Miransertib in Overgrowth Syndromes in Adults and Children

(NCT03094832)

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

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Disclosures:

No conflict of interest
Mosaic Overgrowth Syndromes Due to PI3K/AKT Mutations

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

**Ranieri et al., Neurogenetics, 2018**

**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 ($C_{\text{max}}$, $T_{\text{max}}$, 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

- 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

<table>
<thead>
<tr>
<th>Type of patient</th>
<th>N° of patients enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children ≥2-&lt;6 yrs</td>
<td>9</td>
</tr>
<tr>
<td>Children ≥6-&lt;12 yrs</td>
<td>4</td>
</tr>
<tr>
<td>Young adults ≥12-&lt;18 yrs</td>
<td>2</td>
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<tr>
<td>Adults ≥18 yrs</td>
<td>2</td>
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</tbody>
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<table>
<thead>
<tr>
<th>PIK3CA H1047R</th>
<th>PIK3CA G106V</th>
<th>PIK3CA H1047L</th>
<th>PIK3CA C378Y</th>
<th>PIK3CA G118D</th>
<th>PIK3CA Q546R</th>
<th>PIK3CA D350G</th>
<th>PIK3CA E542K</th>
<th>PIK3CA C420R</th>
<th>AKT1 E17K</th>
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</thead>
<tbody>
<tr>
<td>CLOVES</td>
<td>6 pts</td>
<td>1 pt</td>
<td>_</td>
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<td>KTS</td>
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<td>1 pt</td>
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<tr>
<td>PROS</td>
<td>2 pts</td>
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<td>FAO</td>
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<td>PS</td>
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<td>1 pt</td>
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Part A: Recommended Doses and Pharmacokinetics

- **Recommended dose**
  - Recommended *initial dose is 15 mg/m²*
  - Maximum dose *increase to 25 mg/m²*

- **Preliminary PK data**
  - Miransertib showed a relatively long half-life of ~49 hrs
  - $T_{\text{max}}$ of 4 hrs
  - Mean steady-state $C_{\text{max}}$ 56.5 nM at 15 mg/m² and 150 nM at 25 mg/m²
### Part A Results: Safety (N=17)

#### Most common AEs (≥3 pts)

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

#### Related AEs

<table>
<thead>
<tr>
<th>AEs</th>
<th>N° of pt (%)</th>
<th>Grade 1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Lymphocytopenia</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>WBC decrease</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Hyperinsulinemia</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
</tr>
</tbody>
</table>

- 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)

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

**AVM* Progression**

- Baseline: Blue 40, Orange 60
- Cycle 4 Day 1: Blue 50, Orange 50
- Cycle 7 Day 1: Blue 70, Orange 30
- Cycle 10 Day 1: Blue 80, Orange 20

*arteriovenous malformation

**Bone Involvement**

- Baseline: Blue 70, Orange 30
- Cycle 4 Day 1: Blue 80, Orange 20
- Cycle 7 Day 1: Blue 90, Orange 10
- Cycle 10 Day 1: Blue 70, Orange 30

**Hemorrhage /bleeding**

- Baseline: Blue 60, Orange 40
- Cycle 4 Day 1: Blue 70, Orange 30
- Cycle 7 Day 1: Blue 80, Orange 20
- Cycle 10 Day 1: Blue 90, Orange 10

**Lymphedema**

- Baseline: Blue 70, Orange 30
- Cycle 4 Day 1: Blue 80, Orange 20
- Cycle 7 Day 1: Blue 90, Orange 10
- Cycle 10 Day 1: Blue 70, Orange 30

**Skin**

- Baseline: Blue 20, Orange 80
- Cycle 4 Day 1: Blue 30, Orange 70
- Cycle 7 Day 1: Blue 40, Orange 60
- Cycle 10 Day 1: Blue 50, Orange 50
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/m²** with subsequent dose increase to **25 mg/m²**
- 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**

**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

**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
References


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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