grade 3 fatigue (n = 2), grade 3 creatinine increase (n = 1), grade 3 nausea (n = 1), grade 3 hyponatremia (n = 1)
2	140 mg by mouth daily	200 mg daily	7	4	2	Creatinine increase, fatigue, anorexia (all grade 3, n = 1 each)