Abstract 3077

Phase 1b Results of c-MET Inhibitor Tivantinib (ARQ 197) in Combination With Gemcitabine in a Cohort of Patients With Advanced Breast, Ovarian, or Uterine Tumors

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BACKGROUND

- c-MET is a receptor tyrosine kinase implicated in tumor cell proliferation, migration, invasiveness, and angiogenesis and is dysregulated in a broad spectrum of human cancers[1-4]
- Tivantinib (ARQ 197) is a selective, oral, non–ATP-competitive, small-molecule inhibitor of the c-MET receptor tyrosine kinase[5]
- Tivantinib demonstrates antitumor activity in a range of human tumor cell lines and in xenograft models of human lung, prostate, colon, pancreas, and breast cancer[6,7]
- Tivantinib is well tolerated and can be combined with a wide range of other anticancer agents to overcome resistance and improve clinical outcomes in multiple tumor types[5,8]
- In vitro studies suggest schedule-dependent, additive or synergistic tumor growth inhibition when cancer cell lines are exposed to tivantinib plus gemcitabine (**Figure 1**)[9]

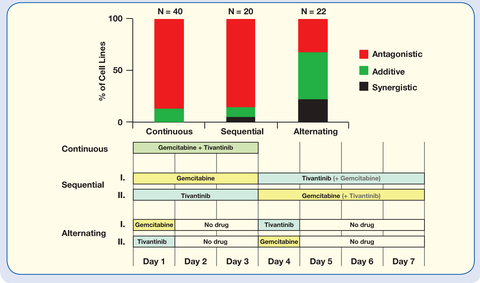


Figure 1. Growth inhibition of cancer cell lines treated with tivantinib (ARQ 197) in combination with gemcitabine.
Cancer cell lines originated from breast, pancreas, lung, ovary, bladder, and uterus.
Pant S, et al. *Ann Oncol.* 2010;21(suppl 8):viii167. Abstract 510P.[9]

STUDY OBJECTIVES

- Primary
  - Safety, maximum tolerated dose (MTD), and recommended phase 2 dose (RP2D) of tivantinib administered with gemcitabine in patients with advanced solid tumors
- Secondary/Exploratory
  - Pharmacokinetic (PK) profile of the combination therapy (previously reported)[9]
  - Preliminary antitumor activity of the combination therapy
  - Changes of hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), and soluble MET in peripheral blood[a]
  - Expression of phospho-c-MET, total MET, and downstream markers of the c-MET signaling pathway in patients' archival or biopsy tumor tissues

[a] To be reported at a later time.

METHODS

- Key inclusion criteria:
  - 18 years of age or older
  - Locally advanced or metastatic solid tumors
  - Measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
  - Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
  - Adequate bone marrow, liver, and renal function
- Key exclusion criteria:
  - Previous cancer within 3 years of trial participation excluding cervical carcinoma in situ, treated basal cell carcinoma, and superficial bladder tumors (Ta, Tis & T1)
  - Anticancer therapy within 4 weeks of study entry
  - History of serious cardiac disease and/or myocardial infarction within 6 months of study entry
  - Active, clinically relevant infections
- Hematology and blood chemistry were obtained weekly throughout the study
- ECG was performed at baseline, and at Week 1 and Week 2 of treatment (4 hours after drug administration)
- PK samples were obtained throughout Cycle 1
- Responses were assessed per RECIST version 1.1 based on computed tomography (CT) scans performed at 8-week intervals

PATIENT DEMOGRAPHICS

- 32 patients with breast, ovarian, and uterine cancer were enrolled as of April 22, 2011, and were treated at the RP2D (**Table 1**)

Table 1. Patient Demographics and Baseline Disease Characteristics, ITT Population[a]

	Primary Tumor Site			
	Breast (n = 12)	Ovarian (n = 14)	Uterine (n = 6)	Overall (N = 32)
Mean age, years (range)	53 (35 - 67)	66 (55 - 77)	64 (57 - 69)	61 (35 - 77)
Race, n (%)				
Asian	1 (8.3)	0	0	1 (3.1)
African American	0	1 (7.1)	1 (16.7)	2 (6.3)
Caucasian	10 (83.3)	12 (85.7)	4 (66.7)	26 (81.3)
Other	1 (8.3)	1 (7.1)	1 (16.7)	3 (9.4)
ECOG performance status, n (%)				
0	8 (66.7)	10 (71.4)	3 (50.0)	21 (65.6)
1	4 (33.3)	4 (28.6)	3 (50.0)	11 (34.4)
Median previous systemic therapies, n (range)	6 (3 - 9)	4 (1 - 9)	2 (1 - 5)	4 (1 - 9)
Previous gemcitabine treatment, n (%)[b]	3 (25.0)	4 (28.6)	0	7 (21.9)
Previous radiation therapy, n (%)	9 (75.0)	2 (14.3)	2 (33.3)	13 (40.6)
Previous cancer surgery, n (%)	11 (91.7)	13 (92.9)	4 (66.7)	28 (87.5)

[a] The ITT population is defined as all patients who took at least 1 dose of study medication.
[b] Best response to previous gemcitabine treatment were available for 6 of 7 patients, and were partial response (n = 1), stable disease (n = 4), and progressive disease (n = 1).
Abbreviations: ECOG, Eastern Cooperative Oncology Group; ITT, intention to treat; RP2D, recommended phase 2 dose.

PATIENT DISPOSITION

- Safety data are reported for the intent-to-treat (ITT) population and efficacy data are reported for the evaluable population (**Table 2**)

Table 2. Patient Disposition

	Primary Tumor Site			
	Breast (n = 12)	Ovarian (n = 14)	Uterine (n = 6)	Overall (N = 32)
Median treatment duration, months (range)[a, b]	2 (1 - 8)	3 (1 - 9)	2 (0 - 8)	2 (0 - 9)
Evaluable patients[c], n (%)	11 (91.7)	11 (78.6)	4 (66.7)	26 (81.3)

[a] In the intent-to-treat population (all patients who took at least 1 dose of study medication).
[b] Based on duration of treatment with tivantinib.
[c] The evaluable population is defined as all patients who completed 4 weeks of treatment with both drugs and who have at least 1 post-baseline tumor evaluation).

DOSING SCHEDULES

- In this study, tivantinib was administered at different dosing schedules starting from Week 1 of treatment, including an alternating dosing schedule (**Table 3**)

Table 3. Dosing Schedules

		Tivantinib		Gemcitabine (1,000 mg/m²)
Schedule	Patients, n	Dose, mg BID	Dosing Schedule	Dosing Schedule Per Cycle[c]
1 (continuous)	1	240	Continuous treatment on Days 1-28[a]	Days 1, 8, 15
0 (continuous)	3	120	Continuous treatment on Days 1-28[a]	Days 1, 8, 15
A (sequential)	0	120	2 weeks on/1 week off[b]	Days 8, 15, 22
B (sequential)	0	240	2 weeks on/1 week off[b]	Days 8, 15, 22
C (sequential)	1	360	2 weeks on/1 week off[b]	Days 8, 15, 22
D (sequential)	6	360	3 weeks on/1 week off[b]	Days 8, 15, 22
E1 (sequential)	1	360	Continuous treatment on Days 1-28[a]	Days 8, 15, 22
E2 (sequential)	14	360	Continuous treatment on Days 1-28[b]	Days 8, 15, 22
E3 (alternating)	6	360	Treatment on Days 1-5, 8-12, 15-19[b]	Days 7, 14, 21

[a] Taken without meals.
[b] Taken with meals.
[c] 1 cycle = 28 days.

SAFETY FINDINGS

- The most frequently reported adverse events occurring in > 10% of patients are shown in **Table 4**

Table 4. Treatment-Emergent Adverse Events Occurring in > 10% of Patients

	Patients (N = 32)		
Adverse Event, n (%)	Grade 1 or 2	Grade 3	Grade 4
Thrombocytopenia	12 (37.5)	9 (28.1)	3 (9.4)
Anemia	10 (31.3)	11 (34.4)	1 (3.1)
Nausea	10 (31.3)	2 (6.3)	0
Fatigue	8 (25.0)	5 (15.6)	0
Neutropenia	8 (25.0)	10 (31.3)	6 (18.8)
Vomiting	4 (12.5)	2 (6.3)	0
Leukopenia	1 (3.1)	3 (9.4)	1 (3.1)

- 3 patients had treatment-emergent serious adverse events
  - Grade 5 interstitial pneumonitis secondary to gemcitabine (n = 1)
  - Grade 3 pancytopenia (n = 1)
  - Grade 3 anemia (n = 1)

EFFICACY RESULTS

- Best response in the evaluable population is shown in **Table 5**

Table 5. Best Tumor Responses

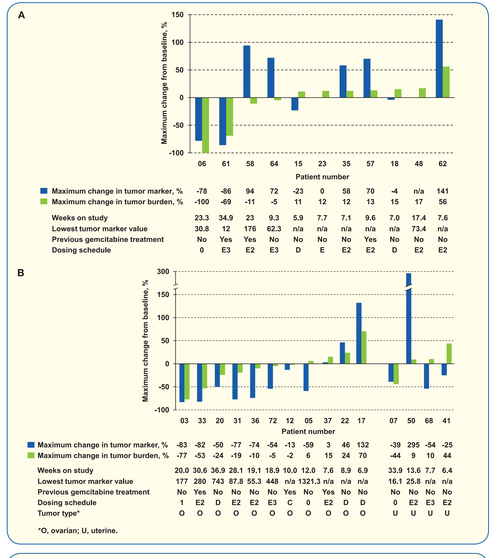
	Patients, n (%) [95% CI]			
	Breast (n = 11)	Ovarian (n = 11)	Uterine (n = 4)	Overall (N = 26)
Partial response	2 (18) [3 - 47]	2 (18) [3 - 47]	1 (25) [1 - 75]	5 (19) [8 - 36]
Stable disease	3 (27) [8 - 56]	5 (45) [20 - 73]	1 (25) [1 - 75]	9 (35) [19 - 53]
Progressive disease	6 (55) [27 - 80]	4 (36) [14 - 65]	2 (50) [10 - 90]	12 (46) [29 - 64]

Abbreviation: CI, confidence interval.

- Decline in tumor markers (CA15.3, CA125, CA27.29) ranging from 4% to 83% was observed in 17 of 28 patients (61%) evaluable for tumor markers
- 2 patients (breast and ovarian) with partial response (PR) and 1 patient (breast) with stable disease (SD) had prior progression on or after previous gemcitabine treatment
- After 6 months of treatment, there were 2 patients with PR (breast and ovarian) and 2 patients with SD (both ovarian)
- To date, best response of PR or SD has been observed in multiple patients in dosing schedules 1, 0, D, E2, and E3
- Tumor response generally coincided with decreased levels of tumor markers (**Figure 2**)
- CT scans of patient with ER⁻/PR⁻/HER2⁻ breast cancer and liver metastases showing reduction in tumor burden during treatment on dosing schedule 0 (**Figure 3**)

EFFICACY RESULTS (continued)

Figure 2. Antitumor activity and tumor marker status in patients with (A) breast, (B) ovarian, or (B) uterine cancer treated with tivantinib plus gemcitabine. Abbreviations: CR, complete response; PD, progressive disease; PR, partial response.



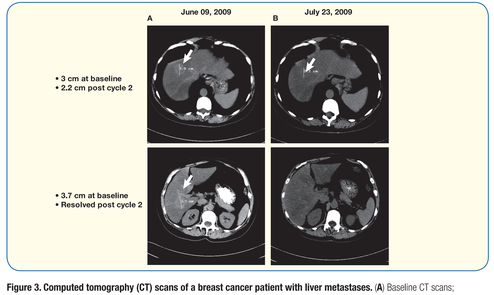


Figure 3. Computed tomography (CT) scans of a breast cancer patient with liver metastases. (A) Baseline CT scans; **(B)** Scans after 2 treatment cycles with tivantinib plus gemcitabine.

EFFICACY RESULTS (continued)

- CT scans of a patient with ER⁻/PR⁻/HER2⁻ breast cancer (**Figure 4**)

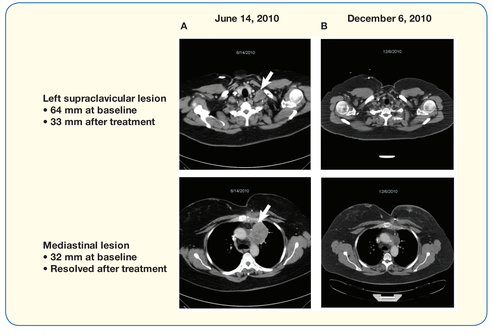


Figure 4. Computed tomography (CT) scans of a breast cancer patient with metastatic lesions. (A) Baseline CT scans; **(B)** Scans after treatment with tivantinib plus gemcitabine.

CONCLUSIONS

- **In vitro studies suggested greater tumor growth inhibition when tivantinib and gemcitabine treatment was alternated**
- **In the current study, 14 of 26 patients (54%) in the evaluable population had PR or SD**
  - **PR or SD were observed with 5 of the 7 evaluated dosing schedules, including the alternating treatment regimen**
  - **Additional patient data are needed to establish whether alternating treatment with tivantinib and gemcitabine will produce synergistic or additive effects on tumor growth inhibition similar to what has been observed in vitro**
- **The combination of tivantinib and gemcitabine demonstrated promising antitumor activity in patients with breast, ovarian, and uterine carcinoma, including patients who had tumor progression after prior gemcitabine therapy**

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Acknowledgments

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