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Clinical Benefit of Alpelisib in Pediatric Patients With *PIK3CA*-Related Overgrowth Spectrum (PROS): An EPIK-P1 Analysis

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KEY FINDINGS AND CONCLUSIONS

- In the EPIK-P1 study, clinically meaningful proportion of pediatric patients (30.4%) attained response (i.e. ≥20% reduction in target lesion[s] volume at week 24 as determined by ICRR). Majority of the patients (68.2%) had any reduction in the sum of their target lesion volume and none of the patients had radiologically confirmed disease progression during the study period.
- Treatment with alpelisib allowed to avoid PROS-related surgeries and resulted in improvement of performance status, PROS-related signs and symptoms. In addition to the previously reported lesion volume reduction and well tolerated safety profile, these real-world data provide a meaningful clinical benefit with alpelisib in pediatric patients with PROS.
- A confirmatory trial (EPIK-P2, NCT04589650) is open to recruitment to further evaluate the efficacy, safety and pharmacokinetics of alpelisib in pediatric and adult patients with PROS.

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INTRODUCTION

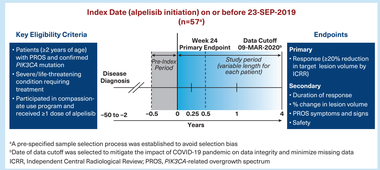
- *PIK3CA*-related overgrowth spectrum (PROS) is an umbrella term encompassing a diverse group of rare, phenotypically variable, disorders stemming from the sporadic somatic gain-of-function mutations in the *PIK3CA* gene[1]
- The prevalence of PROS is difficult to determine due to its broad phenotypic spectrum and frequent misdiagnosis. Estimated prevalence rate is 14 people per million[1-4]
- Alpelisib, an orally bioavailable α-selective PI3K inhibitor, received accelerated approval by US FDA on April 6, 2022, for the treatment of adult and pediatric patients ≥2 years with severe manifestations of PROS who require systemic therapy[5,6]
- Alpelisib targets PROS etiology, studies assessing alpelisib efficacy in patients with PROS demonstrated clinical benefit and a good tolerability profile[7-9]
- Efficacy and safety of alpelisib in adult (≥18 years) and pediatric (2-17 years) patients with PROS was demonstrated in EPIK-P1[10]
  - In the primary endpoint analysis, 37.5% of complete cases (n/N=12/32) showed ≥20% reduction in target lesion volume after 24 weeks or 6 months
  - Improvements at 24 weeks in PROS-related signs/symptoms (top 5: fatigue, vascular malformation, disseminated intravascular coagulation, limb asymmetry, and pain) were also observed in the full study population (N=57)
- Here, we present the results of pre-specifed secondary endpoint i.e. evaluation of clinical benefit in pediatric patients with PROS receiving alpelisib under compassionate use

METHODS

Study Design

- EPIK-P1 (NCT04285723) was a retrospective noninterventional chart review of patients ≥2 years with PROS experiencing severe/life-threatening conditions
  - The retrospective design of EPIK-P1 allowed for a unique approach to rapidly assess the therapeutic potential of a life-changing drug for this rare group of disorders (**Figure 1**)
  - To have been included, patients had to receive at least 1 dose of alpelisib (pediatric, 50 mg/day) on or before September 23, 2019 and had relevant assessments on or before the cut-off date March 09, 2020, which was selected to minimize the impact of COVID-19 on data availability
  - The study period ran from treatment initiation until data cutoff. This time varied from patient to patient, ranging from 3 months to as long as 4 years

Figure 1. EPIK-P1 Study Design

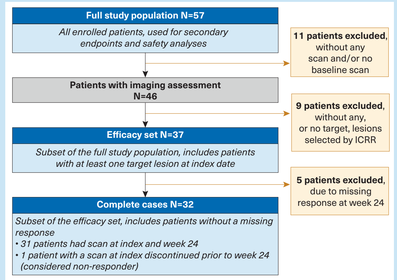


ªA pre-specified sample selection process was established to avoid selection bias
ᵇDate of data cutoff was selected to mitigate the impact of COVID-19 pandemic on data integrity and minimize missing data
ICRR, Independent Central Radiological Review; PROS, *PIK3CA*-related overgrowth spectrum

Endpoint Analyses

- Primary endpoint: proportion of patients with ≥20% reduction from index date in the sum of measurable target lesion(s) volume at week 24, provided that none of the individual target lesions have ≥20% increase from the index date and in the absence of progression of non-target lesions and without new lesions
  - The primary endpoint analysis was descriptive in nature; therefore, no hypothesis testing was conducted. The primary analysis was planned to be conducted on complete cases (**Figure 2**)
  - To increase the robustness and minimize assessment bias, the independent central radiological review (ICRR) assessing lesion volume was blinded to the chronology of patients' scans using prespecified methods and software
  - A 20% volume reduction was selected as it is a commonly accepted threshold in vascular anomalies for the objective assessment of changes of tumor/lesion size and is associated with a clinical benefit in PROS[7]
- Secondary endpoints were assessed with all available data
  - The full study population (**Figure 2**) was used for all efficacy and safety analyses other than the primary endpoint
  - Secondary endpoints include treatment effect on performance status (ECOG, Lansky, Karnofsky), frequency of PROS-related surgeries, changes in signs/symptoms over time, and safety
    - For the ECOG scale, "improvement" is defined as a decrease by ≥1 point and "worsening" is defined as an increase by ≥1 point. For the Lansky and Karnofsky scale, "improvement" is defined as an increase by ≥20 points and worsening is defined as a decrease by ≥20 points
    - Adverse events (AEs) defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occurred during the study period. In some cases, start and/or end dates were partially/completely missing. Pre-specified imputation rules were applied and as a conservative approach, some of the events were assumed to occur during the study period. This has particularly impacted the reporting of the definition of treatment emergent AEs (e.g. vascular malformation and gait disturbance)

Figure 2. Analysis Sets



ICRR, Independent Central Radiological Review

RESULTS

Patient Population and Baseline Characteristics

- Of 57 patients included in efficacy analysis set of EPIK-P1, 39 were pediatric patients with the median age of 10 years (11, aged 2-5 years; 12, aged 6-11 years; and 16, aged 12-17 years)
- The key demographics and disease characteristics at index date (defined as date of alpelisib initiation) are summarized in **Table 1**

Table 1. Patient Population and Baseline Characteristics

Demographic variable/Disease characteristic	Pediatric patients (<18 years), N=39	All patients, N=57
Age (years)		
Median, (min-max)	10.0 (2-17)	14.0 (2-50)
Sex, n (%)		
Female	24 (61.5)	33 (57.9)
Male	15 (38.5)	24 (42.1)
Time since confirmed diagnosis (years)		
Median, (min-max)	10.0 (2-17)	14.0 (2-50)
Onset of disease, n (%)		
Congenital overgrowth	38 (97.4)	53 (93.0)
Early childhood-onset of overgrowth	1 (2.6)	4 (7.0)
Overgrowth type, n (%)		
Mosaic distribution	38 (97.4)	56 (98.2)
Sporadic occurrence	1 (2.6)	1 (1.8)
PROS subtype, n (%)		
CLOVES	27 (69.2)	42 (73.7)
MCAP/MCM	9 (23.1)	9 (15.8)
KTS	2 (5.1)	5 (8.8)
FIL	3 (7.7)	3 (5.3)
Other	2 (5.1)	2 (3.5)

CLOVES, congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal syndrome; FIL, facial infiltrating lipomatosis; KTS, Klippel-Trenaunay syndrome; MCAP/MCM, megalencephaly capillary malformation syndrome; PROS, *PIK3CA*-related overgrowth spectrum; Other includes mixed vascular malformations (lymphatic and venous) and Lipomatosis with pseudoartrogriposis, without vascular anomaly.

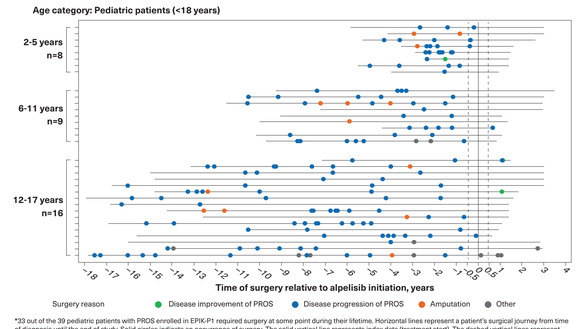
Patient Disposition

- Of the 39 pediatric patients who received treatment, 36 patients (92.3%) continued to receive alpelisib as on cut-off date, while three patients (7.7%) had discontinued study treatment: one patient (2.6%) for each of the following reasons, subject decision, physician decision, and other (reported as no efficacy)
- In pediatric patients, the median duration between the index date and end of study was 17.97 months (range: 4.4 to 41.8 months), corresponding approximately to 78 weeks

PROS-related Surgeries

- Between diagnosis and the pre-index period (24 weeks before index date), 33 of 39 pediatric patients (84.6%) underwent ≥1 surgery with a median number of 4 (range, 1-15), four pediatric patients (10.3%) had at least one surgery during the pre-index period and five pediatric patients (12.8%) underwent a total of nine surgical procedures during the study period of which, two patients had multiple surgical procedures (**Figure 3**)
- Surgeries were reported in all age groups (n/N; 8/11, 2-5 years; 9/12, 6-11 years; 16/16, 12-17 years)
- In the first 24 weeks of alpelisib treatment, no pediatric patients required surgery due to disease progression, one patient required surgery for another reason (reported as debulking)

Figure 3. Incidence of PROS-related Completed Surgeries from Diagnosis to End of Study by Age*

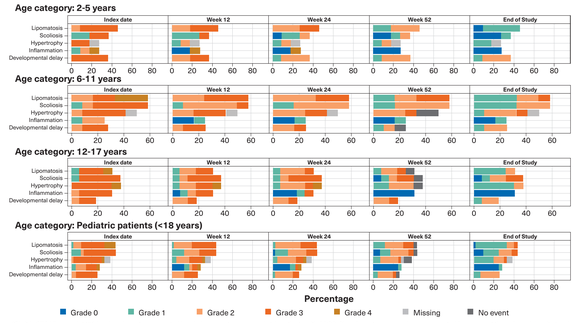


*33 out of the 39 pediatric patients with PROS enrolled in EPIK-P1 required surgery at some point during their lifetime. Horizontal lines represent a patient's surgical journey from time of diagnosis until the end of study. Solid circles indicate an occurrence of surgery. The solid vertical line represents index date (treatment start). The dashed vertical lines represent +/– 24 weeks from index date encompassing the pre-index period and time of primary endpoint assessment.

Changes in PROS Signs and Symptoms

- Lipomatosis, scoliosis, hypertrophy, inflammation, and developmental delays were reported in ≥20% of pediatric patients at index date (**Figure 4**)

Figure 4. Shift in CTCAE Grade from Index Date for PROS-related Signs and Symptoms by Age*



*Shift in CTCAE grade (v4.03) for signs/symptoms reported herein by age category in pediatric patients with PROS. Signs/symptoms are ordered by reported frequency at time of alpelisib initiation in all pediatric patients. Bar colors indicate severity of PROS-related sign/symptoms at different time points. An event is defined as resolved (Grade 0) if there is no subsequent event. "Missing" refers to no CTCAE grade available. "No event" indicates a patient did not reach that time point of the study. End of study refers to the full study period and reports the last available time point for each patient.

- Improvement in these signs/symptoms was seen as early as 12 weeks
- Improvement in performance status score (ECOG, Lansky, Karnofsky) at 24 weeks was seen in (24.2%) pediatric patients (n/N; 3/9, 2-5 years; 2/9, 6-11 years; 3/15, 12-17 years)

Safety

- Pediatric patients received a median (range) dose of 50.0 mg (50.0-250.0) per day
- Most of the pediatric patients started alpelisib at 50 mg, except one patient in the age group of 6 to 11 years (100 mg) and three patients in the age group of 12 to 17 years (150 mg in two patients and 250 mg in one patient)
- The majority of patients in the pediatric population (31 patients, 79.5%) experienced at least one adverse event (AE) and treatment-related AEs were experienced by 9 (23.1%) patients (**Table 2**)
  - Most common AEs of any grade were diarrhea (n=5, 12.8%), vascular malformation (n=4, 10.3%), stomatitis (n=3, 7.7%), aphthous ulcers (n=3, 7.7%), inflammation (n=3, 7.7%), hypoglycemia (n=3, 7.7%), hyperglycemia (n=2, 5.1%), disseminated intravascular coagulation (n=2, 5.1%) and gait disturbance (n=2, 5.1%)
  - Grade 3 or 4 AE were cellulitis, adrenal insufficiency, dyspnea and wound infection (n=1, 2.6% each)
  - Most common treatment-related AEs were aphthous ulcer, stomatitis (n=3, 7.7% each), and hyperglycemia (n=2, 5.1%)
  - No AE led to treatment discontinuation. Two patients (5.1%) experienced dose interruptions due to AEs
  - Most common serious adverse events (SAEs) in pediatric patients were gait disturbances (n=2, 5.1%) and vascular malformations (n=2, 5.1%). None of the SAEs reported among pediatric patients were suspected to be treatment-related
- No deaths were reported during the study

Table 2. Overview of Adverse Events by Preferred Term (any grade ≥5% or reported at least by one patient as grade ≥3 in pediatric population)

Category	Pediatric patients (<18 years), N=39		All patients, N=57	
	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Overall Adverse events (AEs)	31 (79.5)	4 (10.3)	47 (82.5)	13 (22.8)
Diarrhea	5 (12.8)	0	9 (15.8)	0
Vascular malformation	4 (10.3)	0	4 (7.0)	0
Stomatitis	3 (7.7)	0	3 (5.3)	0
Aphthous ulcer	3 (7.7)	0	6 (10.5)	0
Inflammation	3 (7.7)	0	5 (8.8)	1 (1.8)
Hypoglycemia	3 (7.7)	0	3 (5.3)	0
Hyperglycemia	2 (5.1)	0	7 (12.3)	0
Disseminated intravascular coagulation	2 (5.1)	0	5 (8.8)	1 (1.8)
Gait disturbance	2 (5.1)	0	3 (5.3)	0
Cellulitis	1 (2.6)	1 (2.6)	3 (5.3)	2 (3.5)
Adrenal insufficiency	1 (2.6)	1 (2.6)	1 (1.8)	1 (1.8)
Dyspnea	1 (2.6)	1 (2.6)	1 (1.8)	1 (1.8)
Wound infection	1 (2.6)	1 (2.6)	1 (1.8)	1 (1.8)
Overall Treatment-related AEs	9 (23.1)	0	22 (38.6)	1 (1.8)
Stomatitis	3 (7.7)	0	3 (5.3)	0
Aphthous ulcer	3 (7.7)	0	6 (10.5)	0
Hyperglycemia	2 (5.1)	0	7 (12.3)	0

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