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CLINICAL TRIAL REPORT

A Phase I Trial of the MET/*ALK*/*ROS1* Inhibitor Crizotinib Combined with the VEGF Inhibitor Pazopanib in Patients with Advanced Solid Malignancies

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Background: Crizotinib inhibits ALK, MET and ROS1 tyrosine kinases but the development of resistance to monotherapy is an issue. The anti-angiogenic properties of pazopanib could overcome crizotinib drug resistance. Additionally, the anti-angiogenic properties of crizotinib could augment the clinical efficacy of pazopanib.

Methods: We evaluated the safety and responses in patients with advanced solid tumors treated with crizotinib and pazopanib.

Results: Eighty-two patients (median age 53 years, range 18–78 years) were enrolled. The median number of prior systemic therapies was 3 (range, 0–8). We were able to dose escalate to dose level 8 (crizotinib 250 mg twice daily and pazopanib 800 mg daily) with no MTD identified. Grade 3 or 4 toxicities were seen in 32% of patients with the highest prevalence being fatigue (n=9, 11%), diarrhea (n=6, 7%), vomiting (n=3, 4%), anemia (n=2, 2%) and ALT increased (n=2, 2%). Of the 82 patients, 61 (74%) had measurable disease by RECISTv1.1 and reached first restaging (6 weeks). Partial response (PR) was observed in 6/61 (10%) patients, and stable disease (SD) lasting ≥6 months was observed in 10/61 patients (16%) (total = 16/61 (26%) of patients with SD ≥6 months/PR).

Conclusion: Dose level 6 (crizotinib 200 mg twice daily and pazopanib 600 mg daily) was the most tolerable dosing of the combination and can be used in future studies. We also observed moderate clinical activity in patients with advanced solid tumors that had received numerous prior therapies.

Keywords: crizotinib, pazopanib, VEGF, ALK/ROS1, MET

Introduction

Crizotinib is a potent first-generation inhibitor of the anaplastic lymphoma kinase (ALK), MET (c-MET), and c-ROS oncogene 1 (ROS1) receptor tyrosine kinases and is approved for the treatment of patients with non-small cell lung cancer (NSCLC), who have tested positive for either *ALK* or *ROS1* rearrangement.[1–4] Crizotinib approval as a first-line therapy for patients with previously untreated ALK-positive NSCLC was based on its superior objective response rate and improved progression free survival compared to standard first-line doublet chemotherapy.[5] Additionally, in preclinical studies, crizotinib (previously known as PF-02341066) was found to inhibit tumor cell growth in other solid tumors cell lines and xenograft models, including prostate, squamous head and neck cancer, osteosarcoma, ovarian cancer and renal cancer.[6–10]

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Studies have shown that the majority of patients treated with crizotinib initially have tumors that show a robust response, but eventually and almost invariably, develop drug-resistance.[11,12] To address this, next-generation ALK inhibitors have been developed and are approved for first, second, and third line ALK positive NSCLC. However, ultimate recurrence through this sequence of ALK inhibitors occurs over time. Thus, there is an interest in developing combination therapies for ALK inhibitors with other therapeutic agents to increase the duration of response and sustain clinical benefit. Multiple bypass molecular pathways are ascribed to ALK resistance.[13] The angiogenesis pathway, for example, is considered as one of the essential requirements for disease progression in various solid tumors.[14] Blocking the angiogenesis pathway has been shown to be effective in multiple solid tumors inclusive of thyroid, lung, ovarian and other cancers.[15] The combination of existing chemotherapy with anti-angiogenesis drugs has been tested in multiple cancer types;[16,17] for example, bevacizumab combined with pemetrexed[18,19] and sunitinib in combination with pemetrexed.[20] Dual inhibition of cMET and VEGF has also been shown to be more effective than single pathway inhibition alone in pre-clinical models.[21] Interestingly, crizotinib is also shown to have some anti-angiogenic activity in addition to its anti-proliferative effects.[22]

Pazopanib is a multi-kinase, angiogenesis inhibitor known to block VEGFR, PDGFRα, PDGFRβ and C-KIT and is approved for the treatment of patients with renal cell cancer[23] and advanced soft tissue sarcoma (STS) who have received prior chemotherapy.[24] We hypothesized that the combination of crizotinib with pazopanib would augment the clinical efficacy of pazopanib through dual inhibition of angiogenesis pathways in patients and additionally that in patients whose tumors harbored *ALK, MET* or *ROS1* deleterious aberrations, pazopanib would augment crizotinib therapy and help overcome drug resistance. Here we report our experience treating patients with advanced malignancies with this combination therapy.

Patients and Methodology

Study Design and Dosing

This is a single institution, open-label, phase I dose-escalation study in patients with advanced malignancies (NCT 01548144). This trial was open to all patients with advanced or metastatic cancer refractory to standard therapy, relapsed after standard therapy, or who had no standard therapy available that could improve survival by at least three months.

Treatment was administered on an outpatient basis at the University of Texas, MD Anderson Cancer Center. The cycle of therapy was 21 days. No investigational, commercial agents or therapies other than those described here could be administered with the intent to treat the patient's malignancy. Pazopanib was given orally once daily, while the crizotinib schedule varied according to dose levels. This single institution study protocol was approved by the Institutional Review Board at the University of Texas, MD Anderson Cancer Center and was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and all local and federal regulatory guidelines. All patients signed informed consent prior to enrolling onto the study.

The protocol followed a standard 3+3 design.[25] If one patient in a cohort experienced a dose-limiting toxicity (DLT) during the first cycle, three additional patients were enrolled and treated at that dose level. If at any time more than 33% of patients in a cohort experienced a DLT, that cohort was closed to additional patients. Adverse events (AE) were graded, based on the Common Terminology Criteria for Adverse Events, version 4.0 (CTCAEv4.0). DLTs were defined as any grade 3 or 4 non-hematologic toxicity related to any of the study drugs (except nausea and vomiting responsive to appropriate medical interventions, correctable electrolyte imbalances or alopecia); any grade 4 hematologic toxicity lasting 3 weeks or longer despite supportive care; any grade 4 nausea or vomiting > 5 days despite maximum anti-nausea regimens; any other grade 3 non-hematologic toxicity including symptoms/signs of vascular leak or cytokine release syndrome; any severe or life-threatening complication/abnormality not defined in the CTCAEv4.0 that was attributable to the therapy. The maximum tolerated dose (MTD) was defined by DLTs that occurred in the first cycle (three weeks). If a response was observed in a particular tumor type with the study drug combination, expanded enrollment was permitted for up to a total of 14 patients with that tumor type at the highest dose level deemed safe at the time of patient enrollment. Furthermore, expansion group also included patients with activating abnormalities for which there is evidence that crizotinib has antitumor activity including *ALK* translocations, amplification and mutations, *MET* amplification and mutations and *ROS1* rearrangements (e.g. *FIG1-ROS1* translocation).

All enrolled participants, including patients in the expansion group, were considered in the DLT analysis. For the purpose of dose expansion, a tumor response was

defined as one or more of the following: 1) stable disease for more than or equal to four months (SD ≥ 4 months), or 2) decrease in the sum of target lesions by more than or equal to 20% by Response Evaluation Criteria in Solid Tumors (RECIST criteria v1.1).

Eligibility Criteria

Key inclusion criteria included patients with any advanced cancer, either refractory to standard therapy or for which no effective standard therapy exists; evaluable or measurable disease by RECISTv1.1 criterion; Eastern Cooperative Oncology Group (ECOG) status ≤2; adequate organ functions with absolute neutrophils > 1000 cells/uL, platelets ≥ 75,000/uL, total bilirubin ≤ 2 x ULN (upper limit of normal), alanine transaminase (ALT) ≤ 2.5 x ULN (≤ 5 x ULN if liver metastases present) and serum creatinine < 2 x ULN; and women of child-bearing potential and men must agree to use adequate contraception. Key exclusion criteria were patient receiving any concurrent chemotherapy other than study drugs; any uncontrolled inter-current illness including, but not limited to, ongoing or active infection requiring intravenous antibiotics; any symptomatic congestive heart failure; any history of stroke or transient ischemic attack within 6 months prior to study enrollment; any history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to study enrollment and patients with proteinuria ≥ 2+ by urine test.

Assessment of Tumor Response

Tumor measurements were performed on patients with measurable disease at baseline and every two cycles (6 weeks) thereafter. Measurable target lesions were evaluated for response using RECIST v1.1.[26,27] RECIST v1.1 defines partial response (PR) as at least 30% reduction in the sum of target lesions compared to baseline. Progressive disease (PD) is defined as an increase in disease of at least 20% compared to the smallest sum recorded (nadir) with an increase of at least 5 mm in absolute value. Stable disease (SD) is defined as neither PR, nor PD. For the purpose of this report, prolonged stable disease (SD) was defined as lasting ≥ 6 months.

Results

Patient Characteristics

Eighty-two patients with advanced or metastatic solid malignancies were enrolled between April 2012 and December 2017. Out of 82 patients, 49 patients participated in dose-escalation and the remaining 33 patients participated in dose-expansion. Demographics, clinical characteristics and patient distribution are summarized in Table 1. The median age of patients was 53 years (range, 18–78 years). The median number of prior systemic therapies was 3 (range, 0–8). Before enrollment onto the trial, one NSCLC patient with an undocumented/unknown history of an ALK translocation had received prior crizotinib for 9 months while 16 patients including sarcoma (6) and renal cancer (10) had received prior pazopanib. The median duration of prior pazopanib therapy was 9.3 months (range, 1.4 to 38.5 months). Out of 82 patients, 34 patients had other prior anti-angiogenic therapy, either as single agent or in combination. These anti-angiogenic therapies mainly consisted of bevacizumab (23), sunitinib (12), and/or

Table 1 Baseline Demographics and Clinical Characteristics

Characteristics	Total Patients
	N=82
Age (Mean, years)	53
Sex	
Male	44 (54%)
Female	38 (46%)
ECOG at Baseline	
0	16 (20%)
1	58 (71%)
2	8 (9%)
Prior Treatment	
Crizotinib	1
Pazopanib	16
Genomic/IHC testing	
Performed	66 (80%)
Not performed	16 (20%)
Tumor Types	
Renal	16 (20%)
Ovarian	10 (12%)
Colorectal	7 (8%)
Breast	6 (7%)
Salivary Gland	3 (4%)
Uveal Melanoma	3 (4%)
Thyroid	3 (4%)
Other tumor types**	34(41%)

Notes: **Other tumor types includes (N): cholangiocarcinoma (2), sarcoma (14), hepatocellular carcinoma (2), non-small cell lung cancer (2), urothelial carcinoma (2), adrenocortical carcinoma (1), appendiceal carcinoma (1), squamous cell carcinoma of tonsil (1), granular cell tumor of the foot (1), melanoma (1), mesothelioma (1), gastroesophageal junction cancer (2), nasopharyngeal carcinoma (1), pancreatic cancer (1), pilocytic astrocytoma (1), and squamous cell carcinoma of vulva (1).
Abbreviations: N, number of patients; ECOG, Eastern Cooperative Oncology Group.

Table 2 Crizotinib and Pazopanib Dose-Escalation Schedule (21-Day Cycle), Grade 3/4 Toxicities and Response

Dose Level	Crizotinib, mg PO	Pazopanib, mg PO Daily	Total (N)	Escalation Phase (N)	Expansion Phase (N)	Grade (G) 3/4 Toxicity (N)*	SD≥6 Month or PR/Total Evaluable[#]
1	250 QOD	200	4	4	0	Fatigue (2)	0/3
2	200 daily	200	4	4	0	–	1/3
3	200 daily	400	5	5	0	–	1/3
4	250 daily	400	10	7	3	Thrombocytopenia (2), perforation of colon (1)	3/8
5	250 daily	600	9	7	2	Subdural hemorrhage (1), vomiting (1), diarrhea (1), anemia (1), ALT increase (1), AST increase (1), shortness of breath (1)	3/8
6	200 BID	600	33	5	28	Fatigue[Δ] (4), fever (1), hematuria (1), diarrhea[Δ] (2), hyponatremia[Δ] (1), ALT increased (1), ALP increased (1), anemia (1), neutropenia (1), nausea (1), vomiting (1), dizziness (1), abdominal pain[Δ] (1)	6/26
7	200 BID	800	9	9	0	Diarrhea[Δ] (2), esophagitis (1), fatigue[Δ] (2), rash (1), vomiting (1), fatigue (2)	1/5
8	250 BID	800	8	8	0	Dyspnea (1), anorexia (1), fatigue (1), diarrhea (1),	1/5

Notes: *Adverse events deemed at least possibly related to treatment were graded based on the Common Terminology Criteria for Adverse Events, version 4.0 (CTCAEv4.0). [#]Patients were evaluable for response if they had at least one post-baseline scan. [Δ]Event was defined as a dose-limiting toxicity.
Abbreviations: N, number of patients; QOD, every other day; BID, twice a day; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase.

axitinib (6). The most common cancer type was renal cell carcinoma (n=16) followed by ovarian cancer (n=10). All patients had experienced disease progression during their prior therapy. The median number of cycles completed for all patients was 4 (range, 1–69). Fifty patients (61%) received more than 2 cycles. For patients with SD ≥ 6 months or better, the median number of cycles completed was 10 (range, 8–69). A total of 33 patients were recruited into the expansion cohort designed to further evaluate toxicity and antitumor activity in select tumor types. The following tumor types were enrolled: renal cancer (n=11), ovarian cancer (n=7), colorectal cancer (n=3), soft tissue sarcomas (n=5), salivary gland tumors (n=2), breast cancer (n=1) and additional tumors with either *ALK* or *MET* aberrations (n=4).

Toxicity Assessment

Patients were enrolled in accordance with the planned 3 +3 study design until dose level 4 (Table 2, Table 3), at which point an expansion cohort for response (as described in the Methodology section) was initiated. Dose escalation for the remaining four levels continued in accordance with the original dose escalation plan. Dose level 8 (crizotinib 250 mg twice daily and pazopanib 800 mg daily) was reached and no MTD was obtained as we were able to reach the highest FDA-approved doses of both drugs.

Seventy-seven patients (94%) experienced at least one adverse event that was possibly drug related. These events were mostly grade 1 or 2 and reversible. In fact, 56 patients (68%) experienced no treatment-related

Table 3 Adverse Events at Any Dose Level

Adverse Events		Dosing Level								Total Events
		1	2	3	4	5	6	7	8	
		Count	Count	Count	Count	Count	Count	Count	Count	
Fatigue	Grade ≤2	1	2	3	6	5	23	6	4	50
	Grade ≥ 3	2	0	0	0	0	4	2	1	9
Nausea	Grade ≤2	0	4	2	8	2	19	6	6	47
	Grade ≥ 3	0	0	0	0	0	1	0	0	1
Diarrhea	Grade ≤2	1	1	2	3	2	15	2	0	26
	Grade ≥ 3	0	0	0	0	1	2	2	1	6
Vomiting	Grade ≤2	0	2	2	2	2	13	1	4	26
	Grade ≥ 3	0	0	0	0	1	1	1	0	3
Anorexia	Grade ≤2	2	0	1	2	1	9	4	6	25
	Grade ≥ 3	0	0	0	0	0	0	0	1	1
ALT increased	Grade ≤2	1	1	2	1	1	9	1	0	16
	Grade ≥ 3	0	0	0	0	1	1	0	0	2
AST increased	Grade ≤2	1	1	2	2	2	11	2	0	21
	Grade ≥ 3	0	0	0	0	1	0	0	0	1
Anemia	Grade ≤2	2	1	0	1	3	6	1	2	16
	Grade ≥ 3	0	0	0	0	1	1	0	0	2
Other AEs	Grade ≤2	5	1	8	7	13	76	21	27	158
	Grade ≥ 3	0	0	0	3	2	7	2	1	15*

Notes: *Other AEs Grade ≥3 (number of patients in parenthesis) includes thrombocytopenia (2), abdominal pain (1), increased alkaline phosphatase (1), dyspnea (1), fever (1), hematuria (1), esophagitis (1), dizziness (1), hyponatremia (1), neutropenia (1), colon perforation (1), rash (1), subdural hemorrhage (1), shortness of breath (1).

toxicity greater than grade 2. The most common grade 3 or 4 toxicities were as follows: fatigue (n=9, 11%), diarrhea (n=6, 7%), vomiting (n=3, 4%), anemia (n=2, 2%) and ALT increased (n=2, 2%) (Table 3). Among this subset of patients (≥ grade 3 AEs), we observed 3 DLTs (Table 2). At dose level 7, we observed 2 DLTs out of 9 patients enrolled (<33%). One patient had grade 3 fatigue while another patient had concurrent grade 3 fatigue and grade 3 diarrhea. The first patient recovered after a brief interruption in dosing and subsequent dose-reduction. He went on to complete 6 cycles of treatment before being taken off the study for disease progression. The second patient was taken off the study after only 4 days of dosing due to increased fatigue and poor tolerance to therapy. At dose level 8, one patient had grade 4 dyspnea outside the DLT period. The therapy was discontinued for this patient to remediate toxicity. Considering two occurrences of DLTs at dose level 7 and 1 patient's discontinuation at dose level 8 due to toxicity, it was decided to continue all further expansion enrollment at dose level 6. During expansion, an additional patient at dose level 6 experienced DLT, with concurrent grade 3 hyponatremia, grade 3 fatigue and grade 3 diarrhea. In total, we observed DLT in 1 of 33 (3%) patients treated at dose level 6 including our expansion cohort patients. During this study, seven patients died while active in this trial, but none of these deaths were attributed to the study drugs. All deaths were due to disease progression except in one patient (NSCLC) at dose level 1 who died of post-obstructive pneumonia.

Overall, 16/82 (20%) patients had dose reduction of either crizotinib (n=3) or pazopanib (n=9) or both (n=4) during their course of treatment. Of these 16 patients, nine patients (56%) were dose-reduced for pazopanib at dose level 6 for various toxicities, including fatigue (5), increased transaminases (2), diarrhea (1) and nausea (1). Three patient additionally had crizotinib dose reduced from 200mg BID to 250mg daily for fatigue (1), diarrhea (1) and nausea (1). At dose level 7, two patients had pazopanib dose reduced from 800 mg daily to either 600 mg daily or 400 mg daily for diarrhea (1) or fatigue (1) while one patient had crizotinib dose reduced from 250 mg BID to 250 mg daily for grade 3 rash. Another patient had both pazopanib dose reduction to 400mg daily and crizotinib dose reduction to 250mg daily for grade 2 elevated bilirubin. At dose level 8, two patients had crizotinib dose reduced for bradycardia (1) and esophagitis (1) while one patient had pazopanib dose reduced for fatigue. Most of the dose reductions helped patients continue on the trial for at least one more cycle of treatment.

Antitumor Activity

Of 82 total patients on the trial, 61/82 (74%) patients had disease that was measurable by RECISTv1.1 and reached first restaging (6 weeks); 1/82 (1%) patient had a non-measurable disease at baseline and was excluded from image analysis for tumor efficacy; and 20/82 (24%) patients were taken off the study before first restaging for various reasons including drug-related toxicities (n=2), clinical disease progression (n=11), death (n=4) or voluntary withdrawal from the clinical trial (n=3). Figure 1 is a waterfall plot depicting the best response of the 61 response-evaluable patients. Partial response (PR) was observed in 6/61 (10%) patients and stable disease (SD) lasting ≥ 6 months was observed in 10/61 patients (16%) (total = 16/61 (26%) of patients with SD ≥6 months/PR). Supplementary Figure 1 shows swimmer plots depicting best RECISTv1.1 response and duration of time during treatment.

Tumor types of patients with best response of PR include ovarian cancer (1), colorectal cancer (1), sarcoma (2), clear cell renal cancer (1) and granular cell tumor of the foot (1). In total, 3 out of 9 (33%) evaluable patients with ovarian cancer and 3 out of 14 (21%) evaluable patients with renal cancer had SD≥6 months/PR. Out of 9 patients enrolled in this trial with either *MET* or *ALK* aberrations, one patient with colon cancer and *ALK* p.R1209Q mutation had a best response of PR (−33%) on dose level 6 and one patient with salivary gland tumor and *MET* p.N375S mutation had a best response of SD ≥6 months on dose level 5. Among other patients with PR as best response to therapy, we had a clear cell renal cancer patient (−32%, PR) with a Kinase Insert Domain Receptor *(KDR)* p.C482R mutation previously treated with

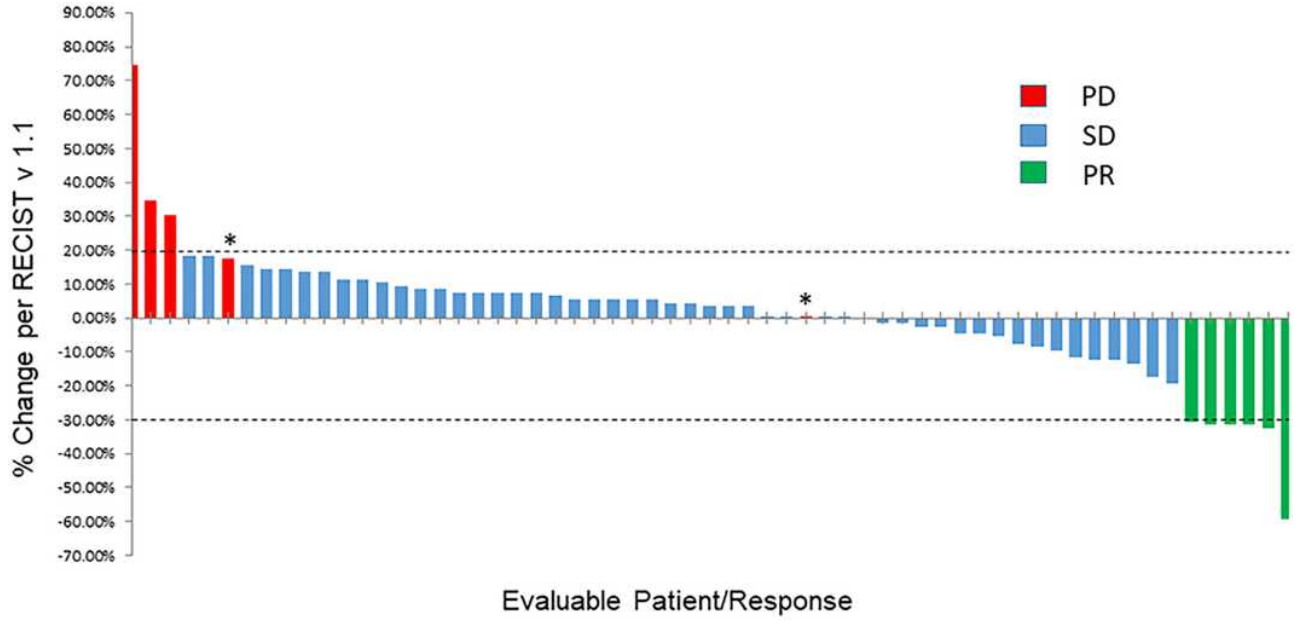

Figure 1 Waterfall plot depicting best RECISTv1.1 response. Individual patients are represented by vertical bars on the X-axis and best RECISTv1.1 response is depicted as percentage on the Y-axis. Sixty one of 82 patients had at least one post-baseline scan and were evaluable for response. Two patients were marked as progressive disease even though their percentage of tumor increase was less than 20% because of new lesions (*). Dotted lines show 20% increase and 30% decrease in tumor size by RECISTv1.1.

multiple lines of therapy including pazopanib monotherapy for a year (best response on monotherapy was SD). After progression on pazopanib monotherapy, she completed 36 weeks on our crizotinib and pazopanib combination study before being taken off the trial because of a new lesion in the spine.

Interestingly, patients with fusion transcripts also showed good response including patients (N=1 for each fusion) with Ewing Sarcoma Breakpoint 1 (*EWSR1*)-CAMP Responsive Element Binding Protein (*CREB1*) (−60%, PR), Dynactin Subunit 1 (*DCTN1*)-*ALK* (−32%, PR) and *EWSR1-CREB3L1* (4%, SD). The patient with an *EWSR1-CREB1* fusion who had clear cell sarcoma of the bowel completed 69 cycles at dose level 5 before withdrawing consent to participate in another clinical study closer to home. The patient with a *DCTN1-ALK* gene fusion (detected by next-generation sequencing genomic testing and confirmed by diffuse ALK expression by immunohistochemistry) who had a myxoid neoplasm of the uterus completed 41 cycles at dose level 6. Finally, the patient with *EWSR1-CREB3L1* fusion who had a sclerosing epithelioid fibrosarcoma (SEF) of the abdominal wall completed 26 cycles of treatment at dose level 8.

Discussion

This is the first report of combining crizotinib with pazopanib and results demonstrate that this combination has a tolerable safety profile, with mild to moderate adverse events in patients with advanced solid tumors. No new or unexpected adverse events were observed during this study. Despite having eight dose levels, we were unable to define the MTD of crizotinib plus pazopanib in combination as the Food and Drug Administration (FDA) approved doses for both drugs were administered without any significant DLTs. The toxicity evaluation revealed that 94% (77/82) of patients had at least one adverse event that was possibly drug-related but approximately two-thirds of these patients (68%) had toxicity of grade 2 or less. The most common grade 3 and 4 toxicities included: fatigue (11%), diarrhea (7%), vomiting (4%), anemia (2%) and increased ALT (2%). The most common (occurring in more than 30% of all patients) non-hematologic adverse events, irrespective of grade, were fatigue (71%), nausea (58%), diarrhea (39%), vomiting (35%) and anorexia (30%) and for hematological toxicities, irrespective of grade, were anemia (22%) and leukopenia (13%).

Most of the AEs experienced in our study are consistent with prior reported AEs with either crizotinib and/or pazopanib monotherapy. Clinical trials with crizotinib monotherapy in patients with advanced NSCLC that was ALK-positive or ROS-positive reported visual effects, nausea, diarrhea, vomiting, constipation, edema, elevated transaminases, and fatigue as the common adverse events (in >25% of patients) irrespective of their grades.[5,28–31] Visual disorders of grade 1 or 2 severity were the most frequently observed AEs with crizotinib monotherapy and were captured by using a patient-reported questionnaire. Unfortunately, our study lacked this type of assessment and may be a reason for the lack of visual changes being reported in any of our treated patients.

More serious toxicities associated with crizotinib monotherapy include hepatotoxicity, interstitial lung disease/pneumonitis, and QT-interval prolongation.[32] In fact, ALT increase (17%) was the most common grade 3–4 toxicity observed in these prior studies. In our study, hepatotoxicity was also observed, albeit much milder in comparison to these previous reports as 26% of patients in our study experienced grade 1–2 increased AST and 20% patients experienced grade 1–2 increased ALT. Further, only 2% of all enrolled patients in our study experienced grade ≥ 3 increase in ALT.

A previous Phase III randomized study (VEG105192) with pazopanib as single agent in patients with advanced renal cell carcinoma (RCC) reported diarrhea (52%), increased AST (53%), increased ALT (53%), hypertension (40%), hair color changes (38%), nausea (26%), vomiting (21%) and fatigue (19%) as the most common AEs of any grade.[23] A phase III study (COMPARZ) in RCC evaluated pazopanib versus sunitinib and reported diarrhea (63%), increased AST (61%), increased ALT (60%), fatigue (55%), hypertension (46%), nausea (45%), hair depigmentation (30%), hand-foot syndrome (29%), and vomiting (28%), irrespective of severity of grade. In our study, we observed less hepatotoxicity and diarrhea compared to the COMPARZ and VEG105192 studies but more fatigue which occurred in 71% of the patients.[23,33]

In terms of efficacy, in 61 response evaluable patients, we had 6 PRs (10%) and 10 patients (16%) with SD ≥ 6 months (SD ≥ 6 months/PR of 26%). Three patients (3/16; 19%) with SD ≥ 6 months or PR, had deleterious *ALK* or *MET* aberrations (Table 4). Of these 3 patients, none had received prior ALK or ROS1 inhibitors and only 1 patient had received a prior MET inhibitor. FDA accelerated approval of crizotinib for advanced NSCLC (ALK positive) was based on findings from two phase I and II trials.[4,34,35] In a phase I study (PROFILE 1001) with

Table 4 Stable Disease (SD) ≥6 Months or Partial Response (PR) by RECIST and Characterization by Patient

Cancer Type	Dose Level	Duration of Treatment (Weeks)	Best Response by RECIST 1.0	Number of Prior Therapies	Prior Anti-Angiogeneic Therapy[#] (Y/N)	Mutation Analysis			
						MET Mut	ROS1 Mut	ALK Mut	Other Alterations**
Ovarian	2	24	0%	5	Y	ND	ND	ND	
Ovarian	3	63	−32%	1	N	ND	ND	ND	
Renal	4	36	−32%	6	Y	N	N	N	VHL D121Y, KDR C482R, KIT M541L
HNSCC	4	30	0%	3	N	ND	ND	ND	
Bladder	4	24	9%	4	Y	ND	ND	ND	
Salivary Gland^	5	30	−12%	4	N	Y, cMET N375S	ND	N	
Renal	5	24	3%	1	Y	ND	ND	ND	
Clear Cell Sarcoma	5	207	−60%	0	N	ND	ND	ND	EWSR1-CREB1 fusion
Colorectal	6	48	−33%	5	Y	N	N	Y, ALK R1209Q	p53 H214FS*33, APC R876*, NTRK3 S165I, RUNX1 S5N
Renal	6	27	−2%	1	N	N	N	N	
Myxoid Neoplasm (Sarcoma)	6	123	−32%	0	N	ND	ND	Y, DCTN1-ALK fusion	
Colorectal	6	36	18%	5	Y	N	N	N	KRAS G12C, APC R499*
Ovarian	6	27	−2%	3	Y	N	N	N	NSD1 R1019C
Salivary Gland	6	24	−20%	3	N	N	N	N	
Granular Cell Tumor	7	27	−31%	1	Y	N	ND	N	
Sclerosing Epithelioid Fibrosarcoma	8	78	4%	1	N	N	N	N	EWSR1-CREB3L1 fusion, CDKN2A/B loss

Notes: **Indicates other alterations as detected by fluorescence in situ hybridization (FISH) or next-generation sequencing (NGS). [#]Indicates that none of these patients had received prior ALK or ROS1 inhibitors. ^Indicates the one patient who had received prior MET inhibitor.

Abbreviations: Mut, mutation; ND, not done; N, no mutation; HNSCC, squamous cell carcinoma of the head and neck.

ALK-positive NSCLC patients, Camidge et al[29] reported a 60.8% objective response rate (ORR) among 143 response-evaluable patients. Of these 143 patients, 3 patients had a CR and 84 patients had a PR and the clinical benefit rate (CR+PR+SD) at weeks 8 and 16 was 82.5% and 70.6%, respectively.[29] Updated results from a Phase II study with crizotinib (PROFILE 1005) demonstrated 54% ORR among 908 response-evaluable patients with central ALK-testing with 11 (1%) patients having achieved CR and 480 (53%) patients having achieved PR.[28] Six patients (6/16; 38%) with SD ≥ 6 months or PR, had wild type *ALK, MET* and *ROS1* on molecular testing (Table 4). Of these 6 patients, 3 had had prior antiangiogenics (prior bevacizumab n=2; prior axitinib n=1). A phase II study with pazopanib in patients with advanced metastatic RCC showed a response rate (CR+PR) of 35% with 1.3% CR, 33.3% PR and 44.9% SD (>8 weeks).[36] Reasons for the differences in response between our study and these studies are multifactorial, including: 1) heterogeneous tumor types enrolled in our study; 2) heavily pre-treated patients with a median of 3 prior systemic therapies in our study; and, 3) lack of genomic selection for enrollment into our study.

Interestingly, a patient with *DCTN1-ALK* gene fusion showed a partial response (−32%) to therapy.[37] *DCTN1-ALK* fusions have been observed recurrently in multiple tumor types including spitz tumors, lung cancer and inflammatory myofibroblastic tumors.[38–40] Shimada et al[41] has characterized the *DCTN1-ALK* fusion protein and showed that it is a potential oncogene that can be used as a target for ALK tyrosine kinase inhibitors including crizotinib and alectinib. The gene fusion event confers constitutive activation of ALK and treatment with crizotinib inhibited constitutive phosphorylation of ALK and activation of downstream PI3K and MAPK signaling cascades.[38] Recently, Michels et al[42] has demonstrated that an *ALK* p.G1269A mutation was detected in a patient with *DCTN1-ALK* fusion who developed acquired resistance to crizotinib. Unfortunately, we were unable to obtain a repeat biopsy in our patient and therefore we could not confirm if any new mutations in ALK could have possibly contributed to the emergence of therapeutic resistance.

We also observed that a patient with EWSR1-CREB1 fusion favorably responded to crizotinib and pazopanib combination treatment. Our clear cell sarcoma patient was negative for EWSR1-activating transcription factor-1 (ATF1) fusion transcripts and was able to complete 69 cycles (>4 years) on dose level 5 with a best response of PR (−60%). Ultimately, the patient withdrew consent from the study in order to pursue treatment closer to home.[43] Most EWSR1 fusions involve the 5′ portion of EWSR1 which acts as an activator of the DNA binding region of its fusion partner targeting the fusion of specific promoters. CREB1 binds cAMP response elements within target genes to upregulate gene expression. EWSR1-ATF1 fusion protein is known to activate the melanocyte master transcription factor (MITF) which further activates the *MET* gene.[44] It is however not known if all EWSR1-fusion proteins are capable of activating cMET expression. Nevertheless, it is hypothesized that these fusions sensitize tumor cells to cMET and/or ALK inhibitors.

Similarly, another patient with sclerosing epithelioid fibrosarcoma (SEF) and *EWSR1-CREB3L1* fusion completed 26 cycles of treatment with a best response of SD. SEFs are considered rare but aggressive tumors arising from deep tissues and characterized by *EWSR1-CREB3L1* translocation.[45] Unfortunately, there are no standardized treatment regimens for SEFs and these tumors are quite challenging to manage. The unusual response of SEFs with *EWSR1-CREB3L1* fusion to combination therapy with crizotinib and pazopanib has not been reported. Intriguingly, a recent phase II trial (90,101 "CREATE") evaluated the efficacy and safety of crizotinib in patients with advanced clear cell sarcoma (CCSA) with *EWSR1/ATF1* fusions and showed an ORR of only 3.8%,[46] and adds to speculation that fusion partner genes of *EWSR1* may be an important determinant of clinical efficacy to crizotinib. This however needs further testing.

Apart from the interesting gene-fusion patients discussed, we observed that a patient with *KDR* p.C482R mutation achieved PR with our combination therapy. *KDR* is also known as vascular endothelial growth factor receptor-2 (*VEGFR-2*). The p.C482R mutation is a gain-of-function mutation leading to constitutive dimerization and activation of VEGFR-2 and this variant of *KDR* has been shown to highly correlate with serum-soluble VEGFR-2 level which is recognized as a pharmacodynamic response marker for pazopanib.[47,48] Our study lends support to the use of pazopanib either as a single agent or in combination with crizotinib for patients with *KDR* p.C482R mutation.

In conclusion, we determined that dose level 6 (crizotinib 200 mg twice daily and pazopanib 600 mg daily) was the most tolerable dosing of this drug combination and could be used for future studies. We also

demonstrated moderate clinical activity in patients with advanced solid tumors that had received numerous prior therapies.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding authors on reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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