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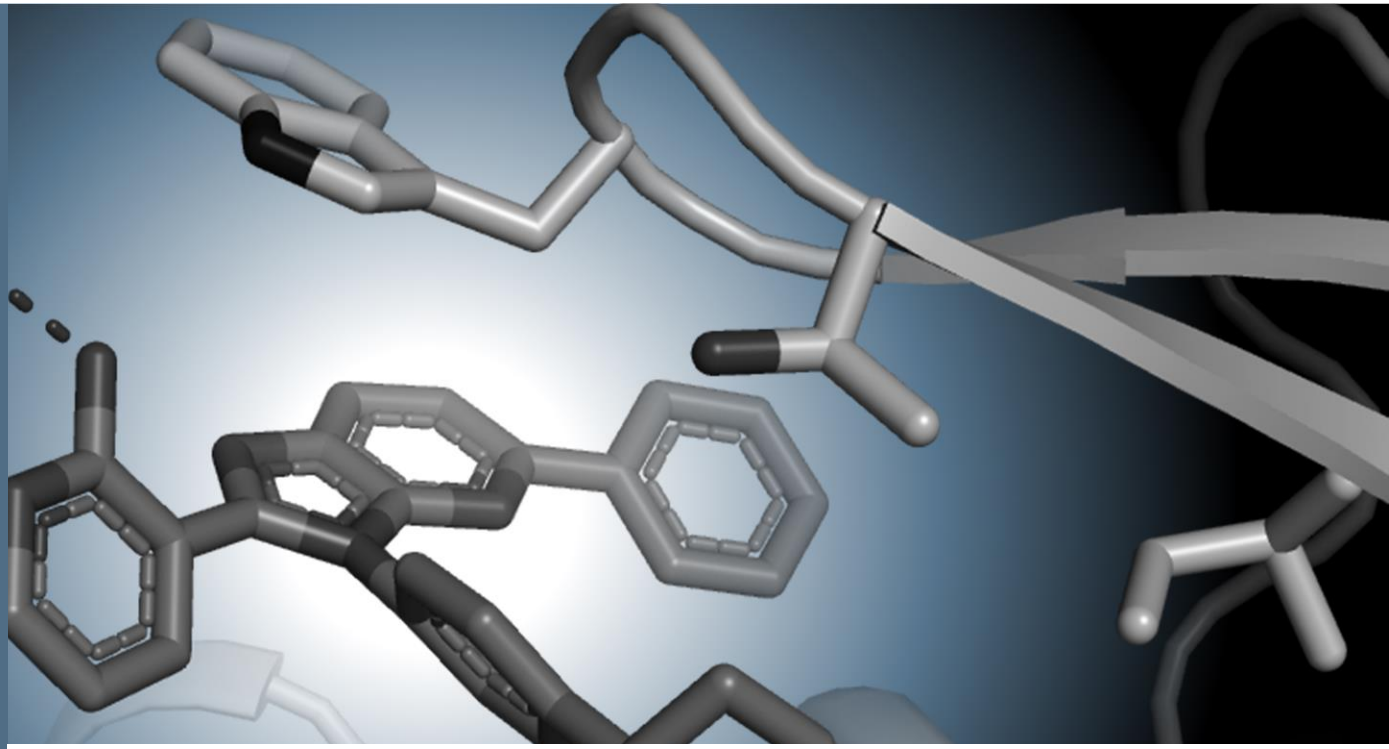
MOSAIC

Miransertib in Overgrowth Syndromes in Adults and Children



An open-label, phase 1/2 study of miransertib (ARQ 092), an oral pan-AKT inhibitor, in patients with PIK3CA-related Overgrowth Spectrum (PROS) and Proteus Syndrome (PS): study design and preliminary results

(NCT03094832)

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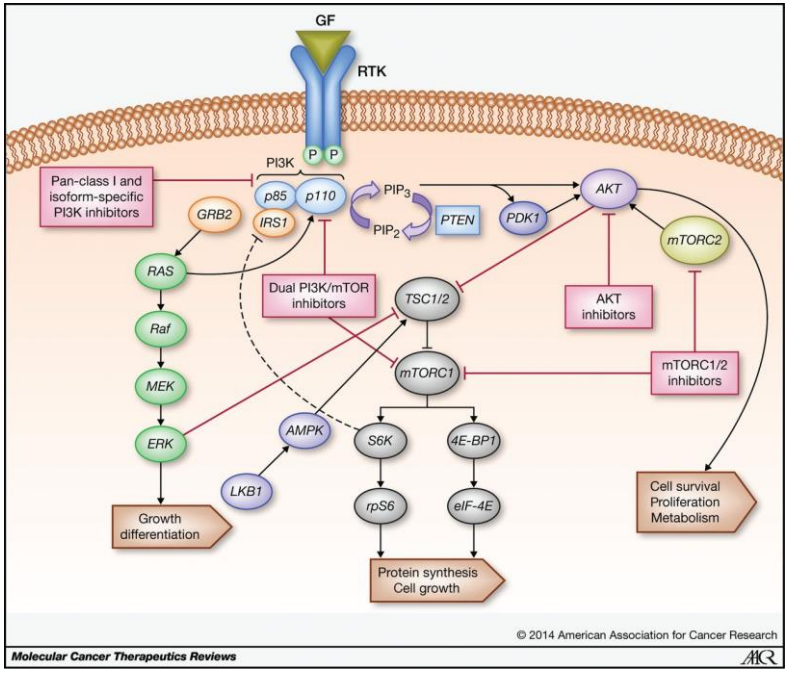
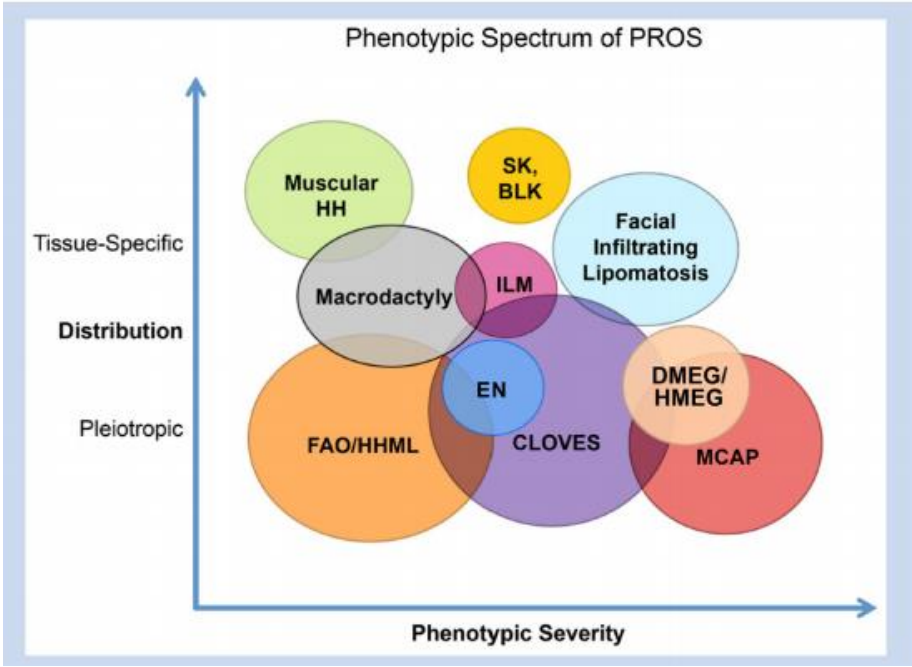
Disclosures:

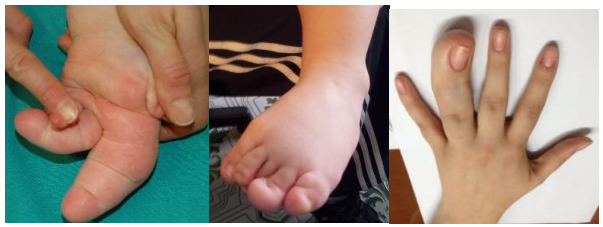
No conflict of interest

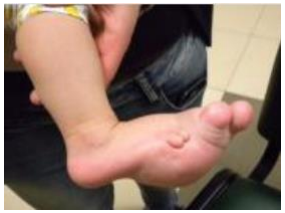
Mosaic Overgrowth Syndromes Due to PI3K/AKT Mutations

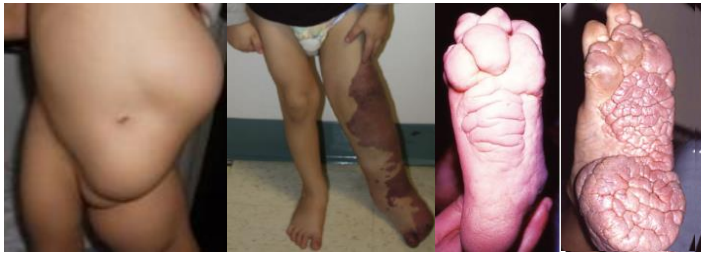




Mild **Moderate** **Severe**

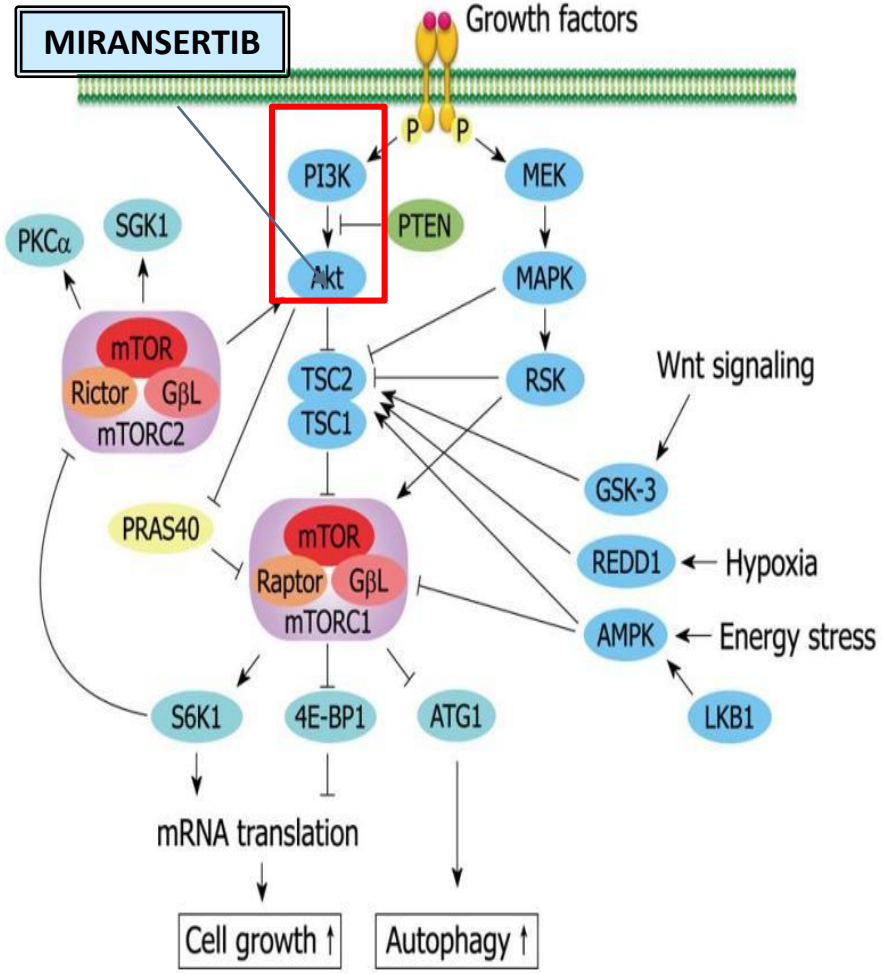






Keppler Noreuil et al., 2015

Miransertib



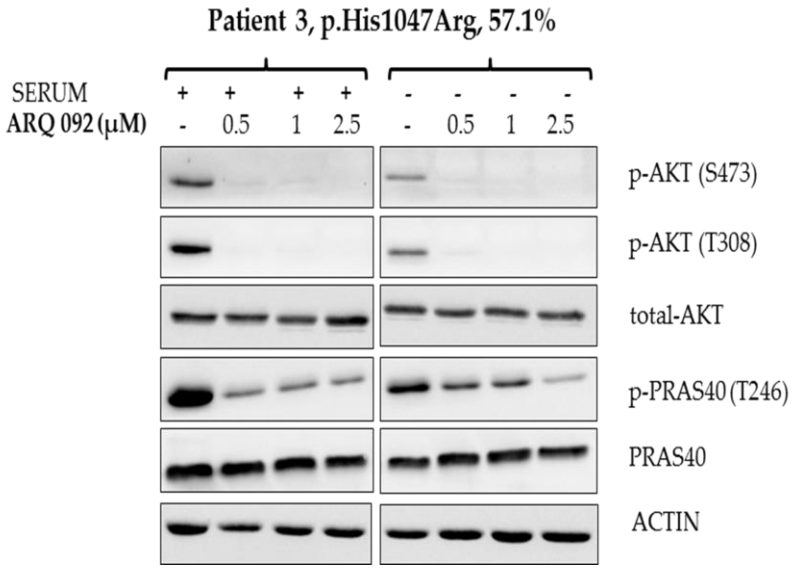
- Novel, oral, allosteric, pan-AKT inhibitor that potently inhibits all AKT isoforms
- Binds to the inactive form of AKT and prevents its membrane localization and activation
- Binds membrane associated active form of AKT, causing its direct inhibition
- In fibroblasts derived from patients with PROS and PS with *PIK3CA* or *AKT1* (E17K) mutations, **inhibition of cell proliferation and AKT phosphorylation** were shown
- Has been administered to 155 adult cancer pts and 32 pts with overgrowth disorders

Itamochi H. World J Biol Chem 2010

PI3K/ATK Pathway Inhibition by Miransertib

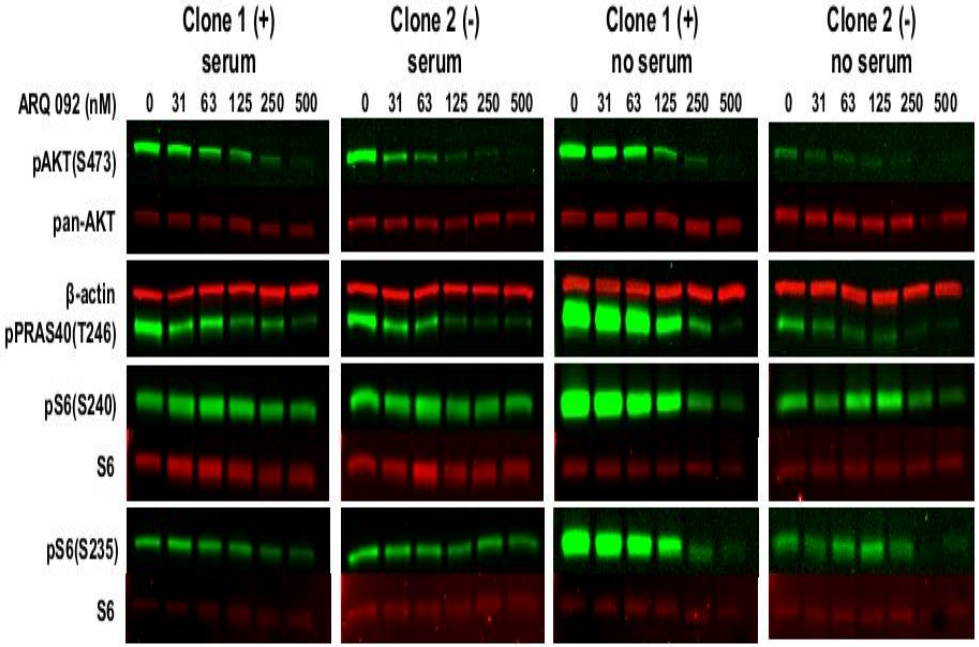
In PROS and PS patient-derived cells: **miransertib decreased pAKT and pPRAS40 in cells** (primarily fibroblasts) in a **dose-dependent manner**

PROS



Ranieri et al., Neurogenetics, 2018

PS



Lindhurst et al., Sci Rep 2015

The MOSAIC Study

- ARQ 092-103 (**miransertib**): a **phase 1/2 study** in patients with PIK3CA-related Overgrowth Spectrum (**PROS**) and Proteus Syndrome (**PS**)
- International, multi-center, open-label, non-randomized 2-part study

  - **Part A:** dose and signal-finding part of the study
  - **Part B:** registrational part of the study

- **Part A**: the 1st patient was dosed 30 May 2017. As of 15 May 2019, a total of 17 PROS and PS patients with *PIK3CA* or *AKT1* mutations have been enrolled and treated. **Enrollment closed**
- **Part B**: undergoing regulatory authorities/IRB/EC reviews and approvals (65 patients to be enrolled)

Part A: Study Objectives and Endpoints

- To assess **safety, tolerability** of miransertib
  - by the frequency, duration, and severity of adverse events (AEs)
- To determine **PK profile** of miransertib (C_{max}, T_{max}, and AUC)
- To determine **recommended dose** of miransertib
- To evaluate **preliminary evidence of clinical activity** of miransertib assessed as:
  - change from baseline in lesion(s) size and/or volume as evaluated by imaging examination (e.g., MRI, CT, US)
  - change in clinical function tests, performance scales, pain and QoL questionnaires from baseline

(Note: all efficacy assessments were done by investigators in accordance with their institutional guidelines and standard of care)

Part A: Key Eligibility Criteria

- Male or female patients (**≥ 2 yrs** or older) with clinical diagnosis of PROS or PS with **documented somatic *PIK3CA* or *AKT1* mutation**
- Have **poor prognosis, significant morbidity, and/or progressive disease** (e.g., worsening of the disease/increase in number or size of the overgrowth lesions in the last 12 months)
- Have **measurable disease** (at least one overgrowth lesion that can be accurately measured in size by imaging and/or linear or circumference measure)
- Have **adequate bone marrow, cardiovascular, hepatic, and renal function**
- Prior use of systemic therapy, including PIK3CA, mTOR or AKTi was allowed

Part A: Demographics

- Patient Population (**N=17**)
- Mean age: **8.2 years** (SD 9.8)
- Sex: male 8 (47%)/ female 9 (53%)
- Race: all White

Type of patient	N° of patients enrolled
Children ≥2- <6 yrs	9
Children ≥6- <12 yrs	4
Young adults ≥12-<18 yrs	2
Adults ≥18 yrs	2

	PIK3CA H1047R	*PIK3CA G106V*	*PIK3CA H1047L*	*PIK3CA C378Y*	*PIK3CA G118D*	*PIK3CA Q546R*	*PIK3CA D350G*	*PIK3CA E542K*	*PIK3CA C420R*	*AKT1 E17K*
CLOVES	6 pts	1 pt	_	_	_	_	_	_	_	_
KTS				1 pt	1 pt	1 pt	1 pt	1 pt		
PROS	2 pts	_	_	_	_	_	_	_	1 pt	_
FAO	_	_	1 pt	_	_	_	_	_	_	_
PS	_	_	_	_	_	_	_	_	_	1 pt

- Median time on treatment: 54 wks (7 to 91 wks)
- Number of patients with prior surgeries: 15 (88%)/17
- Prior systemic therapies (sirolimus): 5 (29%)/17

Part A: Recommended Doses and Pharmacokinetics

- Recommended dose
  - Recommended **initial dose is 15 mg/m^2**
  - Maximum dose **increase to 25 mg/m^2**

- Preliminary PK data
  - Miransertib showed a relatively long half-life of ~49 hrs
  - T_{max} of 4 hrs
  - Mean steady-state C_{max} 56.5 nM at 15 mg/m^2 and 150 nM at 25 mg/m^2

Part A Results: Safety (N=17)

Most common AEs (≥3 pts)	N° of pt (%)	Grade 1/2
Pyrexia	14 (82%)	13 (76%)*
Vomiting	9 (53%)	9 (53%)
Cough	7 (41%)	7 (41%)
Abdominal pain	5 (29%)	5 (29%)
Diarrhea	5 (29%)	5 (29%)
Constipation	4 (24%)	4 (24%)
Pharyngitis	3 (18%)	3 (18%)
Rhinitis	3 (18%)	3 (18%)
Upper respiratory infect.	3 (18%)	3 (18%)
Neutropenia	3 (18%)	3 (18%)
Gastroenteritis	3 (18%)	3 (18%)
Pain in extremity	3 (18%)	3 (18%)
Headache	3 (18%)	3 (18%)
Maculopapular rash	3 (18%)	3 (18%)

Related AEs	N° of pt (%)	Grade 1/2
Diarrhea	1 (6%)	1 (6%)
Stomatitis	1 (6%)	1 (6%)
Vomiting	1 (6%)	1 (6%)
Anemia	1 (6%)	1 (6%)
Lymphocytopenia	1 (6%)	1 (6%)
Neutropenia	1 (6%)	1 (6%)
Thrombocytopenia	1 (6%)	1 (6%)
WBC decrease	1 (6%)	1 (6%)
Hypercholesterolemia	1 (6%)	1 (6%)
Hyperinsulinemia	1 (6%)	1 (6%)

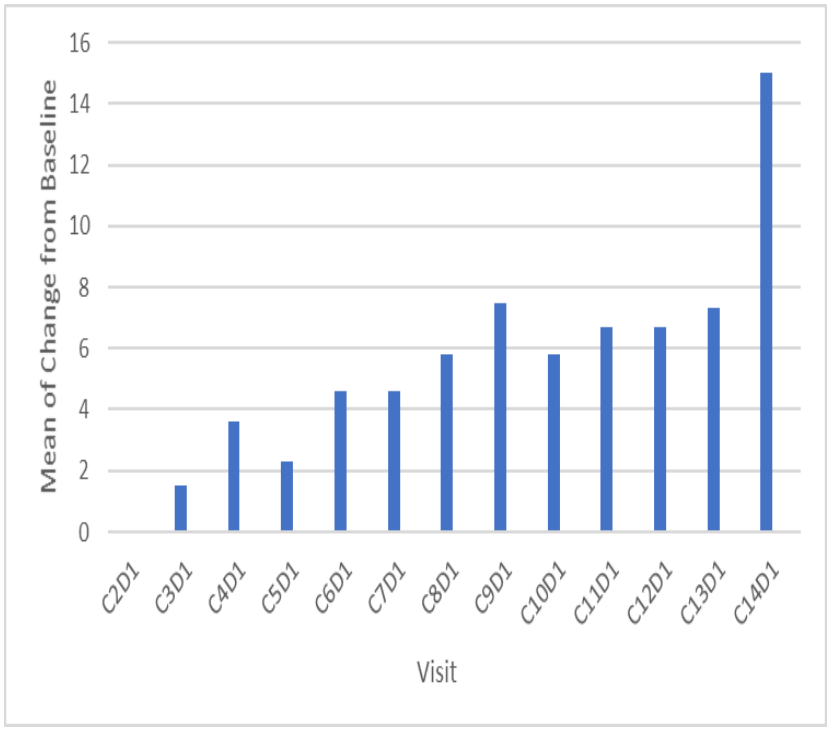
- **17 (100%) pts had at least one AE**
- **5 (29%) pts had at least one drug-related AE, all Gr 1 or 2**
- **15 pts ongoing: 2 pts discontinued (non drug-related Gr 5 “suspected dehydration” & Gr 1 drug-related thrombocytopenia)**
- **2 non-related AEs were assessed as Gr 3 (*pyrexia & cellulitis) & 1 non-related AE was assessed as Gr 5**

Part A: Exploratory Evaluation of Efficacy

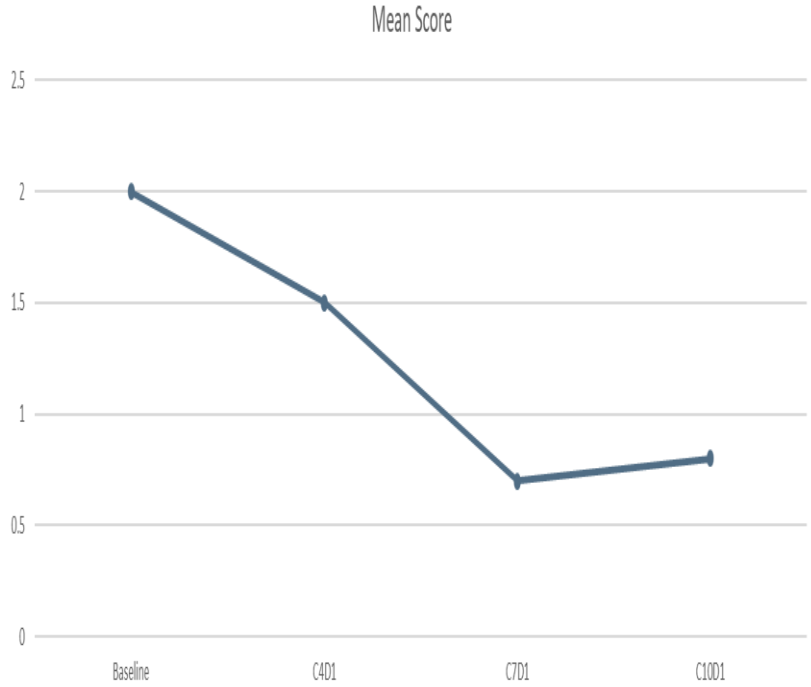
- Physical examination
- Karnofsky/Lansky Performance Scale
- Imaging examination (MRI, CT, US, photography)
- Linear and/or circumference measurement of lesions
- Pain assessment: FLACC scale, PedsQL™ Pediatric Pain Questionnaire and the short-form McGill Pain Questionnaire
- The PedsQL™ questionnaire used to assess quality of life
- AEs were evaluated for severity using NCI CTCAE version 4.03

Part A: Functional Activity and Pain

Karnofsky/Lansky Performance Status (n=17)

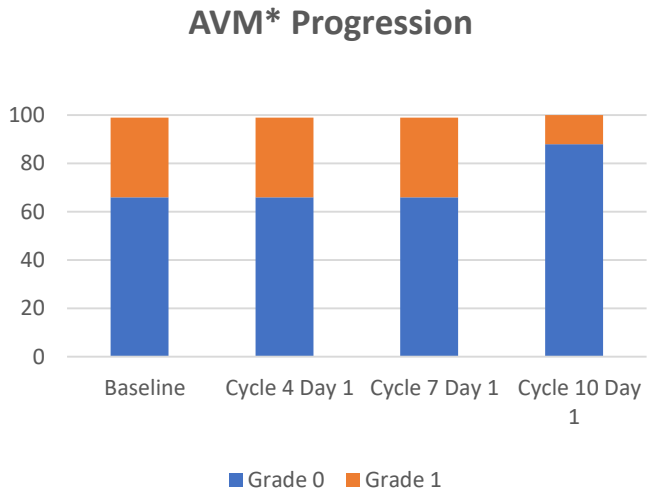


FLACC Pain Scale* (2 – 4 years old) (N=7)

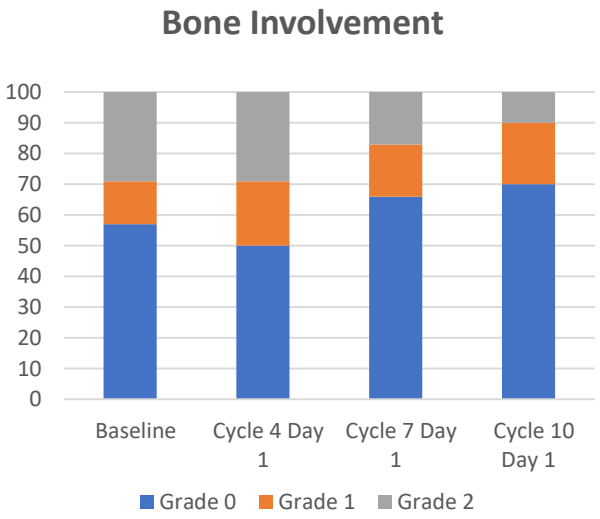


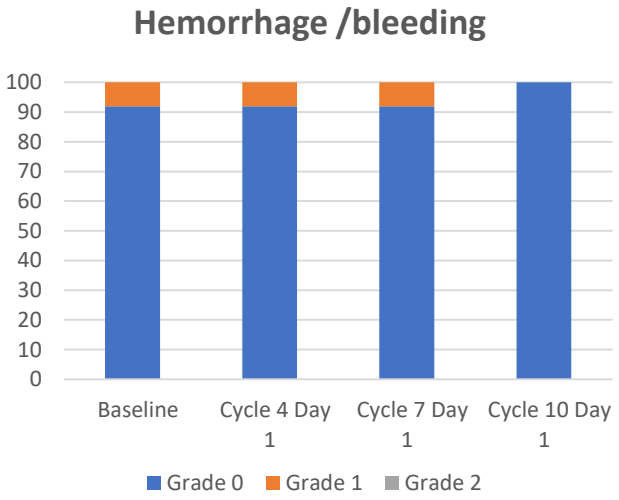
*depending on age, different pain assessment scales were used; FLACC represents the most utilized scale in Part A

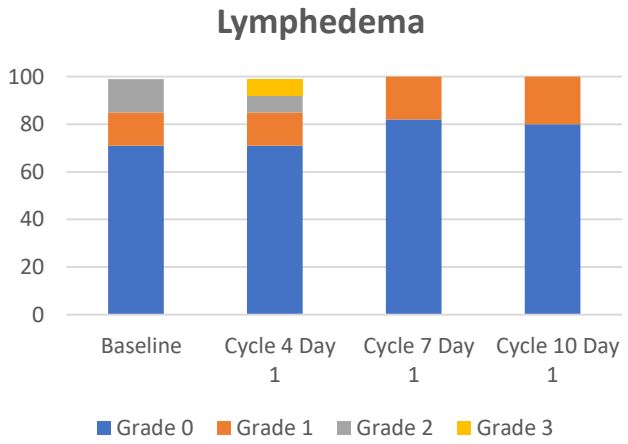
Part A: Selected Clinical Function Assessment

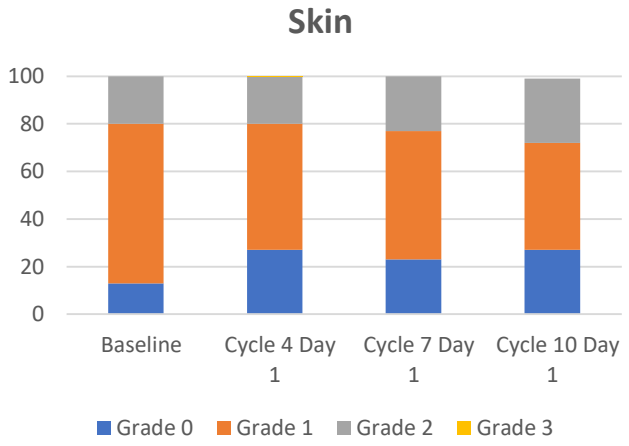


*arteriovenous malformation









Part A: Summary of Preliminary Efficacy Results

- Radiologic (MRI) response to treatment (as assessed by investigators)
  - Stable disease > 1 yr: 9 patients
  - Stable disease < 1 yr: 3 patients (ongoing)
  - Reduction in lesions by 15 %: 1 patient
- Decrease in pain: 11 patients
- Improved walking: 2 patients
- Reduction in lesion sizes by clinical assessments: 2 patients
- Decrease in nevi pigmentation and lip angioma: 1 patient
- Epilepsy is controlled, no changes to anti-seizure medications for > 1 year: 1 patient
- Normalized Hb, no more blood transfusions: 1 patient
- Started eating by mouth: 1 patient

MOSAIC Study Part A: Conclusions

- Miransertib showed **manageable safety profile** with mostly grade 1/2 adverse events
- Recommended dose has been defined as **15** mg/m^2 with subsequent dose increase to **25** mg/m^2
- Miransertib demonstrated **preliminary evidence of clinical activity** with overall improvement in performance status, pain questionnaires, physical function evaluation
- Majority of patients showed durable **stable disease by imaging** without further progression of the disease

Challenges

- Exceedingly rare diseases
- Heterogeneity of the disease presentation
- Lack of practice guidelines/standard of care and/or validated disease-specific instruments of disease response assessment

MOSAIC Study Part B: Open to Enrollment in 3Q 2019

Part B: total of 65 patients

- Cohort 1: 20 PROS patients, whose primary lesion is measurable by vol MRI and evaluated by central lab
- Cohort 2: 10 Proteus subjects, evaluated by central photography of CCTN lesional area
- Cohort 3: All (~25) PROS and PS subjects who are not eligible for Cohorts 1 and 2
- Cohort 4: 10 PROS and PS subjects previously treated with ARQ 092 or currently receiving ARQ 092 under Compassionate Use/Expanded Access

Study primary objective

To demonstrate the efficacy of miransertib in patients with PROS and PS as assessed by **standardized efficacy assessments**:

- change in lesion size (imaging evaluated by blinded, independent central lab)
- pain score and patients reported outcomes (Wong-Baker Faces Pain Rating Scale)
- physical functioning by PROMIS physical functioning instruments
- duration of response
- long term safety and tolerability

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

Thank you for attention.

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