Results of A Phase 1 Dose Escalation Study of ARQ 751 in Adult Subjects 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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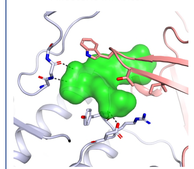
BACKGROUND

Dysregulation of the PI3K-AKT signaling pathway is associated with a number of cancers, and plays a critical role in cancer initiation and progression. AKT can be activated through activated receptor tyrosine kinases, gain-of-function mutations of PIK3CA, PTEN deficiency, and AKT amplification or activating mutations such as AKT1E17K. As the second generation of an allosteric AKT inhibitor, ARQ 751 potently inhibits AKT1, 2 and 3 with biochemical IC_{50} values of 0.55 nM, 0.81 nM and 1.31 nM, respectively. In addition, ARQ 751 is very selective; it does not inhibit any other kinases (out of the 245 tested) by greater than 50% at 5 µM. The objective of this study is to determine maximum tolerated dose in patients with advanced solid tumors.

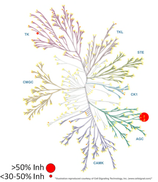
ARQ 751: Second-Generation Allosteric AKT Inhibitor

Highly selective; demonstrates potent anti-tumor activity in PI3K/AKT pathway driven tumors

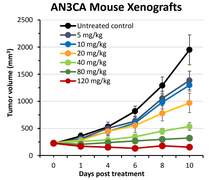
Allosteric Inhibitor



Kinase Selective



Inhibition of Tumor Growth in AN3CA Mouse Xenografts



MATERIALS AND METHODS

Key Inclusion Criteria:

- Locally advanced, inoperable or metastatic solid tumors
- AKT1, 2, 3 genetic alterations, activating PI3K mutations, PTEN-null, or other known actionable PTEN mutations
- Failure to respond to standard therapy or standard or curative therapy does not exist or is not tolerable
- Measurable disease
- Adequate organ function

Key Exclusion Criteria:

- Previous treatment with AKT inhibitors
- History of type 1 or 2 diabetes mellitus requiring regular medication (other than oral hypoglycemic agents) or fasting glucose ≥ 160 mg/dL at baseline

Study Design

- Single arm, phase 1, dose escalation study
- Dose escalation according to 3+3 design
- Treatment-emergent adverse events (TEAEs)/related TEAEs assessed per CTCAE v. 4.03
- Responses were evaluated per RECIST 1.1
- One treatment cycle is 28 days (4 weeks)

Pharmacokinetic (PK) Sampling

- Blood PK samples were collected pre-dose and at 1, 2, 4, 6, 8, 10, 12, and 24 hours post-dose on Days 1 and 22 of Cycle 1. Additionally, pre-dose samples were collected on Days 8 and 15 of Cycle 1 and Days 1 and 15 of Cycle 2.
- Blood samples were processed and the resulting plasma samples were stored at -70˚C until analyzed using a validated LC/LC/MS assay.

RESULTS

Patient Demographics

	N=18
Median age (Range)	**60.5 (29-76) years**
Gender, N (%)	
Male	4 (22%)
Female	14 (78%)
Race, N (%)	
White	17 (94%)
Black	1 (6%)
Tumor type, N (%)	
Breast	6 (33%)
Endometrial	3 (17%)
Others*	9 (50%)
Baseline ECOG, N (%)	
0	2 (11%)
1	16 (89%)
Median number (range) of prior systemic therapy	4 (3-19)
Mutation Status, N (%)	
AKT1 mutation	1 (6%)
Activating PI3K mutation	11 (61%)
PTEN null/mutation	5 (28%)
PI3K mutation and AKT3 amplification	1 (6%)

*Others: colon, cervical, gastroesophageal, prostate, ovarian, cecum, head and neck, leiomyosarcoma of the uterus, and cholangiocarcinoma (1 each)

Treatment Dose Level and Number of Patients

Dose Level	Number of Patients
5 mg QD	4
10 mg QD	4
25 mg QOD	3
20 mg QD	1
25 mg QD	3
50 mg QD	3
Total	**18**

Dose-Limiting Toxicities (DLTs) and Severe/Serious Adverse Events (AEs)

- No DLTs observed
- No ARQ 751-related ≥ Grade 3 AEs observed
- No ARQ 751-related serious AEs observed
- MTD/RP2D was not reached

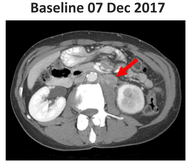
MTD: maximum tolerated dose; RP2D: recommended phase 2 dose

ARQ 751-related Adverse Events

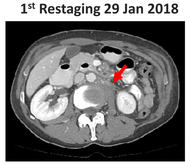
Preferred Term	All Grade N (%)	≥ Grade 3 N (%)
Nausea	5 (27.8)	0
Diarrhoea	2 (11.1)	0
Rash	2 (11.1)	0
Stomatitis	1 (5.6)	0
Vomiting	1 (5.6)	0
Fatigue	1 (5.6)	0
Mucosal inflammation	1 (5.6)	0
White blood cell count decreased	1 (5.6)	0
Hyperkalaemia	1 (5.6)	0
Cough	1 (5.6)	0
Oropharyngeal pain	1 (5.6)	0
Sinus congestion	1 (5.6)	0
Pain of skin	1 (5.6)	0
Pruritus	1 (5.6)	0
Hot flush	1 (5.6)	0

Patient 084-0015 CT Scan Data

Baseline 07 Dec 2017



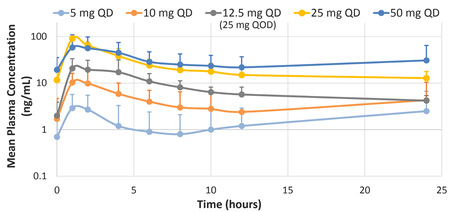
1st Restaging 29 Jan 2018



Patient 084-0015, an 66 years old white female with stage IV ER+, PR+ and HER2- breast cancer with PTEN mutation, who has received 8 prior anti-cancer systemic regimens including hormonal and chemotherapies showed 32.5% tumor size reduction in CT scans after 7.6 weeks on study treatment. The patient's treatment with ARQ 751 is ongoing awaiting confirmation CT scan.

Preliminary Pharmacokinetics (PK)

Day 22 ARQ 751 Mean Plasma Concentration-Time Profiles



Day 22 ARQ 751 Mean Plasma PK Parameters

Dose (mg QD)	n	T_{max} (h)	C_{max} (ng/mL)	AUC_{last}
5	2	13	5	52
10	3	1	14	71
12.5*	3	1	23	199
25	3	2	72	515
50	3	2	65	730

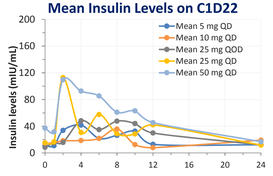
*Actual dose = 25 mg QOD

Preliminary PK data showed:

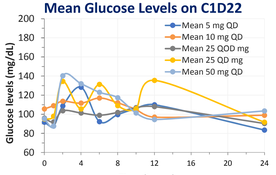
- In general, increases of ARQ 751 mean exposure were greater than dose proportional as the dose was increased from 5 to 50 mg QD.

Pharmacodynamics (PD)

Mean Insulin Levels on C1D22



Mean Glucose Levels on C1D22



Mean glucose and insulin levels generally correlate with ARQ 751 plasma concentration. As the ARQ 751 plasma exposure increases, insulin and glucose levels also increase and generally are proportionate with dose indicating ARQ 751 is achieving *in vivo* PD at dose levels of 25 and 50 mg QD.

Responses

	N=18
Overall Response Rate, N (%)	**1 (5.6%)**
Complete Response (CR)	0
Partial Response (PR)	1 (5.6%)*
Stable Disease (SD)	5 (27.8%)
Progressive Disease (PD)	9 (50.0%)
Not evaluable	3 (16.7%)**

* The patient's treatment with ARQ 751 is ongoing awaiting confirmation CT scan
** No post-treatment restaging data available for response assessment

Treatment Outcome by Patient: PR and SD

Pt ID	Tumor Type	Mutation	Dose Level	No. of prior therapies	Best response (confirmed)	Duration on Tx (weeks)
0015	Breast	PTEN mutation	25 mg QD	8	PR*	17+
0010	Breast	PI3K mutation (PIK3CA:c.3140A)	25 mg QOD	9	SD	26**
0011	Head and Neck	PTEN Null	20 mg QD	3	SD	16
0013	Breast	PTEN Mutation	25 mg QD	8	SD	16**
0014	Endometrial	AKT1 (49G>Ap.E17K)	25 mg QD	3	SD	23+
0018	Endometrial	PI3K mutation (E545D)	50 mg QD	4	SD	11+

* The patient's treatment with ARQ 751 is ongoing awaiting confirmation CT scan
**Patient 0010 had PD at 26 weeks but continues for ongoing benefit at 53+ weeks; patient 0013 had PD at 16 weeks but continues for ongoing benefit at 24 weeks.

CONCLUSIONS

- No DLTs or ≥ Grade 3 ARQ 751-related TEAEs have been observed at doses up to 50 mg QD
- Increases of ARQ 751 plasma exposure were generally greater than dose proportional
- Increased glucose/insulin levels correlate with increased drug plasma concentration and indicate ARQ 751 is achieving target knockdown
- Preliminary anti-tumor activities were observed
- Dose escalation is ongoing