Results of a Phase 1b Study of ARQ 092 in Combination with Carboplatin (C) Plus Paclitaxel (P) or with Paclitaxel in Patients with Solid Tumors

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BACKGROUND

- The serine/threonine kinase AKT plays important roles in cellular processes such as cell growth, metabolism, proliferation, and survival.
- AKT is one of the most frequent aberrantly activated protein kinases in human cancer.
- Breast tumor cells with PIK3CA or HER2 amplification have been shown to be dependent on AKT signaling.
- ARQ 092 is an oral, potent AKT inhibitor with single agent antitumor activity.
- Paclitaxel alone or in combination with carboplatin is the standard therapy or the therapy of choice for patients with various solid tumors.
- ARQ 092 potentiated antitumor activity of paclitaxel in *in vivo* xenograft models, providing the rationale for this study.

METHODS

Objectives

Primary: to assess the safety and tolerability of ARQ 092 in combination with carboplatin plus paclitaxel (CP arm) or in combination with paclitaxel alone (P arm)

Secondary: to assess pharmacokinetic profile, preliminary anti-tumor activity, and determine Recommended Phase 2 Dose (RP2D)

Study Design

- **Open label, phase 1, dose-escalation study; 3+3* subjects per cohort (*if DLT)**
- **Dose Limited Toxicity (DLT), if occurs in first treatment cycle:**
  - **Standard DLT criteria; Grade 3 or asymptomatic Grade 4 hyperglycemia not improving to < 250 mg/dL despite appropriate treatment for 1 week or symptomatic Grade 4 hyperglycemia (> 500 mg/dL)**
- **Maximum Tolerated Dose (MTD):**
  - **Dose level at which ≤ 1 of 6 subjects experienced DLT**

Key Inclusion Criteria

- **Age ≥ 18 years**
- **Any tumor type (except lung) for which carboplatin+ paclitaxel or paclitaxel alone would be appropriate**
- **Failed or did not tolerate previous standard therapies**
- **Measurable or evaluable disease**
- **Eastern Cooperative Oncology Group (ECOG) ≤ 2**
- **Adequate organ function**

Key Exclusion Criteria

- **Received oral or IV anti-cancer systemic therapy within 2 or 4 weeks; received radiotherapy or surgery within 4 weeks**
- **Previous treatment with AKT inhibitors**
- **Unstable central nervous system metastases**
- **History of, or current clinically significant disorders**
- **History of diabetes mellitus requiring regular medication other than oral agents (e.g. metformin) or fasting glucose ≥ 160 mg/dL**

Assessments	
Tumor measurement	Tumors were measured at baseline and in 6-week (CP arm) or 8-week (P arm) intervals until disease progression and were assessed according to RECIST (v1.1) for solid tumors or Revised Response Criteria for Malignant Lymphoma.
Pharmacokinetic (PK) analysis	Serial PK samples were collected on Day 1 and on Day 12 or Day 15 before dosing and at multiple time points between 1 hour and 12 hours post-dosing. Single pre-dose PK samples were also collected on Day 8 for CP arm and Day 8, 15 and 22 for P arm. Noncompartmental PK parameters were calculated using Phoenix 64 WinNonlin version 7.0 (Pharsight, Mountain View, CA).
Adverse event assessment	Common Terminology Criteria for Adverse Events (CTCAE) version 4.03

RESULTS

Table 1. Treatment Arm and Cohort

As of 28 April 2017, 16 subjects were enrolled and treated in the two combination arms.

Arm	Cohort	ARQ 092	Carboplatin (C)	Paclitaxel (P)	N
CP	1	200 mg BID 1 day/week	AUC 6 Q3W	175 mg/m^2, Q3W	10
CP	3	100 mg QD 5 days on/5-6 days off	AUC 6 Q3W	175 mg/m^2, Q3W	3
P	1	200 mg BID weekly	—	80 mg/m^2, weekly	3

BID: twice daily, QD: daily, Q3Q: once every 3 weeks.

Table 2. Demographics and Baseline Parameters

Parameter	CP Arm (n=13)	P Arm (n=3)	Total (n=16)
Age (years)			
Median	62	58	62
Min, Max	26, 72	54, 67	26, 72
Sex, n (%)			
Male	2 (15.4)	2 (66.7)	4 (25.0)
Female	11 (84.6)	1 (33.3)	12 (75.0)
Race, n (%)			
Black or African American	0	1 (33.3)	1 (6.3)
White	12 (92.3)	2 (66.7)	14 (87.5)
Other	1 (7.7)	0	1 (6.3)
ECOG, n (%)			
0	3 (23.1)	0	3 (18.8)
1	10 (76.9)	3 (100.0)	13 (81.3)
Tumor Type, n (%)			
Breast	1 (7.7)	0	1 (6.3)
Esophageal	1 (7.7)	0	1 (6.3)
Gastric	1 (7.7)	0	1 (6.3)
Head and neck	0	2 (66.7)	2 (12.5)
Neuroendocrine	0	1 (33.3)	1 (6.3)
Ovarian	4 (30.8)	0	4 (25.0)
Pancreatic	3 (23.1)	0	3 (18.8)
Other	3 (23.1)[1]	0	3 (18.8)
Any Prior Surgery, n (%)			
Yes	13 (100.0)	3 (100.0)	16 (100.0)
Any Prior Radiation, n (%)			
No	7 (53.8)	0	7 (43.8)
Yes	6 (46.2)	3 (100.0)	9 (56.3)
Regimen Number of Systemic Cancer Therapy, n (%)			
0	0	1 (33.3)	1 (6.3)
1	1 (7.7)	2 (66.7)	3 (18.8)
2	2 (15.4)	0	2 (12.5)
3	3 (23.1)	0	3 (18.8)
4	5 (38.5)	0	5 (31.3)
>5	2 (15.4)	0	2 (12.5)

Date of data extraction: 19 Apr 2017
1. vulva, soft tissue sarcoma, Ewing sarcoma

Table 3. Dose-Limiting Toxicities (DLTs)

In the CP Arm, 4 DLTs were observed in 3 subjects. In the P arm, no DLTs were observed.

Arm	Cohort	Pt ID	DLT	Grade	Related to ARQ 092	Outcome	Treatment discontinued
CP	200 mg BID	053-0001	Neutrophil count decreased	4	Related*	Recovered with sequelae	No
CP	200 mg BID	053-0001	Thrombocyto-penia	4	Related*	Recovered with sequelae	Yes
CP	200 mg BID	053-0002	diarrhea	3	Related	Recovered with sequelae	No
CP	100 mg QD 5 days on/ 5-6 days off	083-0001	Hypokalaemia	3	Related	Recovered	No

* These events were also related to carboplatin and paclitaxel.

Table 4. Drug-related Treatment Emergent Adverse Event (TEAE) (any grade) in ≥ 20% of Subjects

Preferred Term, n (%)	ARQ 092[1] (n=16)	CP[2] (n=13)	P (n=3)	Total[3] (N=16)
Fatigue	8 (50.0)	10 (76.9)	1 (33.3)	11 (68.8)
Alopecia	1 (6.3)	8 (61.5)	1 (33.3)	9 (56.3)
Diarrhoea	9 (56.3)	1 (7.7)	0	9 (56.3)
Thrombocytopenia	2 (12.5)	9 (69.2)	0	9 (56.3)
Neutropenia	1 (6.3)	6 (46.2)	0	6 (37.5)
Nausea	4 (25.0)	4 (30.8)	1 (33.3)	5 (31.3)
Hyperglycaemia	4 (25.0)	1 (7.7)	0	4 (25.0)
Leukopenia	0	4 (30.8)	0	4 (25.0)
Lymphopenia	1 (6.3)	4 (30.8)	0	4 (25.0)
Mucosal inflammation	4 (25.0)	3 (23.1)	0	4 (25.0)
Peripheral sensory neuropathy	0	4 (30.8)	0	4 (25.0)
Rash maculo-papular	4 (25.0)	0	0	4 (25.0)

1. Related to ARQ 092 in either CP or P arm. 2. Related to carboplatin and/or paclitaxel in CP arm. 3. Related to either ARQ 092 or any chemotherapy.

Table 5. Drug-related ≥ Grade 3 TEAEs

Preferred Term, n(%)	ARQ 092[1] (n=16)	CP[2] (n=13)	P (n=3)	Total[3] (n=16)
Neutropenia	1 (6.3)	6 (46.2)	0	6 (37.5)
Thrombocytopenia	2 (12.5)	5 (38.5)	0	5 (31.3)
Leukopenia	0	3 (23.1)	0	3 (18.8)
Lymphopenia	1 (6.3)	3 (23.1)	0	3 (18.8)
Hyperglycaemia	2 (12.5)	0	0	2 (12.5)
Alanine aminotransferase increased	1 (6.3)	0	1 (33.3)	1 (6.3)
Anaemia	0	1 (7.7)	0	1 (6.3)
Aspartate aminotransferase increased	1 (6.3)	0	1 (33.3)	1 (6.3)
Diarrhoea	1 (6.3)	0	0	1 (6.3)
Hypokalaemia	1 (6.3)	1 (7.7)	0	1 (6.3)
Upper gastrointestinal haemorrhage	0	1 (7.7)	0	1 (6.3)

1. Related to ARQ 092 in either CP or P arm. 2. Related to carboplatin and/or paclitaxel in CP arm. 3. Related to either ARQ 092 or any chemotherapy.

Table 6. Best Overall Response

Response, n (%)	CP Arm (n=13)	P arm (n=3)	Total (n=16)
Complete Response	1 (8)	0	1 (6)
Partial Response	1 (8)	0	1 (6)
Stable Disease	6 (46)	2 (67)	8 (50)
Progressive Disease	4 (31)	1 (33)	5 (31)
No assessment available	1 (8)	0	1 (6)
Clinical benefit (PR+SD)	**8 (62)**	**2 (67)**	**10 (63)**

Figure 1. Best Percent Tumor Size Change from Baseline

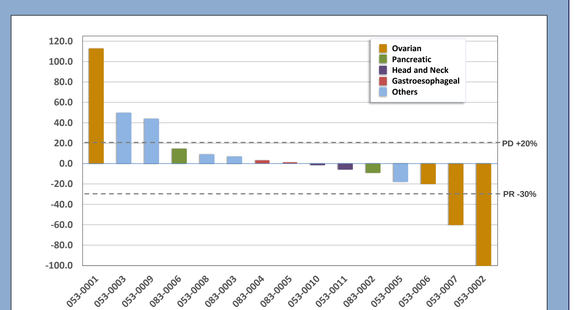

Figure 2. CT Scan of Subjects 053-0002 with CR

- A 69-year-old white female with ovarian cancer and 4 lines of prior systemic cancer regimens including carboplatin and paclitaxel, received ARQ 092 200 mg BID weekly, carboplatin 6 mg/mL (AUC 6) and paclitaxel 175 mg/m^2 every 3 weeks.

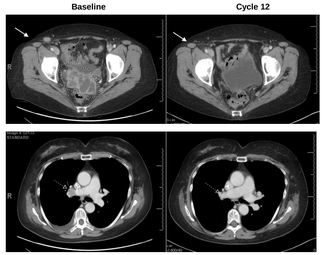

Figure 3. CT Scan of Subject 053-0007 with PR

- A 63-year-old white female with ovarian cancer and 8 lines of prior systemic cancer regimens, received ARQ 092 at 200 mg BID weekly, carboplatin 6 mg/mL (AUC 6) and paclitaxel 175 mg/m^2 every 3 weeks. On day 83, there was 60% reduction. CA 125 decreased from baseline 126 to nadir of 12.

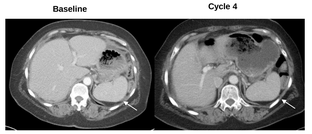

Table 7. Preliminary ARQ 092 PK Parameters in Combination with Carboplatin and Paclitaxel

Arm	ARQ 092 Dose (mg)	ARQ 092 Dosing Schedule	Cycle	Day	# of subjects	Statistic	T_{max} h*	C_{max} nM	T_{last} h*	C_{last} nM	AUC_{all} h*nM
CP	200	BID, QW	1	1	9	mean	10	513	12	473	2739
						sd	-	342	-	303	1956
						cv (%)	-	67	-	64	71
				15	8	mean	10	454	12	412	3325
						sd	-	381	-	341	2129
						cv (%)	-	84	-	83	64
			2	1	7	mean	10	462	12	436	2384
						sd	-	247	-	252	1442
						cv (%)	-	53	-	58	60
CP	100	QD, 5 days on/ 5-6 days off	1	1	3	mean	8	58	8	58	225
						sd	-	49	-	49	178
						cv (%)	-	85	-	85	79
				12	3	mean	4	113	8	81	625
						sd	-	102	-	78	693
						cv (%)	-	90	-	97	111
			2	1	2	mean	7	114	8	110	565
						sd	-	64	-	69	321
						cv (%)	-	56	-	63	57

* Median value are reported. sd and cv (%) are not calculated.
Carboplatin Dosing Schedule - AUC 6, Q3W
Paclitaxel Dosing Schedule - 175 mg/m^2, Q3W

CONCLUSIONS

- **The most common (in ≥ 50% subjects) TEAEs related to ARQ 092 were fatigue and diarrhea. The most common TEAEs related to C/P were fatigue, alopecia and thrombocytopenia. Grade ≥3 neutropenia and thrombocytopenia related to C/P occurred in 46% and 38% of subjects, respectively.**
- **Full-dose CP was not tolerated by most subjects.**
- **For the 200 mg BID, QW cohort (n=8), the Day 15 C_{max} and the AUC_{last} were 454 nM and 3325 h*nm, respectively.**
- **For the 100 mg QD 5 days on/5-6 days off cohort (n=3), the Day 12 C_{max} and the AUC_{last} were 113 nM and 625 h*nm, respectively.**
- **Encouraging anticancer activity was demonstrated in heavily pretreated ovarian cancer subjects**
  - **1 CR with response duration of 316 days**
  - **1 PR with 60% tumor reduction and response duration of 127 days**

ACKNOWLEDGEMENTS

The authors express their sincere appreciation and gratitude to patients, their families and investigators who participated in this trial.

Presented at: 2017 ASCO Annual Meeting, 2-6 June 2017, Chicago, IL, USA