A Phase 1 Dose Escalation Study of ARQ 751 in Adult Patients with Advanced Solid Tumors with AKT1, 2, 3 Genetic Alterations, Activating PI3K Mutations, PTEN-null, or Other Known Actionable PTEN Mutations

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BACKGROUND

Dysregulation of the PI3K/AKT signaling pathway has been implicated in a number of human cancers and plays a critical role in cancer initiation and progression. As a critical node in mediating PI3K/AKT pathway, AKT can be activated through receptor tyrosine kinases, gain-of-function mutations of PIK3CA, activating mutations of AKT such as AKT1E17K, and PTEN deficiency.

ARQ 751 is a potent, selective, orally bioavailable pan-AKT inhibitor with IC_{50} values of 0.54 (AKT1), 0.79 (AKT2), and 1.3 (AKT3) nM. It binds to both active and inactive forms of AKT in an allosteric fashion.

MATERIALS AND METHODS

This is a phase 1, single-arm, open-label, dose-escalation study of ARQ 751 in patients with advanced solid tumors with PIK3CA/AKT/PTEN genetic aberrations (NCT02761694).

Primary Endpoints
Safety and tolerability in subjects with advanced solid tumors with AKT1, 2, 3 genetic alterations, activating PI3K mutations, PTEN-null, or other known actionable PTEN mutations

Secondary Endpoints
- Pharmacokinetic profile
- Pharmacodynamic activity
- MTD and/or RP2D
- Preliminary evidence of activity

Exploratory Endpoints
- To evaluate the association among markers of the AKT signaling pathway, toxicity, and clinical activity
- To evaluate changes in different pathways and to predict potential combinations of interest

Key Eligibility Criteria
- Male/Female ≥ 18 years of age; ECOG PS ≤ 2
- Histologically or cytologically documented locally advanced, inoperable or metastatic solid tumors with documented AKT1, 2, 3 genetic alterations, activating PI3K mutations, PTEN-null, or other known actionable PTEN mutations
- Measurable disease
- Failure to respond to standard therapy or standard or curative therapy does not exist or is not tolerable
- Adequate bone marrow, cardiovascular, hepatic, and renal function
- No previous treatment with AKT inhibitors
- No prior anti-cancer treatment within 4 wks prior to dosing or 5 times the half-life (which ever shorter)
- No history of type 1 or 2 diabetes mellitus requiring regular medication (other than oral hypoglycemic agents) or fasting glucose ≥ 160 mg/dL at baseline
- No concurrent serious co-morbidities that could limit subjects' full participation and compliance

Statistical Methods
Safety analyses included all subjects who have received at least one dose of ARQ 751. Descriptive statistics used for all other secondary and exploratory analyses. Preliminary efficacy analyses include subjects who received at least one cycle of ARQ 751 and have had at least one post-baseline disease assessment.

Dose Escalation Schema and Enrollment Status

Cohort	1	2	3*	4*	4	5	6**	7
Dose Schedule	5 mg QD	10 mg QD	20 mg QD	25 mg QOD	25 mg QD	50 mg QD	100 mg QD	75 mg QD
No. pts planned	3-6	3-6	3-6	3-6	3-6	3-6	3-6	6
No. pts actual	4	4	1	3	3	3	8	8
No. active pts	0	0	0	0	1	0	0	6

* The original planned dose was 20 mg QD, it was changed to 25 mg QOD due to availability of capsule strength.
** One DLT (grade 3 pruritic rash) and other drug-related AEs/SAEs, the cohort was expanded and eventually was considered as not tolerable. Further dose escalation was stopped.

- Dose escalation followed standard 3+3 design.
- Dose-limiting toxicities (DLT) will be determined during first treatment cycle (4 weeks/28 days).
- 34 patients enrolled: 7 patients ongoing, 27 discontinued.

Baseline Patient Characteristics

N=34, n (%)			
Median age (range) in years	59.5 (29-76)	**Baseline ECOG, n (%)**	
Gender, n (%)		0	3 (9)
Male	8 (24)	1	31 (91)
Female	26 (76)	**Median number (range) of prior systemic therapies**	5 (2-19)
Race, n (%)		**Mutation status, n (%)**	
White	31 (91)	AKT1 mutation	3 (9)
Black	3 (9)	AKT3 mutation	1 (3)
Tumor type, n (%)		PI3K mutation	18 (53)
Breast	13 (38)	PTEN null	6 (18)
Endometrial	5 (15)	PTEN mutation	4 (12)
Others*	16 (47)	More than one abnormalities (PI3K + AKT)	2 (6)

*Other: prostate (3), colon (2), head and neck (2), cervical (1), gastroesophageal (1), ovarian (1), cecum (1), leiomyosarcoma of the uterus (1), cholangiocarcinoma (1), gallbladder (1), jejunum (1), and Osteosarcoma of bone (1).
Data cut-off on 31 Oct 2018

RESULTS

Efficacy

Overall Responses

	All Patients N=34, n (%)	Patients on ≥ 25 mg QD N=22, n (%)
Complete response (CR)	0	0
Partial response (PR)	2 (5.9)	2 (9.1)
Stable disease (SD)	11 (32.4)	9 (40.9)
Progressive disease (PD)	12 (35.3)	4 (18.2)
Not evaluable*	9 (26.5)*	7 (31.8)*
Disease control rate**	13 (38.2)	11 (50.0)

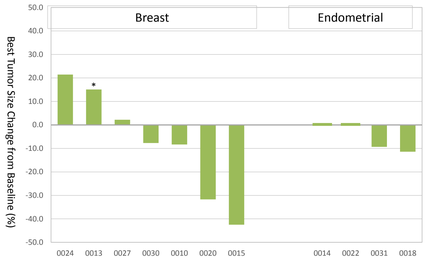
*3 patients have not reached their time for 1st post-treatment tumor measurement ; ** PR+PD; Data cut off 31 Oct 2018

Patients with Partial Response (PR) or Stable Disease (SD)

	Tumor Type	Mutation	Dose Level	No. of prior therapies	Best response	Time on treatment (weeks)	ER,PR Her2	% Tumor marker Change from BL
Breast Cancer								
0015	Breast	*PTEN C296fs*2*	25 mg QD	8	PR	24	+,+,-	20#
0020	Breast	*PIK3CA H1047R*	100 mg QD	8	PR	18	+,+,-	-79**
0010	Breast	*PIK3CA H1047R*	25 mg QOD	9	SD	46	+,+,-	
0027	Breast	*PIK3CA E542K*	75 mg QD	7	SD	16+	+,+,-	-52**
0013	Breast	*PTEN L247fs*5*	25 mg QD	8	SD	16	TNBC	-13*
0030	Breast	*PIK3CA E542K*	75 mg QD	3	SD	12+	+,+,-	
0024	Breast	*AKT 1 E17K*	100 mg QD	5	SD	6	+,+,-	-37#
Endometrial Cancer								
0014	Endometrial	*AKT1 E17K*	25 mg QD	3	SD	52+		-26*
0018	Endometrial	*PIK3CA E545D*	50 mg QD	4	SD	16	-, -, unk	-82*
0022	Endometrial	*PTEN Null*	100 mg QD	4	SD	8		20*
0031	Endometrial	*PIK3CA E542K*	75 mg QD	7	SD	9+	-, unk, unk	-39*
Other Cancer								
0011	Head and neck	*PTEN Null*	20 mg QD	3	SD	16	NA	
0023	Osteosarcoma	*AKT3 G324A*	100 mg QD	9	SD	24	NA	

* CA125; ** CEA; # CA15.3
+ Active patients. Data cut off 31 Oct 2018

Best Tumor Size Change from Baseline Breast and Endometrial Cancers (PRs and SDs)

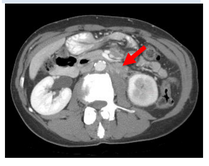


* Patient 0013 was TNBC. All other patients with breast cancer were ER+, PR+ and Her2-.

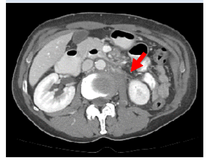
Patient 0015 CT Scan Data

This 66-year-old white female with stage IV ER+, PR+ and HER2- breast cancer with PTEN C296fs*2 mutation has received 8 prior anti-cancer systemic regimens including hormonal therapy and chemotherapy. Her tumor size was reduced by 32.5% in CT scans after 8 weeks on study treatment at 25 mg QD. The PR was confirmed after 19 weeks on study treatment with a further tumor size reduction to 42.5% from baseline. Treatment with ARQ 751 was discontinued due to clinical disease progression after 24 weeks on study treatment.

Baseline



1st Restaging Study Day 53

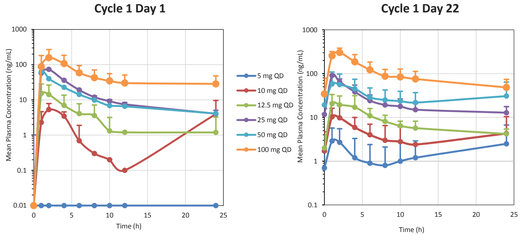


Pharmacokinetics (PK) and Pharmacodynamics

Summary of PK Findings (Preliminary)

- ARQ 751 (Day 22) increases in exposure were greater than dose proportional as dose increased from 10 to 100 mg QD (except for the 50 mg QD dose).
- Drug half-life ($t_{1/2}$) ranged from 6 to 67 hours.
- Preliminary data suggest minimal drug accumulation up to the 50 mg QD dose level. However, at 100 mg QD, some patients showed slightly greater than 2-fold accumulation.
- There is high variability in the PK data which may in part be attributed to CYP2D6 polymorphism.
- Target inhibition (i.e. increasing insulin and glucose levels) is observed at ≥ 25 mg QD dose levels.

ARQ 751 Mean Plasma Concentration-Time Profiles (semi-log plots)



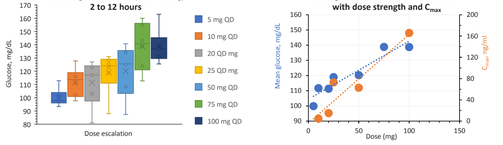
Note: All day 1 PK samples at 5 mg QD were BLQ, NA or BLQ points were substituted with a non-zero value to generate the log scale plot and for plot continuity.
See individual concentration-time profiles for reference.

PK Sample Collection

- Blood PK samples were collected predose and at 1, 2, 4, 6, 8, 10, 12, and 24 hours postdose on days 1 and 22 of cycle 1.
- Predose samples were also collected on days 8 and 15 of cycle 1 and days 1 and 15 of cycle 2.

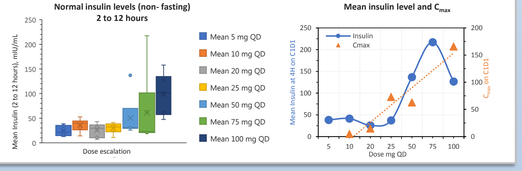
ARQ 751 Exposure Is Dose Proportional and Linearly Correlated with Increase in Glucose Levels

ARQ 751 induced hyperglycemia in patients during study drug exposure at various cohorts.
Transient glucose level increase is in linear correlation with dose proportional increase in ARQ 751 C_{max}.



Effect of ARQ 751 Exposure on Insulin Levels

ARQ 751 induced hyperinsulinemia in patients during study drug exposure at various cohorts and correlation of insulin changes with C_{max} increase.



Drug Safety

Adverse Events (AE) Summary

	All Grades N=34 (n%)
Number of patients with any AEs	33 (97.1)
Number of patients with SAEs	17 (50.0)
Number of patients with DLTs	1 (2.9)
Number of patients with ARQ 751-related AEs	24 (70.6)
Number of patients with treatment interruption and/or dose reduction due to AEs	19 (55.9)
Number of patients with reduction with/without interruption	3 (8.8)
Number of patients with treatment discontinuation due to AEs	4 (11.8)

DLT

One DLT, grade 3 pruritic rash, was reported in one patient treated in the 100 mg QD cohort.

The DLT occurred on study Day 18. The study treatment was interrupted due to this event, then restarted at 50 mg QD on Study Day 29. The grade 3 pruritic rash resolved on Study Day 43.

Most Common (≥5%) ARQ 751-related AEs

AE term	All Grade N=34 n (%)	Grade 3-4 N=34 N (%)	Grade 5 N=34 N (%)
Diarrhoea	11 (32.4)	3 (8.8)	0
Rash	8 (23.5)	0	0
Nausea	7 (20.6)	0	0
Vomiting	4 (11.8)	0	0
Mucosal inflammation	3 (8.8)	0	0
Hyperglycaemia	3 (8.8)	2 (5.9)	0
Fatigue	3 (8.8)	0	0
Stomatitis	2 (5.9)	0	0

Most Common (≥10%) Adverse Events

Preferred Term	All Grades N=34 n (%)	Grade 3-4 N=34 n (%)	Grade 5 N=34 n (%)
Diarrhoea	18 (52.9)	5 (14.7)	0
Nausea	12 (35.3)	1 (2.9)	0
Fatigue	12 (35.3)	3 (8.8)	0
Decreased appetite	11 (32.4)	0	0
Vomiting	11 (32.4)	1 (2.9)	0
Rash/pruritic rash	11 (32.4)	1 (2.9)	0
Cough	7 (20.6)	0	0
Abdominal pain upper	5 (14.7)	1 (2.9)	0
Constipation	5 (14.7)	0	0
Urinary tract infection	5 (14.7)	0	0
Headache	5 (14.7)	0	0
Oedema peripheral	4 (11.8)	0	0
AST increased	4 (11.8)	4 (11.8)	0
Dyspnoea exertional	4 (11.8)	0	0
Hyponatraemia	4 (11.8)	3 (8.8)	0

Please note: 8 (23.5%) patients died of disease progression.

ARQ 751-related ≥Grade 3 AEs

AE term	≤ 50 mg QD N=18 n (%)	75 mg QD N=8 n (%)	100 mg QD N=8 n (%)	All N=34 n (%)
Diarrhoea	0	2 (25.0)	1 (12.5)	3 (8.8)
Hyperglycaemia	0	1 (12.5)	1 (12.5)	2 (5.9)
Rash pruritic	0	0	1 (12.5)	1 (2.9)

ARQ 751-related AEs of Special Interest

TEAE	All Grades N=34 n (%)	Grade 3-4 N= 34 n (%)	Grade 5 N=34 n (%)
Diarrhea	11 (32.4)	3 (8.8%)	0
Hyperglycemia	3 (8.8)	2 (5.9%)	0
Skin rash/pruritic rash	9 (26.5)	1 (2.9)	0
Stomatitis	2 (5.9)	0	0
AST/ALT increase	0	0	0

CONCLUSIONS

- **RP2D was determined to be 75 mg QD. ARQ 751 has demonstrated manageable toxicity at doses from 5 mg QD to 75 mg QD.**
- **ARQ 751 demonstrated preliminary anti-tumor activities in tumors with PIK3CA/AKT/PTEN mutations and PTEN null. Two ER+, PR+ and HER2- stage IV breast cancer patients, one with PTEN C296fs*2 mutation, one with PIK3CA H1047R mutation, achieved a partial response after 8 weeks on study treatment. In addition, 11 patients had stable disease.**
- **Further development of ARQ 751 as a monotherapy or in combination with other anti-cancer agents is deemed feasible considering its manageable safety profile and preliminary evidence of biological activity.**

REFERENCES

1. LoRusso PM. *J Clin Oncol*. 2016;34(31):3803-3815.
2. Yu Y, et al. *PLoS ONE*. 2015;10(12):e0140479

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