RESULTS (continued)

Tumor Reduction

- Maximum reductions from baseline in target lesions by RECIST for 20 evaluable patients with RCC are shown in **Figure 3**

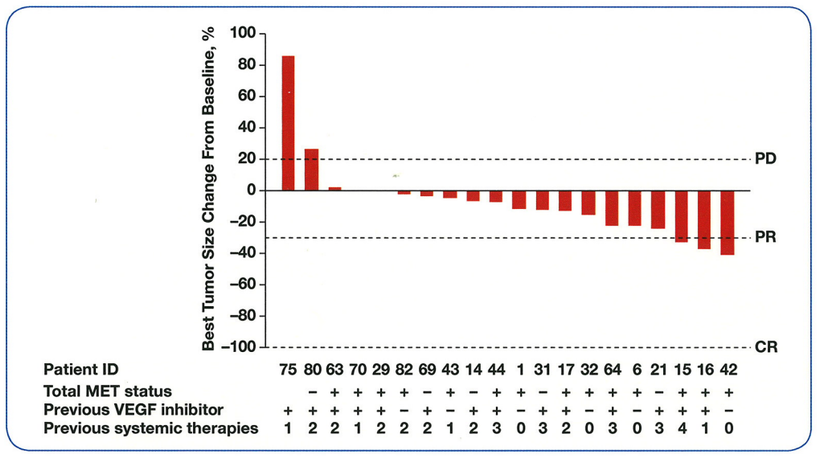

Figure 3. Maximum percentage change from baseline in size of target lesion.
Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; VEGF, vascular endothelial growth factor.

Computed Tomography Scans

- Patient with multiple lesions including left pleural lesion achieved a partial response at cycle 23

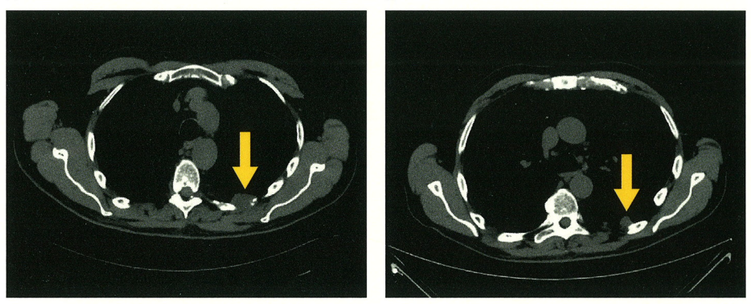

Figure 4. Computed tomography scans of patient 15 at baseline (panel A) and cycle 23 (panel B).

- Patient with multiple lung lesions achieved a partial response at cycle 23

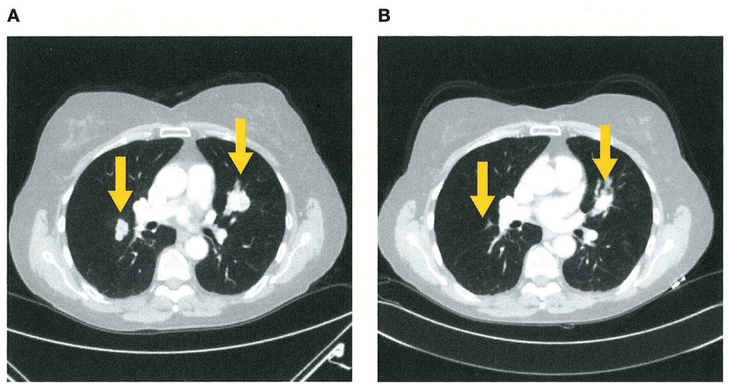

Figure 5. Computed tomography scans of patient 16 at baseline (panel A) and cycle 23 (panel B).

RESULTS (continued)

Adverse Events

Table 6. Common Adverse Events Occurring in ≥ 25% of Patients With RCC (n = 20)[a]

	Patients, n (%)	
Adverse Event	**All Grades**	**≥ Grade 3**
Rash	15 (75)	2 (10)
Hyperglycemia	14 (70)	1 (5)
Hypophosphatemia	11 (55)	1 (5)
Diarrhea	9 (45)	0
Alopecia	8 (40)	0
Anemia	8 (40)	2 (10)
Weight decreased	7 (35)	0
Anorexia	6 (30)	0
Cough	6 (30)	0
Fatigue	6 (30)	0
Aspartate aminotransferase increased	5 (25)	0
Hyperuricemia	5 (25)	2 (10)
Lymphopenia	5 (25)	0
Pain of skin	5 (25)	1 (5)
Palmar-plantar erythrodysesthesia syndrome	5 (25)	2 (10)
Pruritus	5 (25)	0
Stomatitis	5 (25)	0

[a] 1 (5%) patient experienced neutropenia (grade 4). No patient experienced bradycardia/sinus bradycardia.

CONCLUSIONS

- The combination of tivantinib plus sorafenib was well tolerated at full standard single-agent doses (tivantinib 360 mg BID plus sorafenib 400 mg BID) in patients with RCC
- Preliminary evidence of anticancer activity was observed
  - Antitumor activity was observed in patients previously treated with a VEGF inhibitor
- The observed antitumor activity suggests that the combined inhibition of MET and angiogenic signaling has therapeutic potential in the treatment of RCC

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Safety and Efficacy of MET Inhibitor Tivantinib (ARQ 197) Combined With Sorafenib in Patients With Renal Cell Carcinoma From a Phase 1 Study

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Puzanov I, Sosman JA, Armando S, et al. Safety and efficacy of MET inhibitor tivantinib (ARQ 197) combined with sorafenib in patients with renal cell carcinoma from a phase 1 study. Presented at: 48th Annual Meeting of the American Society of Clinical Oncology; June 1-5, 2012; Chicago, IL. Abstract 4545.

BACKGROUND

- MET, a receptor tyrosine kinase implicated in tumor cell proliferation, migration, invasiveness, angiogenesis, and metastasis, is dysregulated in a broad spectrum of human cancers[1]
  - Approximately 54% to 87% of renal cell carcinoma (RCC) tumor samples over express hepatocyte growth factor/MET[2]
- Inhibitors of MET are being investigated in clinical trials and show promising efficacy in a variety of solid tumors[3]
- Tivantinib (ARQ 197) is a selective, oral, small-molecule inhibitor of the MET receptor[4] with demonstrated antitumor activity in a wide range of human tumors[5,6]
- Tivantinib is well tolerated and can be combined with sorafenib to improve clinical outcomes in multiple tumor types[7,8]
  - Combination treatment with tivantinib plus sorafenib resulted in synergistic inhibition of cell proliferation in several human tumor cell lines[9]
  - The phase 1 dose-escalation phase of this study established the recommended phase 2 dose (RP2D) to be 360 mg twice daily (BID) tivantinib plus 400 mg BID sorafenib[7]

OBJECTIVES

Primary

- Evaluate the safety, tolerability, maximum tolerated dose, and RP2D of tivantinib combined with sorafenib

Secondary

- Evaluate the pharmacokinetic and pharmacodynamic profiles of tivantinib plus sorafenib combination therapy
- Evaluate preliminary antitumor activity of tivantinib plus sorafenib combination therapy

METHODS

Study Design

- Open-label, phase 1, dose-escalation study in patients with advanced solid tumors

Drug Dosing

- An expanded cohort of up to 20 patients with RCC could be enrolled at the established RP2D

Drug Administration and Dosing Schedule

- Tivantinib capsules (360 mg) and sorafenib tablets (400 mg) were administered orally BID
- A treatment cycle was defined as 4 weeks for both drugs

Tumor Tissue Collection and Biomarker Analysis

- When available, archival tissue samples were collected at baseline
- Total MET expression status was determined by immunohistochemical (IHC) analysis performed by the sponsor and confirmed by a CLIA-certified central laboratory using the Ventana CONFIRM anti-total MET (SP44) rabbit monoclonal antibody (Ventana Medical Systems, Inc., Tucson, AZ)*
  - Staining intensity was scored on a scale of 0, 1+, 2+, or 3+
  - Samples that scored ≥ 2+ in ≥ 50% of tumor were considered MET positive

Tumor Measurement and Assessment

- Tumors were measured at baseline and in 8-week intervals until disease progression
- Responses were assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1

* Sponsor's IHC tests were done on small batches on an ongoing basis during the study. The central lab IHC tests were performed as one batch at the end of patient enrollment. When discrepancy occurred, to avoid the effect caused by MET degeneration over time, the sponsor's results were presented if the tissue sections tested by the central lab were prepared at the site and stored as slides.

RESULTS

Extension Cohort

- As of March 31, 2012, 20 patients with RCC have been enrolled
  - 1 patient initiated tivantinib treatment at 360 mg BID and sorafenib at 200 mg BID; all other patients initiated treatment at the RP2D
- Patient demographic and baseline characteristics are listed in **Table 1**

RESULTS (continued)

Patient Demographics

Table 1. Demographic and Baseline Characteristics of Patients With RCC

Characteristic	Patients (n = 20)
Median age, years	62
Range	23-75
Sex, n (%)	
Male	16 (80)
Female	4 (20)
Race, n (%)	
White	19 (95)
Black	1 (5)
Baseline ECOG performance status, n (%)	
0	14 (70)
1	6 (30)
RCC subtype, n (%)	
Clear cell	16 (80)
Papillary	3 (15)
Clear cell/chromophobe	1 (5)
Patients with previous surgery, n (%)	16 (80)
Patients with previous radiotherapy, n (%)	3 (15)
Patients with previous VEGF inhibitor treatment, n (%)	14 (70)
Median lines of previous systemic anticancer therapy, n (range)	2 (0-4)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor.

Pharmacodynamics

IHC Analysis of Archival Tissue Samples

- IHC results for total MET were available for 19 patients
  - 14 patients were MET positive and 5 were MET negative
- Tumor responses by MET status are shown in **Table 2**

Table 2. Best Response Stratified by MET Status

	Total (n = 19)	Total MET positive (n = 14)	Total MET negative (n = 5)
Partial response, n (%)	3 (16)	3 (21)	0
Stable disease, n (%)	15 (79)	11 (79)	4 (80)
Progressive disease, n (%)	1 (5)	0	1 (20)
Objective response rate, %	16	21	0
Disease control rate, %	95	100	80

- IHC positive staining for total MET in archival tissue samples from patients 15 and 42 (both partial response) are shown in **Figure 1**

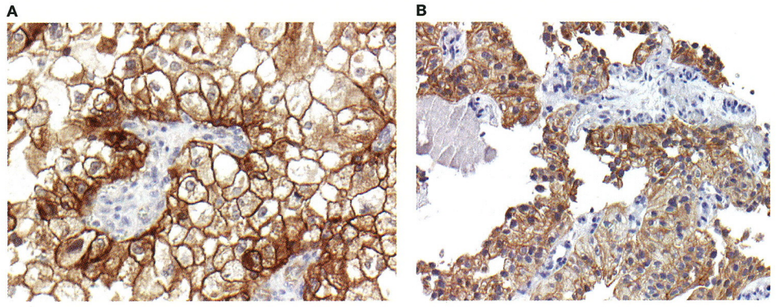

Figure 1. MET expression in archival tumor tissue from 2 patients with renal cell carcinoma: A) patient 15 with a partial response and B) patient 42 with a partial response.

RESULTS (continued)

Efficacy

Best Response and Progression-Free Survival

Table 3. Best Response in Patients With RCC (n = 20)

Active patients, n	2
Best response, n (%)	
Partial response	3 (15)
Stable disease	15 (75)
Progressive disease	2 (10)
Overall response rate, %	15
Disease control rate,[a] %	90

[a] Disease control rate calculated as the sum of patients with partial response or stable disease divided into the total number of patients (20).
Abbreviation: RCC, renal cell carcinoma.

Table 4. Progression-Free Survival

	Patients	Events	Censored	Median PFS (95% CI), mo
All RCC	20	75% (15)	25% (5)	7.5 (5.3-14.5)
Clear cell carcinoma	17	71% (12)	29% (5)	12.7 (5.3-14.7)

Abbreviations: CI, confidence interval; mo, months; PFS, progression-free survival; RCC, renal cell carcinoma.

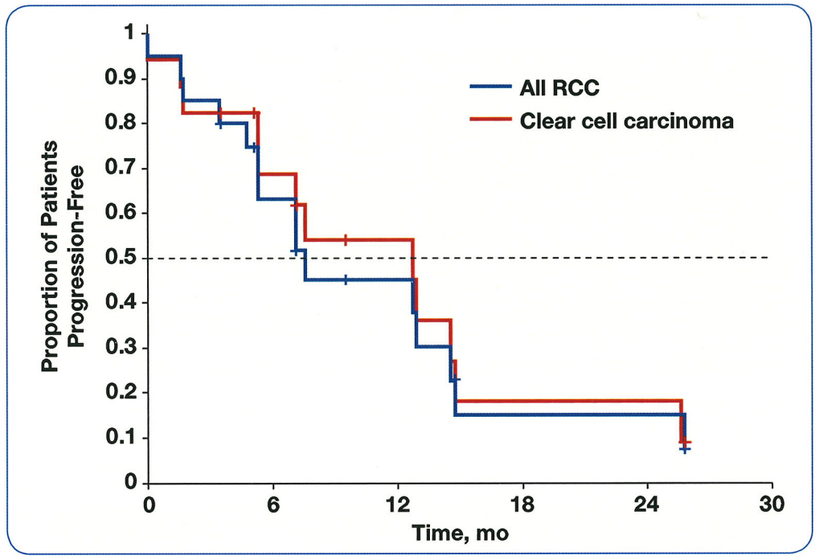

Figure 2. Kaplan-Meier analysis of progression-free survival (PFS) for all patients with RCC and the clear cell carcinoma subgroup (as of March 31, 2012).
Abbreviations: mo, months; RCC, renal cell carcinoma.

Table 5. Progression-Free Survival Rate in Patients With RCC by MET Status and Prior VEGF Inhibitor Treatment

	MET positive (n = 14)	MET negative (n = 5)	Prior VEGF (n = 14)	No prior VEGF (n = 6)
6 months, %	69.3	60.0	61.1	66.7
12 months, %	41.6	60.0	52.4	33.3

Abbreviations: RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor.