Resource use associated with alpelisib for the treatment of patients with PROS: A modeling approach

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Introduction

Disease

PIK3CA-Related Overgrowth Spectrum (PROS) consists of a group of rare diseases with diverse phenotypes, resulting from a genetic alteration in the PIK3CA gene [1]. With a congenital or early-childhood onset, the estimated prevalence of PROS is about 14 per 1,000,000 persons.

Patients with PROS can suffer disfiguring or function-limiting manifestations [2] and disorders that can be severe and affect numerous aspects of patients' lives (e.g., physical limitations to activities of daily living, social stigma, mental health, pain, limited mobility, repeated surgeries).

For many patients, overgrowth is sizable and highly visible. As there is no cure or approved pharmacological treatment for the underlying disease, current treatment relies on best supportive care and debulking surgeries and/or amputations, or occlusive vascular procedures, but recurrence is common.

Alpelisib

Alpelisib (VIJOICE®), an α-specific class I phosphatidylinositol3kinase inhibitor, received accelerated approval from the US Food and Drug Administration in April 2022 for the "treatment of adult and pediatric patients 2 years of age and older with severe manifestations of PROS who require systemic therapy" (VIJOICE US PI 2022). This approval was based on the outcomes of EPIK-P1 (NCT04285723), a single-arm clinical study in patients who were treated as part of an expanded access program for compassionate use which enrolled patients across seven sites in 5 countries (France, Spain, US, Ireland and Australia).[3]

In Europe, alpelisib was granted an orphan drug designation status for the treatment of patients with PROS (EMA 2021) and has been made available to patients through a compassionate access scheme. As of October 2023, it is not approved by EMA.

Objectives

To model and assess the impact on the introduction of alpelisib (i.e., world with alpelisib) compared with current standard of care (SoC, i.e., world without alpelisib) would have on surgery rates for the treatment of adult and pediatric patients, ≥ 2 years of age, with severe manifestations of PROS in France.

Methods

We developed a de novo budget impact model (BIM), from the national French health insurance perspective, with a target population in line with that of alpelisib approved indication for PROS in the US. We modeled surgery use over a cumulative 3-year time horizon and estimated the number of surgeries for PROS, i.e., for disease progression (P), for amputation (A) and for disease improvement (I). Surgery rates per person per year before/after initiation of alpelisib (world without/with alpelisib) were obtained from EPIK-P1 and its extension EPIK-P3. Epidemiology data were obtained from Orphanet and NIH Genetics Home Reference. Half of the estimated population was considered to present with severe manifestations, and more than half (69%) pediatric patients.

EPIK-P1 study

This study was a multi-country site-based retrospective non-interventional medical chart review of patients age ≥2 years who received alpelisib as part of a compassionate use program (i.e., 86% of patients were treated under the ATU (autorisation temporaire d'utilisation) in France and 14% via Managed Access Program (MAP) outside of France) for at least 24 weeks before the cut-off date. Primary objective was to assess efficacy by the proportion of responders (patients with ≥20% reduction from treatment start in the sum of target lesion volume) at Week 24 by independent central review [4].

EPIK-P3 study

This is an interventional Phase II multi center open label study to assess the long-term safety and efficacy of alpelisib, in pediatric and adult participants with PROS. The study enrolled patients aged ≥2 years who participated in EPIK-P1 and who continued to receive treatment with alpelisib after EPIK-P1 cut-off date. [5]. Periods up to 5 years before and up to 5 years after starting treatment with alpelisib (EPIK-P1) were considered OFF-alpelisib and ON-alpelisib periods in the model.

Surgery rates

The rate of surgery per person-time was calculated by dividing the number of surgery events by the observed person-times in the OFF-alpelisib and ON-alpelisib periods, respectively. The 95% CIs were calculated using the Poisson distribution.

Results

Among the 48 patients followed-up in EPIK-P3, 11 patients had no surgeries in the OFF-alpelisib period, and 35 patients had no surgeries in the ON-alpelisib period.

Figure 1: Flow chart of the patients consider for the analysis

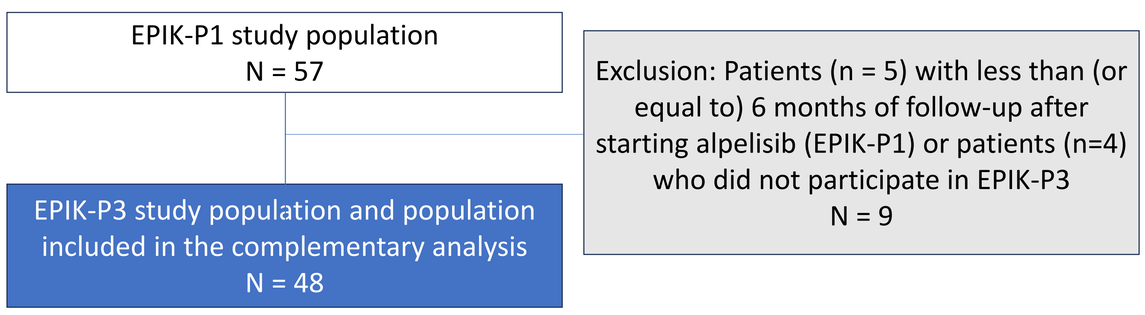
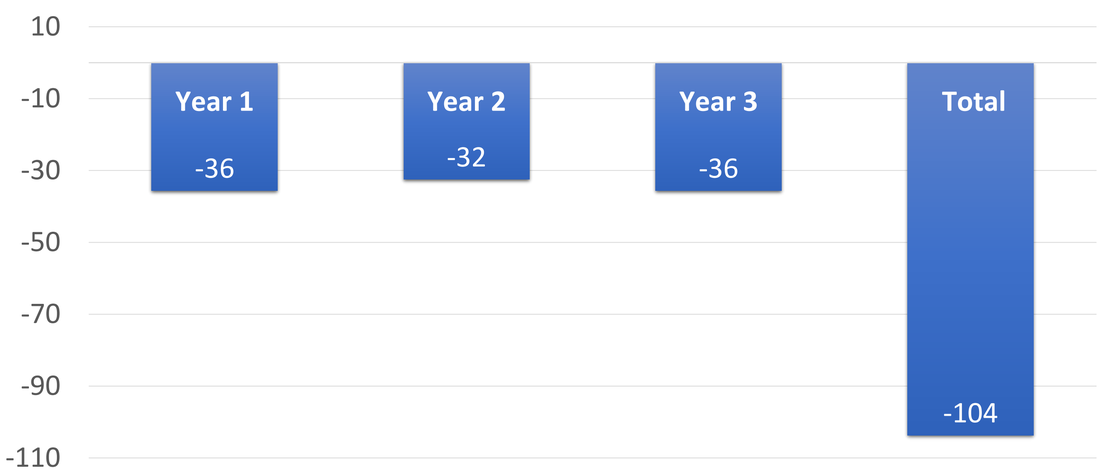


Figure 2: Yearly surgeries avoided per year for 100 patients treated with alpelisib in France

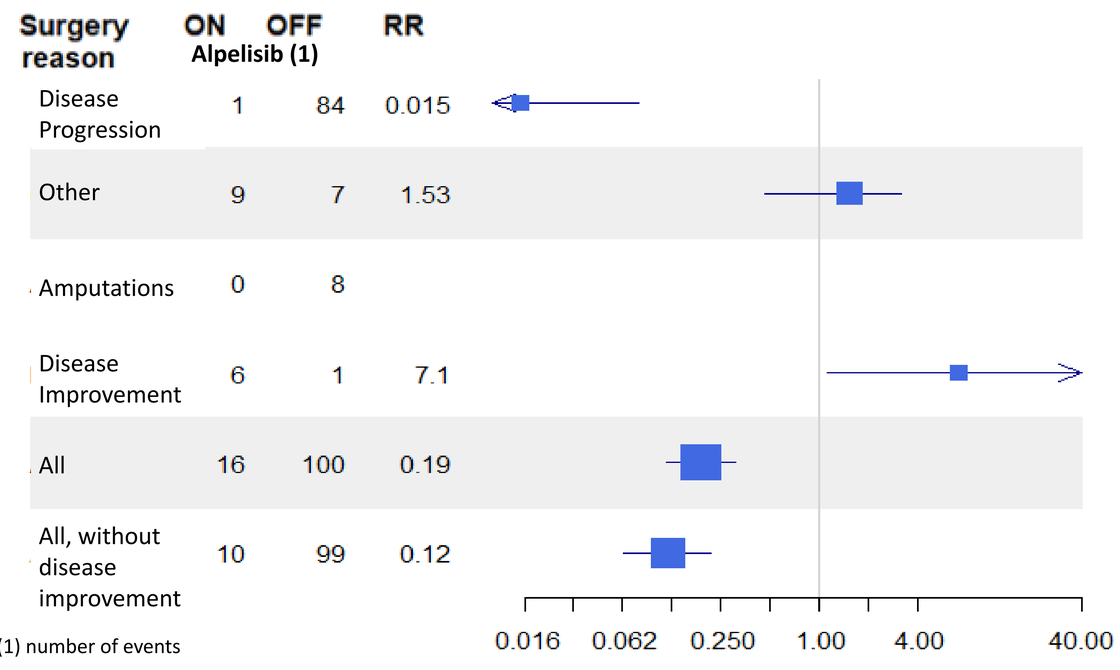


Over a 3-year period, the introduction of alpelisib would be associated with an overall decrease of 104 surgeries for PROS per 100 patients treated with alpelisib.

Table 1: Surgery rates per person years [95 CI%] associated with PROS in the OFF-alpelisib and ON-alpelisib periods

Surgery reason (associated to PROS)	OFF-Alpelisib (5 years maximum)	ON-Alpelisib (5 years maximum)
"Disease progression of PROS"	0.3691 [0.2944 - 0.457]	0.0052 [0.0001 - 0.0291]
"Other"	0.0308 [0.0124 - 0.0634]	0.047 [0.0215 - 0.0891]
"Amputations"	0.0352 [0.0152 - 0.0693]	0
"Disease improvement of PROS"	0.0044 [0.0001 - 0.0245]	0.0313 [0.0115 - 0.0681]
All	**0.4394 [0.3575 - 0.5344]**	**0.0834 [0.0477 - 0.1356]**
All, without disease improvement	0.435 [0.3536 - 0.5296]	0.0522 [0.025 - 0.0959]

Figure 3: Forest plot of the relative risks (RR) by type of surgery and overall



The use of alpelisib would be associated with an 81% significant reduction in the risk of "All Cause" surgeries (RR=0.19), driven by large reduction in risk of surgeries for "Disease Progression" when patients are ON-Alpelisib (RR=0.015), somewhat offset by greater likelihood of surgeries for "Disease Improvement" upon initiation of alpelisib (debulking), with a RR = 7.1. While OFF-alpelisib, patients underwent 84 surgeries for disease progression and 1 surgery while ON-alpelisib.

Conclusion

There remains a significant unmet medical need for a treatment that can address the underlying cause of PROS, reduce the size of the PROS lesions, and provide an improvement in PROS-related signs and symptoms. Results from the study suggest that alpelisib would improve disease management, reducing the need for surgeries related to disease progression. The ongoing randomized placebo-controlled EPIK-P2 [6] study will provide additional information about resource use for patients with PROS.

References

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Author disclosure

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