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Commentary

Belzutifan versus Everolimus in Advanced Kidney Cancer: A Commentary on LITESPARK-005 Trial from ESMO 2023

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Given the upstream location of HIF-2α in the VHL-HIF-VEGF pathway and its role in renal carcinogenesis, HIF-2α has recently become a therapeutic target in renal cell carcinoma (RCC) with drugs such as belzutifan. Belzutifan received FDA approval for patients with VHL-associated RCC based on a phase 2 clinical trial [1]. In the LITESPARK-001 phase 1 dose-escalation study that included 55 patients with previously treated advanced RCC, no dose-limiting toxicities occurred at doses up to 160 mg once daily, and the maximum tolerated dose was not reached [2]. The recommended phase 2 dose for belzutifan from this trial was 120 mg once daily. Subsequently, several clinical trials have been launched using this dose, one of which, LITESPARK-005, was recently presented at ESMO by Albiges et al. [3]. LITESPARK-005 represents a randomized phase-III trial for belzutifan versus the mTOR inhibitor everolimus in patients with previously treated advanced clear cell RCC (ccRCC).

LITESPARK-005 randomized 746 patients between March 10, 2020, and January 19, 2022, where >80% of enrolled patients were treated in the 3rd or 4th line setting, thus representing a heavily pre-treated population. The trial included 80% of patients who had intermediate/poor risk disease, and 70% of patients had undergone a prior nephrectomy. At the landmark 18 months analysis, the trial met its co-primary endpoint: 22.5% of patients remained progression-free with belzutifan, compared to 9% with everolimus (HR: 0.74, 95% CI: 0.63–0.88). However, even though overall survival (OS) was numerically longer for belzutifan compared to everolimus (21 months vs. 18 months); this has not yet met statistical significance, and the final OS analysis remains pending. Among other key secondary endpoints, the objective response rate (ORR) was 22.7% for belzutifan compared to 3.5% for everolimus. The median time to response was similar in both arms at 3.8 vs. 3.7 months; however, the median duration of response was longer with belzutifan (19.5 vs 13.7 months). From a safety and tolerance standpoint, belzutifan seems well tolerated, with lower rates of discontinuation compared to everolimus (∼6% vs. 15%). Anemia and fatigue were the most common adverse events, and there was 1 treatment-related death in the study. The FKSI-DRS and QLQ-C30 GHS/quality of life (QOL) analyses favored belzutifan as well.

The results of this trial are important because this is the first confirmation from a phase-III randomized control trial regarding the activity of belzutifan

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in patients with advanced RCC after progression on multiple standard treatment regimens. However, even though ∼23% of patients responded to belzutifan, about one-third of patients had progressive disease as their best response. Additionally, there are phase-3 data from the TIVO-3 trial where the oral tyrosine kinase inhibitor tivozanib showed a significant improvement in PFS (5·6 months, 95% CI 5·29–7·33) compared with sorafenib (3·9 months,; hazard ratio 0·73, 95% CI 0·56–0·94; $p = 0·016$) in patients who had received 2–3 prior lines of therapy [4]. In this trial, 31% of patients responded to tivozanib, and progressive disease as the best response was seen in about 22% of patients. The choice of therapy between the two agents will ideally require predictive biomarkers and a careful assessment of the adverse effect profile of each drug to choose the ideal candidate.

In addition, examination of the PFS curves from the LITESPARK-5 trial shows crisscrossing of the curves early in the course of the trial, specifically in the first six months, before they eventually separate in favor of the experimental arm. Among the possible explanations for this observation is the presence of a cohort of patients with an unmeasured or yet-to-be-defined molecularly defined phenotype with differential response or benefit from belzutifan or everolimus.

Nevertheless, even though OS benefit is not yet evident, the significant PFS benefit and encouraging duration of response are important practical considerations for belzutifan when it is used in clinical practice. It appears to be reasonably well-tolerated, with an established toxicity profile that includes anemia and hypoxia. QoL outcomes also appear to favor belzutifan, an important consideration in this treatment-refractory cohort of patients with advanced ccRCC. One critique about LITESPARK-005 is the choice of everolimus as the control arm. In clinical practice, everolimus use in this heavily pre-treated setting has been supplanted by other active systemic therapy options. There is also concern that everolimus may have underperformed as a single agent in this trial. The question remains if the results would have been different if a more contemporary control arm was used. It is recognized that the control arm does seem appropriate for the time this trial was designed since drugs such as tivozanib had not yet been approved in this setting. Future strategies to find partnering drugs with belzutifan that will improve efficacy while keeping side effects manageable are warranted.

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AUTHOR CONTRIBUTIONS

SG and PNL contributed to the conception, performance and interpretation of data review for this paper.

CONFLICTS OF INTEREST

PNL is co-Editor-in-Chief and SG is an Editorial Board Member of this journal, but they have not been involved in the peer-review process of this paper, nor had access to any information regarding its peer-review.

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