An Open-Label, Phase 1/2 Study of Miransertib (ARQ 092), an Oral pan-AKT Inhibitor, in Patients with PIK3CA-Related Overgrowth Spectrum (PROS): Preliminary Results

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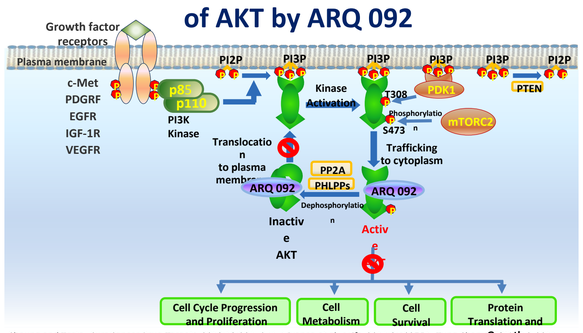
BACKGROUND

Dysregulation of the PI3K/AKT signaling pathway has been implicated in a number of human cancers and overgrowth syndromes, including PROS. In contrast to cancer, characterized by multiple genetic aberrations, in PROS a single activating mutation in *PIK3CA* has been identified and shown to be associated with overgrowth.[1,2] At a National Institutes of Health (NIH) workshop in September 2013, the umbrella term "PIK3CA-Related Overgrowth Spectrum (PROS)" was agreed upon to include clinical entities associated with somatic *PIK3CA* mutations.[2] The prevalence is approximately 1 per 1,000,000 live births for most PROS clinical syndromes.[3]

Overgrowth syndromes are characterized by congenital or early childhood onset with rapid asymmetric overgrowth of different body parts (skeletal deformities, CNS overgrowth or dysplasia, benign and malignant tumors, vascular malformations, etc.) resulting in severe malformations, overall poor quality of life and a lack of disease-specific therapy.[2,5-7]

ARQ 092 is a novel, oral, allosteric, selective pan-AKT inhibitor that potently inhibits AKT1, 2 and 3 isoforms. Biochemical and cellular studies showed that ARQ 092 inhibited AKT activity through binding to its active and inactive forms.[8] In PROS-patient derived cells, ARQ 092 demonstrated higher antiproliferative activity with lower cytotoxicity compared to other PI3K inhibitors.[9]

A Distinct Mechanism of Inhibition of AKT by ARQ 092



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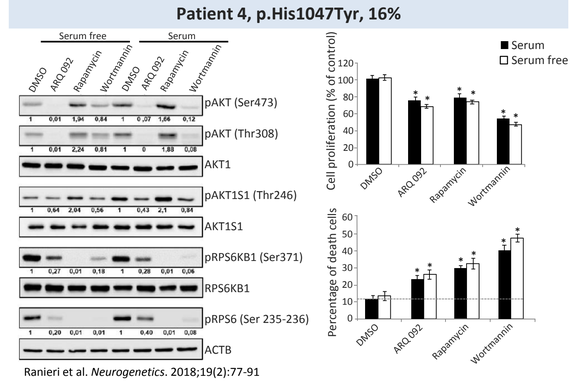
Inhibition of AKT in PROS Patient-Derived Cells with Different PIK3CA Mutations



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Effect of ARQ 092 on AKT signal pathway, proliferation and cell death in fibroblasts derived from patients #3 (A) and #4 (B) with MCAP were assessed in comparison to rapamycin (mTOR inhibitor) and wortmannin (PI3K inhibitor). ARQ 092 potently inhibited cell proliferation, accompanied with decrease in activity of AKT and its downstream targets. ARQ 092 induced less cell death than wortmannin but comparable to rapamycin, suggesting that ARQ 092 is less toxic than wortmannin.

METHODS

Study Design

As of September 10, 2018, 12 patients with PROS were enrolled in the Phase 1/2, open-label study of ARQ 092 (NCT03094832); 8 of these patients have been on treatment for ≥ 6 months.

Study objectives: evaluate dosing schedule, safety, PK profile, and preliminary efficacy of ARQ 092

Assessments: physical examinations, Karnofsky/Lansky performance status, laboratory tests, imaging evaluations, pain and quality of life

Safety analyses: all patients who have received at least one dose of ARQ 092

Preliminary efficacy analyses: descriptive statistics on patients who received at least 6 cycles of ARQ 092 and have had at least one post-baseline imaging disease assessment

Cycle: a 28-day period

Intra-patient dose escalation: allowed after 3 or 6 cycles of continuous daily treatment

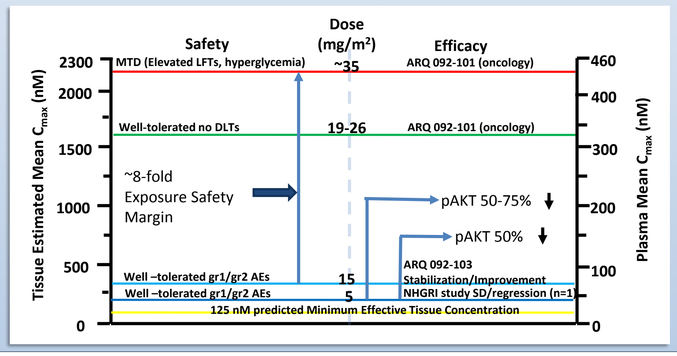
Pharmacokinetics and Dose Justification

- The effective treatment will be a long-term therapy that should cause inhibition of the activated PI3K pathway and the growth of cells harboring the PIK3CA mutation without the inhibition of growth of normal, unaffected cells.
- At the 15 mg/m^2 dose level, the level of p-AKT inhibition is estimated to be between 50% and 75%, indicating target engagement. Should patients not show any signs of clinical benefit at the 15 mg/m^2 dose, but have tolerated treatment well, the dose may be increased to 25 mg/m^2
- Based on the preliminary PK and safety data, the highest safe dose level was determined to be 25 mg/m^2. In Dose escalation oncology study, the MTD for ARQ 092 as a single-agent therapy was determined to be 60 mg QD which is equivalent to 35 mg/m^2 (average BSA 1.7 m^2)

Key Eligibility Criteria

- Patients ≥2 years of age with poor prognosis, significant morbidity, and/or progressive disease
- Clinical diagnosis of PROS or PS with documented somatic PIK3CA or AKT1 mutations
- Availability of archival tissue and/or agreement to undergo paired tumor biopsy
- Evaluable or measurable disease (at least one overgrowth lesion that can be accurately measured in size by imaging and/or linear or circumference measure)
- Adequate bone marrow, cardiovascular, hepatic, and renal function; diabetes well-controlled by oral hypoglycemic agents
- No major surgery, radiotherapy, or immunotherapy within 4 weeks of first ARQ 092 dose
- No history of intolerance of or severe toxicity attributed to AKT inhibitors (e.g., uprosertib, afuresertib, ipatasertib)
- No experimental systemic therapy for purpose of treating PROS or PS (e.g., sirolimus, everolimus, high dose steroids) within 2 weeks of first ARQ 092 dose
- No concurrent serious co-morbidities that could limit full participation and compliance (e.g., ongoing or active infection, known human immunodeficiency virus [HIV] infection, malabsorption syndrome, or psychiatric illness, substance abuse and or social situation

Prediction of Efficacy/Safety in Relation to ARQ 092 Exposure



RESULTS

Patient Baseline Characteristics and Treatment Response

ID	Diagnosis	*PIK3CA* mutation (% mosaicism)/ tissue	Sex	DOB (year)	Year of Diagnosis	Prior PIK3CA/ AKT/mTOR Inhibitors	Miransertib duration (mos)	Study Treatment Status and Dose Level	Disease Manifestations at Baseline	Response to Treatment
087-0001	PROS	c.3140 A>G; p.His1047Arg* lipomatous lesion	M	2005	2005	no	18	On treatment since May 2017; dose increased from 15 to 25 and to 35 mg/m^2 after 3, 6 cycles	Multiple surgeries for recurrent overgrowth (facial overgrowth, macroglossia, tracheostomy) | severe neurocognitive delay | epilepsy | pain	Decrease in pain and seizure severity and frequency | Lansky PS improved from 30 to 50 | No new lesions or increase in lesion size
087-0002	PROS	c.3140 A>G; p.His1047Arg (57.1%)/lipomatous lesion	F	2010	2011	no	13	On treatment since Oct 2017; dose increased from 15 to 25 mg/m^2 after 3 cycles	Multiple surgeries for recurrent overgrowth | overgrowth of left lower limb | abdominal wall mass | pain	Decrease in pain | Lansky PS improved from 80 to 90 | QOL improvement | No new lesions or in lesion size
087-0003	CLOVES	c.3140 A>G; p.His1047Arg (16.1%)/skin	F	2014	2015	rapamycin	9	On treatment since Feb 2018; dose increased from 15 to 25 mg/m^2 after 3 cycles	Hexadactyly of the right foot | left hip dysplasia | multiple skin angiomas | pain	Decrease in pain | Lansky PS improved from 70 to 90 | No new lesions or increase in lesion size
087-0004	CLOVES	c.3140 A>G; p.His1047Arg (46.5%)/skin	M	2014	2015	sirolimus	8	On treatment since Feb 2018; dose increased from 15 to 25 mg/m^2 after 3 cycles	Multiple surgeries for recurrent overgrowth (bilateral inguinal hernias, lipomatous lesions) | multiple subcutaneous lesions | pain	New subcutaneous lesions were noted after 1 cycle of treatment | Currently disease is stable | Lansky PS improved from 70 to 90
089-0001	CLOVES	c.3140 A>G; p.His1047Arg*	F	2014	2015	sirolimus	8	On treatment since Mar 2018; dose increased from 15 to 25 mg/m^2 after 3 cycles	Lipomatous and lymphatic lesions |status post right foot amputated with Grade 2 lymphedema |constipation Grade 2	Lansky PS improved from 80 to 100 | Constipation Grade 1, investigator's note "uses less medication for constipation" | Urinary symptoms improved, prosthetic fitting better I No new lesions or increase in lesion size
087-0005	CLOVES	c.3140 A>G; p.His1047Arg (15.9%)/skin	F	2014	2015	no	7	On treatment since Mar 2018; dose increased from 15 to 25 mg/m^2 after 3 cycles	Overgrowth lesions in right thigh and foot | limited mobility	No change in Lansky PS: 90 | No new lesions or increase in lesion size
052-0001	FAO	c.3140 A>G; p.His1047Leu (17%)/lipomatous lesion	M	2012	2015	sirolimus	7	On treatment since Mar 2018; dose increased from 15 to 25 mg/m^2 after 3 cycles	Overgrowth lesions on trunk | multiple surgeries for recurrent overgrowth (inguinal hernias and lipomatous lesions) | pain	No change in Lansky PS: 100 | No new lesions or increase in lesion size
089-0002	CLOVES	c.3140 A>G; p.H1047R (54%)/skin	M	2015	2015	sirolimus	7	On treatment since Mar 2018; dose increased from 15 to 25 mg/m^2 after 3 cycles	Dysphagia Grade 3, G-tube placement (CTCAE: "…severely altered eating/swallowing; tube feeding") | multiple surgeries for recurrent overgrowth in both feet | constipation Grade | pain	Eating by mouth | Decrease in pain | Constipation improved | Lansky PS improved from 90 to 100

PROS - PIK3CA-related overgrowth spectrum; CLOVES - Congenital Lipomatous Overgrowth, Vascular Malformations, Epidermal Nevi, Scoliosis/Skeletal and Spinal; FAO - Fibroadipose hyperplasia or Overgrowth; CLOVES and FAO are syndromes included in PROS; PS – Performance Scale
* % mosaicism and/or tissue were not reported;

Adverse Events Summary

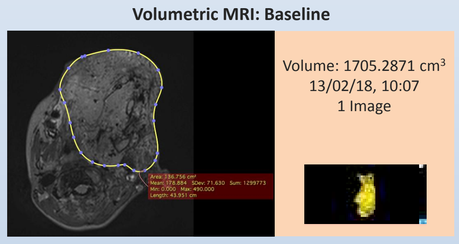
	All Grades N=8 (n%)	Grade 3-4 N=8 (n%)
Number of pts with at least one AEs	7 (87.5)	0
Number of pts with miransertib-related AEs	1 (12.5%)	0
Number of pts with SAE	0	0
Number of pts with treatment interruption due to AEs*	4 (50.0%)	0
Treatment-emergent AEs Observed in ≥2 patients by System Organ Class and Preferred Term		
Gastrointestinal disorders		
Abdominal pain	3 (37.5%)	0
General disorders and administration site conditions		
Pyrexia	4 (50.0%)	0
Infections and infestations		
Rhinitis	2 (25.0%)	0
Respiratory, thoracic and mediastinal disorders		
Cough	2 (25.0%)	0
Skin and subcutaneous tissue disorders		
Skin irritation	2 (25.0%)	0
Miransertib-related AEs by System Organ Class and Preferred Term		
Gastrointestinal disorders		
Stomatitis	1 (12.5%)	0
Investigations		
Neutrophil count decreased	1 (12.5%)	0

*The following AEs required treatment interruption: pyrexia (grade 2); upper respiratory infection (grade 2); influenza (grade 2); oropharyngeal pain (grade 2); aphthous ulcer (grade 1); rash maculopapular (grade 1). All events recovered/resolved, didn't reappear after the drug was restarted and none of the events were treatment-related. Note: No patients have discontinued due to any AEs and no deaths have been reported.

Patient 087-0001

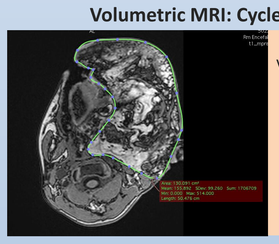
- A measurable reduction in volume of the occipital lesion.
- Standardized CT or MRI scans were not implemented in phase 1.
- Standardized volumetric MRI will be collected and reviewed centrally in phase 2 .

Volumetric MRI: Baseline



Volume: 1705.2871 cm^3
13/02/18, 10:07
1 Image

Volumetric MRI: Cycle 16 Day 1

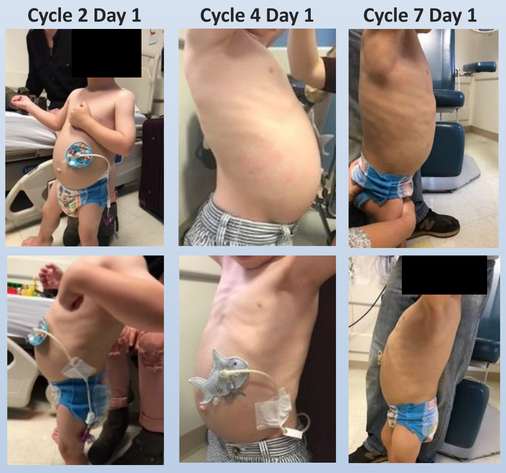


Volume: 1238.5752 cm^3
26/07/18, 14:33
1 Image

Patient 089-0002

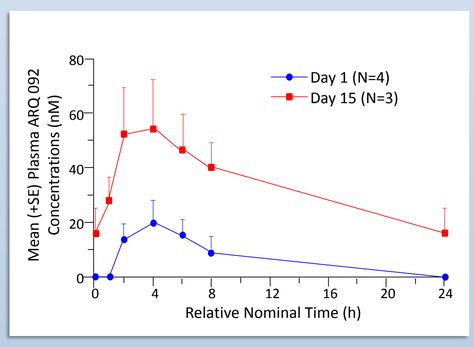
- Eating by mouth!
- Greatly increased interest in food and is now willing and eager to try new foods.
- Abdomen has decreased in appearance and less tense on exam.
- At Cycle 4, mother reported that milk of magnesium is no longer required to manage constipation.
- No abdominal pain or urinary issues

Cycle 2 Day 1 | Cycle 4 Day 1 | Cycle 7 Day 1



Mean Plasma Concentration-Time Profiles and PK Parameters (15 mg/m^2 QD)

Preliminary ARQ 092 PK data are available for four subjects in Study ARQ 092-103 following one cycle of dosing. Mean C_{max} of ARQ 092 was 26.5 nM on Day 1 and 57.3 nM on Day 15. AUC_{last} of ARQ 092 was 128 and 740 on Days 1 and 15,respectively. ARQ 092 accumulates with accumulation ratios of 3.5 and 2.4 based on AUC_{all} and C_{max}, respectively.



Mean (CV%)	ARQ 092 15 mg/m^2 QD	
	Day 1 (N=4)	Day 15 (N=3)
AUC_{last} (h*nM)	128 (48.6)	740 (72.6)
AUC_{all} (h*nM)	231 (62.0)	806 (54.1)
C_{max} (nM)	26.5 (42.1)	57.3 (54.1)
T_{max} (h)[a]	4.00 [4.00, 4.00]	4.00 [2.00, 4.00]
C_{last} (nM)	17.9 (25.4)	24.3 (27.8)
T_{last} (h)[a]	8.00 [6.00, 8.00]	24.0 [8.00, 24.0]
C_{avg} (nM)	NC	42.7 (29.6)[b]
R(AUC_{all})	NC	3.46 (7.3)[b]
R(C_{max})	NC	2.40 (9.5)[b]

NC= Not calculated; [a]Median [Min, Max]; [b]N=2

CONCLUSIONS

- **The study is on-going; in phase 1, ARQ 092 has demonstrated manageable toxicity profile with an encouraging clinical response (assessed by physical examinations, performance status and pain scale) in PROS patients. Retrospective, radiographic assessment, including volumetric MRI, is pending.**
- **The recommended dose has been defined as 15 mg/m^2 with a potential dose escalation to 25 mg/m^2 QD after 3 or 6 treatment cycles.**
- **In phase 2, efficacy will be assessed by prospectively identified radiographic and clinical parameters at 6 or 12 cycles of treatment.**

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