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Clinical Trial Results

A Phase Ib Study of Axitinib in Combination with Crizotinib in Patients with Metastatic Renal Cell Cancer or Other Advanced Solid Tumors

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Trial Information

- **ClinicalTrials.gov Identifier:** NCT01999972
- **Sponsor(s):** Pfizer
- **Principal Investigator:** M. Dror Michaelson
- **IRB Approved:** Yes

Lessons Learned

- The combination of axitinib and crizotinib has a manageable safety and tolerability profile, consistent with the profiles of the individual agents when administered as monotherapy.
- The antitumor activity reported here for the combination axitinib/crizotinib does not support further study of this combination treatment in metastatic renal cell carcinoma given the current treatment landscape.

Abstract

Background. Vascular endothelial growth factor (VEGF) inhibitors have been successfully used to treat metastatic renal cell carcinoma (mRCC); however, resistance eventually develops in most cases. Tyrosine protein kinase Met (MET) expression increases following VEGF inhibition, and inhibition of both has shown additive effects in controlling tumor growth and metastasis. We therefore conducted a study of axitinib plus crizotinib in advanced solid tumors and mRCC.

Methods. This phase Ib study included a dose-escalation phase (starting doses: axitinib 3 mg plus crizotinib 200 mg) to estimate maximum tolerated dose (MTD) in patients with solid tumors and a dose-expansion phase to examine preliminary efficacy in treatment-naïve patients with mRCC. Safety, pharmacokinetics, and biomarkers were also assessed.

Results. No patients in the dose-escalation phase (n = 22) experienced dose-limiting toxicity; MTD was estimated to be axitinib 5 mg plus crizotinib 250 mg. The most common grade ≥3 adverse events were hypertension (18.2%) and fatigue (9.1%). In the dose-expansion phase, overall response rate was 30% (95% confidence interval [CI], 11.9–54.3), and progression-free survival was 5.6 months (95% CI, 3.5–not reached).

Conclusion. The combination of axitinib plus crizotinib, at estimated MTD, had a manageable safety profile and showed evidence of modest antitumor activity in mRCC. ***The Oncologist*** 2019;24:1151–e817

Discussion

Despite the success of agents that target VEGF and VEGF receptors (VEGFRs) [1–3] in mRCC, a subset of patients are refractory to VEGF inhibitor treatment, and most patients who are responsive to treatment will eventually develop resistance [4, 5]. Proposed explanations for resistance include the activation of pathways favoring epithelial-mesenchymal transition, such as MET [5–10]. Preclinical in vivo studies have shown that combining MET and VEGFR inhibition has synergistic effects on tumor growth, angiogenesis, invasiveness,

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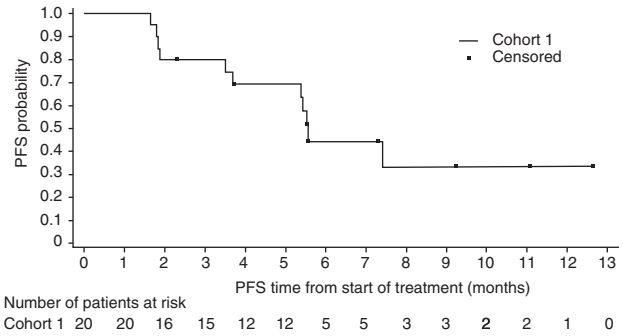

Figure 1. Progression-free survival in cohort 1. Date of data cut-off: May 24, 2017. Cohort 1: no prior systemic therapy directed at advanced renal cell carcinoma.
Abbreviation: PFS, progression-free survival.

and metastasis [6–11]. Crizotinib is an inhibitor of anaplastic lymphoma kinase (ALK), MET/hepatocyte growth factor receptor, and ROS1 receptor tyrosine kinases and is approved for the treatment of ALK-positive or ROS1-positive metastatic non-small cell lung cancer [12, 13]. Axitinib is a specific tyrosine kinase inhibitor of VEGFRs 1–3 that is approved for the treatment of mRCC after failure of one prior systemic therapy [14, 15]. We hypothesized that combining crizotinib with axitinib would provide greater clinical benefit than VEGF-directed therapy alone.

In this study, the combination of axitinib and crizotinib was tolerable in patients with advanced solid tumors, including mRCC. No patient experienced a dose-limiting toxicity in the dose-escalation phase, and axitinib 5 mg twice daily (BID) in combination with crizotinib 250 mg BID was selected as the MTD. No new safety issues for the combination were identified. The overall adverse events for the different treatment groups were manageable through medical intervention and/or dose modification, and a low proportion of patients discontinued because of toxicity.

The confirmed objective response rate (ORR) for treatment-naïve patients with mRCC receiving axitinib and crizotinib (30%) in this trial was similar to results for single-agent axitinib versus sorafenib as first-line therapy in the phase III trial (32%) [15]. A randomized phase II trial of cabozantinib versus sunitinib (CABOSUN) reported an ORR of 46% for first-line poor- or intermediate-risk patients with mRCC treated with cabozantinib [16]. The median progression-free survival (PFS) observed in the dose-expansion phase cohort 1 (treatment-naïve patients) was 5.6 months (95% CI, 3.5–not reached; Fig. 1), which was shorter than the PFS of axitinib alone (10.1 months; 95% CI, 7.2–12.1) as first-line therapy [15]. In CABOSUN, the reported estimated PFS for patients treated with cabozantinib was 8.2 months (95% CI, 6.2–8.8) [17].

In conclusion, the combination of axitinib and crizotinib in patients with solid tumors has a manageable safety profile, consistent with the profiles of the individual agents administered as monotherapy, and demonstrated antitumor activity in treatment-naïve patients with mRCC. Given the more robust antitumor activity of cabozantinib, and promising trial data for newer immuno-oncology treatments, the antitumor activity reported here does not support further study of axitinib plus crizotinib in mRCC.

Trial Information	
Disease	Renal cell carcinoma – clear cell
Disease	Solid tumor
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	None
Type of Study - 1	Phase I
Type of Study - 2	Dose finding and preliminary efficacy
Primary Endpoint	Maximum tolerated dose
Primary Endpoint	null
Secondary Endpoint	Pharmacokinetics
Secondary Endpoint	Efficacy
Secondary Endpoint	Biomarkers
Additional Details of Endpoints or Study Design	
Patients in the dose-expansion phase were enrolled into two cohorts: patients in cohort 1 had received no prior systemic therapy for mRCC, whereas patients in cohort 2 had one or two prior systemic treatment regimens directed at mRCC, with at least one prior therapy being a VEGF pathway inhibitor, and resistance to the most recently received VEGF pathway inhibitor.	
Investigator's Analysis	Active but results overtaken by other developments

Drug Information: Dose Escalation Phase	
Drug 1	
Generic/Working Name	Axitinib
Trade Name	Inlyta

Company Name	Pfizer
Drug Type	Small molecule
Drug Class	VEGFR
Dose	Multiple milligrams (mg) per flat dose
Route	Oral (po)
Schedule of Administration	BID
Drug 2	
Generic/Working Name	Crizotinib
Trade Name	Xalkori
Company Name	Pfizer
Drug Type	Small molecule
Drug Class	ALK
Dose	Multiple milligrams (mg) per flat dose
Route	Oral (po)

Drug Information: Dose Expansion Phase	
Drug 1	
Generic/Working Name	Axitinib
Trade Name	Inlyta
Company Name	Pfizer
Drug Type	Small molecule
Drug Class	VEGFR
Dose	5 milligrams (mg) per flat dose
Route	Oral (po)
Schedule of Administration	BID
Drug 2	
Generic/Working Name	Crizotinib
Trade Name	Xalkori
Company Name	Pfizer
Drug Type	Small molecule
Drug Class	ALK
Dose	250 milligrams (mg) per flat dose
Route	Oral (po)
Schedule of Administration	BID

Dose Escalation Table for Phase I Dose Escalation Phase

Dose level	Dose of drug: Axitinib	Dose of drug: Crizotinib	Number enrolled	Number evaluable for toxicity
1	3 mg	200 mg	5	5
2	3 mg	250 mg	3	3
3	5 mg	200 mg	4	4
4	5 mg	250 mg	10	10

See Table 1 for additional details.

Patient Characteristics: Dose Escalation Phase	
Number of Patients, Male	12
Number of Patients, Female	10
Age	Median (range): 62.0 years (34.0–78.0 years)

Performance Status: ECOG	0 — 1 — 8 2 — 14 3 — Unknown —
Cancer Types or Histologic Subtypes	Head and neck, 1 Bladder, 2 Non-small cell lung cancer, 1 Renal cell carcinoma, 7 Hepatocellular, 1 Adrenal, 1 Breast, 1 Pancreas, 2 Colorectal, 4 Other, 2

Patient Characteristics: Dose Expansion Phase	
Number of Patients, Male	22
Number of Patients, Female	6
Age	Median (range): 62.5 years (45.0–76.0 years)
Performance Status: ECOG	0 — 12 1 — 15 2 — 1 3 — Unknown —

Other

Patients in the dose expansion phase were divided into two cohorts: cohort 1 (n = 21), no prior systemic therapy toward mRCC, and cohort 2 (n = 7), at least one, but no more than two prior systemic treatment regimens directed at renal cell carcinoma, with at least one prior therapy being a regimen containing an approved VEGF pathway inhibitor, and resistance to the most recently approved VEGF pathway inhibitor. For details of patient characteristics, refer to Tables 2 and 3.

Cancer Types or Histologic Subtypes	Metastatic renal cell carcinoma, cohort 1: 21 Metastatic renal cell carcinoma, cohort 2: 7

Primary Assessment Method: Dose Escalation Phase	
Title	Cohort 1
Number of Patients Evaluable for Toxicity	22

Evaluation Method

Patients were monitored for dose-limiting toxicity, which was defined as any of the following events: grade 4 neutropenia; febrile neutropenia; grade ≥3 neutropenic infection; grade ≥3 thrombocytopenia with bleeding; grade 4 thrombocytopenia; any nonhematologic grade ≥3 toxicities, except asymptomatic hypophosphatemia, hyperuricemia without signs and symptoms of gout; or persistent (despite maximal medical therapy) grade ≥3 nausea, vomiting, or diarrhea.

Primary Assessment Method: Dose Expansion Phase	
Title	Cohort 1
Number of Patients Evaluated for Efficacy	20
Evaluation Method	RECIST 1.1
Response Assessment CR	n = 0 (0%)
Response Assessment PR	n = 6 (30%)
Response Assessment SD	n = 10 (50%)

Response Assessment PD	*n* = 4 (20%)
(Median) Duration Assessments PFS	5.6 months
Title	Cohort 2
Number of Patients Evaluated for Efficacy	7
Evaluation Method	RECIST 1.1
Response Assessment CR	*n* = 0 (0%)
Response Assessment PR	*n* = 1 (14.3%)
Response Assessment SD	*n* = 3 (42.9%)
Response Assessment PD	*n* = 1 (14.3%)
Response Assessment OTHER	*n* = 2 (28.6%)

Adverse Events

Full descriptions of adverse events are shown in Tables 3 and 4.

Dose-Limiting Toxicities

Dose level	Number enrolled	Number evaluable for toxicity	Number with a dose-limiting toxicity
1	5	5	0
2	3	3	0
3	4	4	0
4	10	10	0

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Active but results overtaken by other developments

A subset of patients with metastatic renal cell carcinoma (mRCC) are refractory to vascular endothelial growth factor (VEGF) inhibitor treatment, and most patients who are initially responsive eventually develop resistance [1, 2]. Proposed mechanisms of resistance include activation of pathways favoring epithelial-mesenchymal transition, such as tyrosine protein kinase Met (MET), also known as hepatocyte growth factor receptor (HGFR), and changes in the tumor vasculature and dominant VEGF isoform [2–7]. Preclinical in vivo studies have shown that combining MET and VEGF receptor (VEGFR) inhibition has synergistic effects on tumor growth, angiogenesis, invasiveness, and metastasis [3–8]. Specifically, studies using VEGF-targeted therapy-resistant and -sensitive animal models showed increased antitumor effect when a VEGF-targeted and a MET-targeted agent were used together [8]. Furthermore, the proven clinical activity of cabozantinib in advanced renal cell carcinoma (RCC) supports use of this combination [9].

Crizotinib is an inhibitor of anaplastic lymphoma kinase (ALK), MET/HGFR, and ROS1 receptor tyrosine kinases approved for the treatment of patients with ALK-positive or ROS1-positive metastatic non-small cell lung cancer [10, 11]. Axitinib is a specific tyrosine kinase inhibitor (TKI) of VEGFRs 1–3 with proven benefit in mRCC treatment and is approved for patients with mRCC after failure of one prior systemic therapy [12, 13]. We hypothesized that combining the MET inhibitor, crizotinib, with the VEGFR inhibitor, axitinib, would provide greater clinical benefit than VEGF-directed therapy alone.

This study was a phase Ib, open-label, multicenter trial with two phases: a dose-escalation phase in patients with advanced solid tumors to estimate the maximum tolerated dose (MTD) and a dose-expansion phase to examine preliminary efficacy in treatment-naïve patients with mRCC. Safety, pharmacokinetics, and biomarkers were also assessed. In the dose escalation phase, patient de-escalation and escalation of axitinib and crizotinib followed the modified toxicity probability interval (Table 1) [14].

In the dose-expansion phase, patients were enrolled into two cohorts: cohort 1 patients had no prior systemic mRCC-directed therapies, and cohort 2 patients had one or two prior systemic mRCC-directed therapies. Recruitment for cohort 2 was stopped at seven patients because of scarcity of qualified patients.

Enrolled patients were ≥18 years old and had histologically and/or cytologically confirmed diagnosis of advanced solid tumor refractory to standard therapy (dose-escalation phase) or confirmed clear-cell mRCC (dose-expansion phase). Patient demographics and characteristics are presented in Tables 2 and 3.

This study demonstrated that the combination of axitinib and crizotinib is tolerable in patients with advanced solid tumors, including mRCC. No patient experienced a dose-limiting toxicity in the dose-escalation phase, and axitinib

5 mg twice daily (BID) in combination with crizotinib 250 mg BID was selected as the MTD. No new safety issues were identified given the known safety profile of both drugs, and a low proportion of patients had to discontinue therapy due to toxicity. Adverse event profiles are presented in Tables 4 and 5.

The potential drug-drug interaction with combined use of axitinib and crizotinib was evaluated. Clinical data indicates that crizotinib is a moderate time-dependent CYP3A4/5 inhibitor whereas axitinib is primarily metabolized by CYP3A4/5 [15, 16]. Pharmacokinetic parameters for axitinib were calculated for each patient and treatment, as applicable, using noncompartmental analysis of concentration-time data (Table 6). Details of pharmacokinetic effects of crizotinib on axitinib when coadministered are provided in Table 7 and Figure 2. Coadministration of axitinib with crizotinib had no clinically meaningful effect on the pharmacokinetics of axitinib. Therefore, the potential efficacy of the axitinib-crizotinib combination was not compromised by reduced axitinib exposure in patients with mRCC.

The confirmed objective response rate (ORR) for treatment-naïve patients with RCC receiving axitinib in combination with crizotinib (30%; Table 8) was similar to results for single-agent axitinib versus sorafenib as first-line therapy in the phase III trial (32%) [13]. In all, 80% of patients in cohort 1 experienced some degree of tumor response (Fig. 3). A randomized phase II trial of cabozantinib versus sunitinib (CABOSUN) reported an ORR of 46% for first-line poor- or intermediate-risk patients with mRCC treated with cabozantinib [17]. The median progression-free survival (PFS) observed in the dose-expansion phase cohort 1 (treatment-naïve patients) was 5.6 months (95% confidence interval [CI], 3.5–not reached), which was shorter than the PFS of axitinib single agent (10.1 months; 95% CI, 7.2–12.1) as first-line therapy versus sorafenib [13]. In CABOSUN, the reported estimated PFS for patients treated with cabozantinib was 8.2 months (95% CI, 6.2–8.8) [9].

Biomarker analyses in the present study showed a trend toward lower baseline levels of HGF, IL-8, NGAL, TIMP1, and VEGFR3 associating with better radiographic responses. This result aligns with previous studies in patients with mRCC receiving VEGFR TKIs [18, 19]. Additionally, lower soluble MET levels following treatment (cycle 1 day 15 and cycle 5 day 1) were associated with longer PFS, which is consistent with a correlation between MET expression and poor prognosis [20]. Patients with mRCC whose tumors had a higher percentage of $CD8^+$ cells (greater than or equal to the median for the cohort) at baseline experienced prolonged PFS (hazard ratio, 0.239; 95% CI, 0.061–0.940; $p = .027$; Fig. 4). The prognostic value of CD8+ cells in patients with RCC treated with VEGFR TKIs, is controversial as higher amounts or density of infiltrating $CD8^+$ T cells in tumor tissues was associated with both shorter survival and conversely longer disease-free survival [18, 20–23]. Overall, the results of this study suggest that the prognostic value of these biomarkers in mRCC, in particular CD8 expression, warrant further exploration.

A limitation of this trial was the single-arm design with no monotherapy comparator groups, which precluded direct comparison of the combination treatment with the respective drugs used alone in the mRCC population. An additional limitation was halting of accrual in the dose-expansion phase cohort 2, precluding characterization of the combination in previously treated patients with mRCC.

In conclusion, the combination of axitinib and crizotinib in patients with solid tumors has a manageable safety and tolerability profile, consistent with the profiles of the individual agents when administered as monotherapy. The combination demonstrated antitumor activity in treatment-naïve patients with RCC. Given the more robust antitumor activity of cabozantinib, as well as promising trial data for newer immuno-oncology treatments, the antitumor activity reported here does not support further study of the combination of axitinib and crizotinib in mRCC.

Data Sharing Statement

Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (a) for indications that have been approved in the U.S. and/or European Union or (b) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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Disclosures

M. Dror Michaelson: Exelixis, Eisai, Novartis, Pfizer (C/A); **Shilpa Gupta:** Merck, Bristol-Meyers Squibb, Seattle Genetics (C/A), Janssen, Exelixis (H), Astellas, Bristol-Myers Squibb (RF); **Neeraj Agarwal:** Astellas, Astra Zeneca, Argos, Bristol-Meyers Squibb, Bayer, Clovis, Eisai, Exelixis, EMD Serono, Ely Lilly, Foundation One, Genentech, Merck, Medivation, Novartis, Nektar, Pfizer, Pharmacyclics (C/A); **Thomas Powles**: Pfizer, AstraZeneca, Roche, Bristol-Myers Squibb (C/A), Bristol-Myers Squibb, Ipsen, Exelexis, Roche, Merck, Pfizer, Novartis, AstraZeneca, Incyte, Seattle Genetics (H), AstraZeneca, Roche (RF); **Ulka Vaishampayan:** Bayer, Bristol-Myers Squibb, Exelixis, Pfizer, Astellas (C/A), Sanofi, Bristol-Myers Squibb, Exelixis, Bayer, Pfizer, Astellas. (H), Bayer, Bristol-Myers Squibb, Novartis, Pfizer, Exelixis, Astellas (RF); **James Larkin:** Merck, Bristol-Meyers Squibb, Incyte, Dynavax, Novartis, Ivax, Vista, Roche, Pfizer, Syneos Health, Bicycletx Ltd., Ultimovacs, Covance (C/A, H), Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Pfizer, Achilles, Roche, Nektom, Covance, Immunocor, Avro (RF); **Brad Rosbrook:** Pfizer (E); **Erjian Wang:** Pfizer (E, OI); **Danielle Murphy:** Pfizer (E); **Panpan Wang:** Pfizer (E); Maria Josè Lechuga: Pfizer (E); **Olga Valota:** Pfizer (E, OI). The other authors indicated no financial relationships.

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Figures and Tables

Table 1. Dose levels in the dose-escalation phase

Dose level	Crizotinib	Axitinib
–1B	250 mg QD	3 mg BID
–1A	200 mg BID	2 mg BID
1 (starting dose level)	200 mg BID	3 mg BID
2	250 mg BID	3 mg BID
3	200 mg BID	5 mg BID
4	250 mg BID	5 mg BID

Abbreviations: BID, twice daily; QD, once daily.

Table 2. Patient characteristics in the dose-escalation phase by treatment group

Characteristic	Treatment group (BID)				Total (*n* = 22)
	3 mg axitinib + 200 mg crizotinib (*n* = 5)	3 mg axitinib + 250 mg crizotinib (*n* = 3)	5 mg axitinib + 200 mg crizotinib (*n* = 4)	5 mg axitinib + 250 mg crizotinib (*n* = 10)	
Age, years, *n* (%)					
Mean (SD)	63.2 (2.2)	48.7 (14.5)	60.3 (6.2)	63.9 (6.0)	61.0 (8.3)
Median (range)	62.0 (61.0–66.0)	49.0 (34.0–63.0)	60.0 (53.0–68.0)	63.0 (57.0–78.0)	62.0 (34.0–78.0)
Age, years, *n* (%)					
<65	3 (60.0)	3 (100)	3 (75.0)	6 (60.0)	15 (68.2)
≥65	2 (40.0)	0	1 (25.0)	4 (40.0)	7 (31.8)
Sex, *n* (%)					
Male	4 (80.0)	2 (66.7)	1 (25.0)	5 (50.0)	12 (54.5)
Female	1 (20.0)	1 (33.3)	3 (75.0)	5 (50.0)	10 (45.5)
Race, *n* (%)					
White	5 (100)	3 (100)	2 (50.0)	10 (100)	20 (90.9)
Black	0	0	1 (25.0)	0	1 (4.5)
Asian	0	0	0	0	0
Other	0	0	1 (25.0)	0	1 (4.5)
ECOG PS, *n* (%)					
0	1 (20.0)	1 (33.3)	2 (50.0)	4 (40.0)	8 (36.4)
1	4 (80.0)	2 (66.7)	2 (50.0)	6 (60.0)	14 (63.6)
Duration since initial diagnosis, median (range) months	26.7 (1.6–45.3)	49.7 (33.2–60.1)	59.0 (18.6–150.3)	55.3 (6.8–164.0)	NE (NE)
Primary tumor, *n* (%)					
Neck	0	0	1 (25.0)	0	1 (4.5)
Bladder	2 (40.0)	0	0	0	2 (9.1)
Lung	0	0	0	1 (10.0)	1 (4.5)
Kidney	1 (20.0)	0	1 (25.0)	5 (50.0)	7 (31.8)
Liver	0	0	0	1 (10.0)	1 (4.5)
Adrenal	0	1 (33.3)	0	0	1 (4.5)
Breast	0	0	0	1 (10.0)	1 (4.5)
Pancreas	0	1 (33.3)	1 (25.0)	0	2 (9.1)
Colon-rectum	0	1 (33.3)	1 (25.0)	2 (20.0)	4 (17.4)
Other	2 (40.0)	0	0	0	2 (9.1)
Primary diagnosis basis, *n* (%)					
Histology	5 (100.0)	3 (100.0)	3 (75.0)	9 (90.0)	20 (90.9)
Cytology	0	0	1 (25.0)	1 (10.0)	2 (9.1)
Histopathological classification, *n* (%)					
Intestinal adenocarcinoma	0	0	1 (25.0)	0	1 (4.5)
Clear cell carcinoma	0	0	1 (25.0)	4 (4.0)	5 (22.7)
Squamous cell carcinoma	0	0	0	1 (10.0)	1 (4.5)
Adenocarcinoma	0	1 (33.3)	0	2 (20.0)	3 (13.6)
Ductal carcinoma	0	0	0	1 (10.0)	1 (4.5)
Unknown	0	0	1 (25.0)	0	1 (4.5)
Other	5 (100.0)	2 (66.7)	1 (25.0)	2 (20.0)	10 (45.5)

All doses were administered twice daily.
Abbreviations: BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; NE, not evaluated.

Table 3. Baseline demographics and characteristics for patients with metastatic renal cell carcinoma in the dose-expansion phase, by cohort

Characteristic	Cohort 1[a] *n* = 21	Cohort 2[b] *n* = 7	Total *n* = 28
Age, years			
Mean (SD)	62.4 (7.9)	61.9 (8.9)	62.3 (8.0)
Median (range)	62.0 (45.0–76.0)	63.0 (47.0–72.0)	62.5 (45.0–76.0)
Age, years, *n* (%)			
<65	13 (61.9)	5 (71.4)	18 (64.3)
≥65	8 (38.1)	2 (28.6)	10 (35.7)
Sex, *n* (%)			
Male	15 (71.4)	7 (100.0)	22 (78.6)
Female	6 (28.6)	0	6 (21.4)
Race, *n* (%)			
White	21 (100.0)	5 (71.4)	26 (92.9)
Black	0	1 (14.3)	1 (3.6)
Asian	0	1 (14.3)	1 (3.6)
ECOG PS, *n* (%)			
0	11 (52.4)	1 (14.3)	12 (42.9)
1	10 (47.6)	5 (71.4)	15 (53.6)
2[c]	0	1 (14.3)	1 (3.6)
Heng criteria,[d] *n* (%)			
Favorable	5 (23.8)	2 (28.6)	7 (25.0)
Intermediate	13 (61.9)	4 (57.1)	17 (60.7)
Poor	3 (14.3)	1 (14.3)	4 (14.3)

[a]Cohort 1: No prior systemic therapy directed at metastatic renal cell carcinoma (mRCC).
[b]Cohort 2: At least one, but no more than two, prior systemic treatment regimens directed at mRCC, with at least one prior therapy being a regimen containing an approved vascular endothelial growth factor (VEGF) pathway inhibitor, and resistance to the most recently received approved VEGF pathway inhibitor.
[c]One patient with ECOG PS 1 enrolled in the study reported a worsening of ECOG PS from 1 to 2 on cycle 1 day 1 pre-dose.
[d]Heng criteria risk groups: favorable (0 risk factors), intermediate (1–2 risk factors), poor (>3 risk factors), unknown for patients missing any of the individual factors.
Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 4. Adverse events (all causalities) reported in more than two patients in any cohort during the dose-escalation phase

	Treatment group (BID), *n* (%)									
	3 mg axitinib + 200 mg crizotinib *n* = 5		3 mg axitinib + 250 mg crizotinib *n* = 3		5 mg axitinib + 200 mg crizotinib *n* = 4		5 mg axitinib + 250 mg crizotinib (MTD) *n* = 10		Total (*n* = 22) *n* (%)	
Adverse event[a]	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Any adverse event	2 (40.0)	3 (60.0)	0	2 (66.7)	2 (50.0)	1 (25.0)	2 (20.0)	8 (80.0)	6 (27.3)	14 (63.6)
Nausea	2 (40.0)	0	1 (33.3)	0	2 (50.0)	0	7 (70.0)	0	11 (50.0)	1 (4.5)
Fatigue	1 (20.0)	0	1 (33.3)	1 (33.3)	3 (75.0)	0	6 (60.0)	1 (10.0)	11 (50.0)	2 (9.1)
Diarrhea	2 (40.0)	1 (20.0)	0	0	3 (75.0)	0	6 (60.0)	0	11 (50.0)	1 (4.5)
Vomiting	4 (80.0)	0	1 (33.3)	1 (33.3)	2 (50.0)	0	5 (50.0)	0	12 (54.5)	1 (4.5)
Dysphonia	0	0	2 (66.7)	0	1 (25.0)	0	4 (40.0)	0	7 (31.8)	0
Decreased appetite	2 (40.0)	0	3 (100.0)	0	3 (75.0)	0	5 (50.0)	0	13 (59.1)	0
Hypertension	1 (20.0)	1 (20.0)	1 (33.3)	1 (33.3)	2 (50.0)	0	2 (20.0)	2 (20.0)	6 (27.3)	4 (18.2)
Hypoalbuminemia	2 (40.0)	0	1 (33.3)	0	1 (25.0)	0	3 (30.0)	0	7 (31.8)	0
Proteinuria	3 (60.0)	0	2 (66.7)	0	0	0	3 (30.0)	0	8 (36.4)	0
Dyspepsia	0	0	0	0	2 (50.0)	0	3 (30.0)	0	5 (22.7)	0
Weight decreased	0	0	0	0	1 (25.0)	0	3 (30.0)	0	4 (18.2)	0

[a]Per Medical Dictionary for Regulatory Activities.
Abbreviations: BID, twice daily; MTD, maximum tolerated dose.

Table 5. Adverse events by Common Terminology Criteria for Adverse Events grade reported in more than three patients during the dose-expansion phase (patients with metastatic renal cell carcinoma)

	Cohort 1[a], *n* = 21		Cohort 2[b], *n* = 7	
Adverse event	**Grade 1–2 *n* (%)**	**Grade 3–4 *n* (%)**	**Grade 1–2 *n* (%)**	**Grade 3–4 *n* (%)**
Any adverse event	3 (14.3)	16 (79.2)	1 (14.3)	6 (85.7)
Nausea	18 (85.7)	1 (4.8)	2 (28.6)	0
Diarrhea	13 (61.9)	3 (14.3)	2 (28.6)	1 (14.3)
Vomiting	10 (47.6)	1 (4.8)	1 (14.3)	0
Dysphonia	10 (47.6)	1 (4.8)	2 (28.6)	0
Fatigue	7 (33.3)	2 (9.5)	3 (42.9)	1 (14.3)
Weight decreased	9 (42.9)	0	0	1 (14.3)
Decreased appetite	6 (28.6)	1 (4.8)	1 (14.3)	0
Hypertension	3 (14.3)	4 (19.0)	2 (28.6)	1 (14.3)
ALT increased	3 (14.3)	3 (14.3)	0	0
Dehydration	5 (23.8)	1 (4.8)	1 (14.3)	1 (14.3)
Dyspepsia	6 (28.6)	0	0	0
AST increased	4 (19.0)	1 (4.8)	0	0
Proteinuria	5 (23.8)	0	0	0
Arthralgia	3 (14.3)	1 (4.8)	0	0
Dizziness	4 (19.0)	0	1 (14.3)	0
Dyspepsia	4 (19.0)	0	0	0
Hypophosphatasemia	1 (4.8)	3 (14.3)	0	0
Edema peripheral	4 (19.0)	0	0	0

No grade 3–4 adverse events by preferred term (Common Terminology Criteria for Adverse Events) occurred in more than two patients in any cohort.
[a]Cohort 1: No prior systemic therapy directed at metastatic renal cell carcinoma (mRCC).
[b]Cohort 2: At least one, but no more than two, prior systemic treatment regimens directed at mRCC, with at least one prior therapy a regimen containing an approved vascular endothelial growth factor (VEGF) pathway inhibitor, and resistance to the most recently received approved VEGF pathway inhibitor.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 6. Pharmacokinetic parameters determined in study

Parameter	Definition	Method of determination
C_{max}	Maximum observed concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
AUC_{tau}	Area under the concentration–time curve from time zero to time tau (τ), the dosing interval, where tau = 12 hours (BID dosing)	Linear/log trapezoidal method
C_{min}	Minimum observed concentration	Observed directly from data
C_{trough}	Predose concentration	Observed directly from data
C_{max} (dn)[a]	Dose normalized C_{max}	C_{max}/dose
AUC_{tau} (dn)[a]	Dose normalized AUC_{tau}	AUC_{tau}/dose
CL/F[a]	Apparent clearance	Dose/AUC_{tau}
$MRAUC_{tau}$	Metabolite ratio AUC_{tau}	$(AUC_{tau,metabolite}/MW)^b/(AUC_{tau,parent}/MW)^c$
MRC_{max}	Metabolite ratio C_{max}	$(C_{max,metabolite}/MW)^b/(C_{max,parent}/MW)^c$

Values were calculated using an internally validated software system, eNCA (v2.2.4).
[a]Axitinib and crizotinib only.
[b]Crizotinib MW = 450.34 g/mol.
[c]Internal standard MW = 464.33 g/mol.
Abbreviations: BID, twice daily; molecular weight, MW, molecular weight.

Table 7. Summary of plasma axitinib pharmacokinetic parameters following multiple oral doses of axitinib alone and in combination with multiple oral doses of crizotinib (dose-expansion cohort 1)

	Parameter summary statistics[a] by treatment	
Parameter	**Axitinib (lead-in day 7)**	**Axitinib + crizotinib (cycle 1 day 15)**
n	7	7
AUC_{tau} (ng·hr/mL)	197.8 (46)	208.6 (35)
C_{max} (ng/mL)	40.21 (34)	40.91 (55)
T_{max} (hr)	2.00 (1.00–3.98)	2.00 (1.00–3.00)
C_{min} (ng/mL)	4.832 (175)	5.790 (109)
CL/F (L/hr)	25.32 (46)	23.96 (35)

[a]Geometric mean (geometric percent coefficient of variance) for all except median (range) for T_{max}.
Abbreviations: AUC_{tau}, area under the concentration-time curve from time zero to time tau (τ), the dosing interval, where tau = 12 hours (twice-daily dosing); C_{max}, maximum observed concentration; C_{min}, minimum concentration observed during the dosing interval; CL/F, apparent clearance; *n*, number of patients contributing to the summary statistics; T_{max}, time for C_{max}.

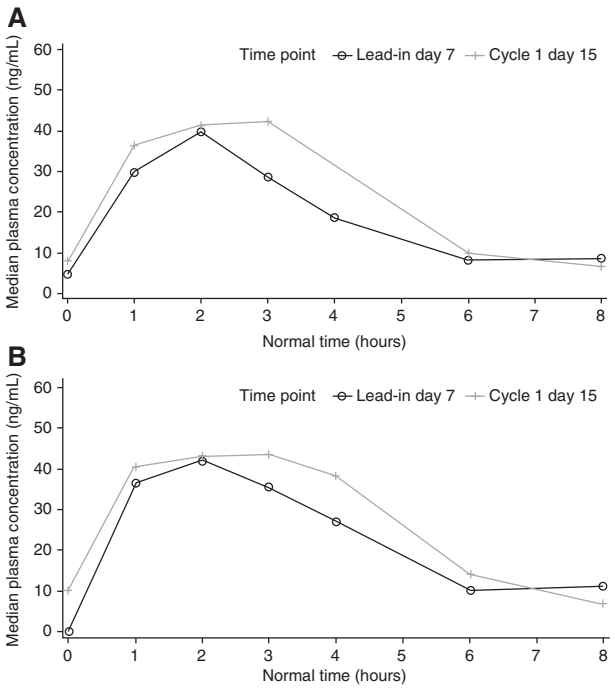

Figure 2. Median plasma axitinib concentration-time profiles following multiple oral doses of axitinib alone and in combination with multiple oral doses of crizotinib for dose-expansion cohort 1. Linear **(A)** and semilogarithmic **(B)** scales. Lead-in day 7, axitinib only; cycle 1 day 15, axitinib + crizotinib.

Table 8. Best confirmed overall response and objective response rate from patients during the dose-expansion phase

Response	**Cohort 1[a] *n* = 20**	**Cohort 2[b] *n* = 7**
Best overall response, *n* (%)		
Complete response (CR)	0	0
Partial response (PR)	6 (30.0)	1 (14.3)
Stable disease	10 (50.0)	3 (42.9)
Disease progression	4 (20.0)	1 (14.3)
Indeterminate	0	2 (28.6)
Overall response rate (CR + PR), *n* (%) [95% exact CI][c]	6 (30.0)[d] [11.9–54.3]	1 (14.3) [0.4–57.9]

Date of data cutoff: May 24, 2017.
[a]Cohort 1: No prior systemic therapy directed at renal cell carcinoma.
[b]Cohort 2: At least one, but no more than two, prior systemic treatments.
[c]Two-sided CI from Fisher's exact method based on the F-distribution.
[d]Overall response rate, including unconfirmed, 45%.
Abbreviations: CI, confidence interval; CR, complete response; PR, partial response.

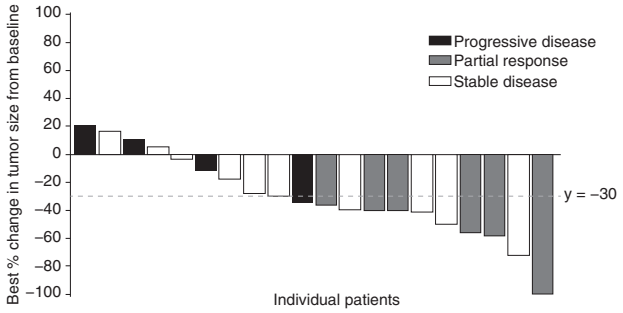

Figure 3. Change in tumor size in patients in cohort 1 of dose-expansion phase. Patients in cohort 1 had no prior systemic therapy directed at advanced renal cell carcinoma. Partial responses are confirmed (tumor reduction ≥30%). Date of data cutoff: May 24, 2017.

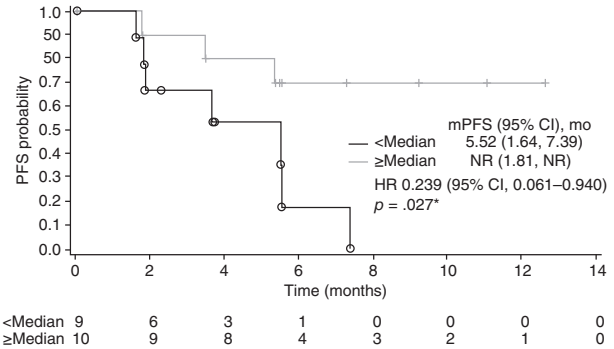

Figure 4. Progression-free survival for patients in cohort 1 by percent of CD8-positive cells greater than or equal to (≥Median) or less than (<Median) the median percent of CD8-positive cells for all patients in cohort 1. Cohort 1, no prior systematic therapy. *, log-rank *p* value.
Abbreviations: CI, confidence interval; HR, hazard ratio; mPFS, median progression-free survival; NR, not reached; PFS, progression-free survival.