LITESPARK-024: Randomized Phase 1/2 Study of Belzutifan With or Without Palbociclib for Treatment of Advanced Renal Cell Carcinoma

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Background

- The combination of anti–PD-1/L1 immunotherapy with antiangiogenic agents is a standard-of-care first-line treatment option for patients with advanced renal cell carcinoma (RCC), but many patients develop resistance, and effective second- or subsequent-line options are needed[1-6]
- The hypoxia-inducible factor 2α (HIF-2α) transcription factor is an oncogenic driver in RCC, and the first-in-class HIF-2α inhibitor belzutifan has shown promising antitumor activity in patients with previously treated advanced clear cell RCC (ccRCC)[7]
  - Patients received oral belzutifan 120 mg once daily (QD); the objective response rate (ORR) was 25%, and median progression-free survival (PFS) was 14.5 months
- The cyclin-dependent kinase (CDK) pathway is also altered in RCC, and the CDK 4/6 inhibitor palbociclib inhibited cell growth in RCC cell lines[8,9]
- The effects of CDK 4/6 inhibition were synergistic with HIF-2α inhibition in ccRCC cell lines[10]; therefore, combination belzutifan + palbociclib treatment may be an effective option in patients with advanced ccRCC
- This open-label, multicenter, randomized, phase 1/2 LITESPARK-024 study (NCT05468697) will evaluate belzutifan + palbociclib versus belzutifan alone in patients with advanced ccRCC who have received prior treatment with anti–PD-1/L1 immunotherapy and a vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI) (alone or in combination)

Objectives

Primary

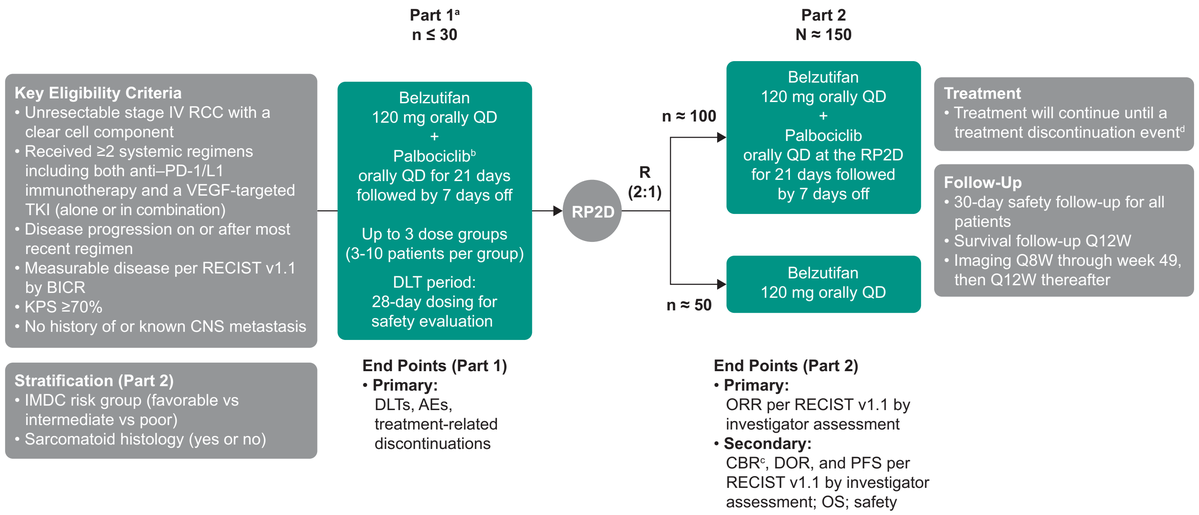
- Part 1: To assess the safety and tolerability and to establish the recommended phase 2 dose (RP2D) of belzutifan + palbociclib
- Part 2: To evaluate ORR per RECIST v1.1 by investigator assessment for belzutifan + palbociclib and belzutifan alone

Secondary

- Part 2: To compare the following for belzutifan + palbociclib and belzutifan alone
  - Clinical benefit rate (CBR) per RECIST v1.1 by investigator assessment
  - Duration of response (DOR) per RECIST v1.1 by investigator assessment
  - PFS per RECIST v1.1 by investigator assessment
  - Overall survival (OS)
  - Safety and tolerability

Methods

Study design



AE, adverse event; BICR, blinded independent central review; CNS, central nervous system; CR, complete response; DLT, dose-limiting toxicity; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; KPS, Karnofsky performance status; PR, partial response; Q8W, every 8 weeks; Q12W, every 12 weeks; R, randomization; SD, stable disease.

[a]Patients who complete part 1 are eligible to participate in part 2.
[b]Part 1 is an ascending dose escalation, starting with palbociclib 75 mg (group 1), increasing to 100 mg (group 2), and then increasing to 125 mg (group 3), depending on DLTs observed.
[c]CR + PR of any duration or SD for ≥6 months.
[d]Confirmed disease progression, pregnancy, start of new anticancer therapy, withdrawal of consent, end of study, or death, whichever occurs first.

Patient eligibility criteria

Key inclusion criteria	Key exclusion criteria
• Age ≥18 years • Histologically confirmed diagnosis of RCC with clear cell component, with or without sarcomatoid features • ≥2 prior systemic regimens for advanced RCC including both an anti–PD-1/L1 immunotherapy and VEGF-targeted TKI (alone or in combination) • Radiographic disease progression on or after the most recent systemic regimen as assessed by the investigator • KPS ≥70% assessed within 10 days before allocation/randomization	• Pulse oximeter reading <92% at rest or requires intermittent or long-term supplemental oxygen • History of or known CNS metastases and/or carcinomatous meningitis • Known additional malignancy that is progressing or has required active treatment within the past 3 years • Clinically significant cardiovascular disease within 6 months before allocation/randomization • Active infection that requires systemic therapy • Received prior treatment with belzutifan or another HIF-2α inhibitor • Received prior treatment with palbociclib or another CDK 4/6 inhibitor • Received any type of small molecule kinase inhibitor ≤2 weeks before allocation/randomization • Received any type of systemic anticancer antibody ≤4 weeks before allocation/randomization

Assessment and follow-up

Assessment	Details
DLTs (part 1)	• DLTs will be assessed by the investigator within 28 days after the first dose is administered
Tumor response (part 2)	• Radiologic evaluation by computed tomography or magnetic resonance imaging will occur at week 9, then Q8W through week 49, and then Q12W thereafter or until confirmed disease progression, pregnancy, start of new anticancer therapy, withdrawal of consent, end of study, or death, whichever occurs first • Bone imaging is required for all patients at baseline
Safety (parts 1 and 2)	• AEs will be monitored during the study and graded in severity per NCI CTCAE v5.0, from time of documented informed consent until 30 days after cessation of study treatment (90 days for serious AEs)

NCI CTCAE v5.0, National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

Analyses

Analyses	Details
Safety (parts 1 and 2)	• In part 1, safety analyses will be performed for all allocated patients who received ≥1 dose of study treatment • In part 2, safety analyses will be performed in the all-patients-as-treated population (all randomly assigned patients who received ≥1 dose of study treatment)
Efficacy (part 2)	• The intention-to-treat population (all randomly assigned patients) will serve as the population for efficacy analyses – ORR and CBR will be assessed by investigator – ORR and its 95% CI will be analyzed using the stratified Miettinen and Nurminen method[11] with strata weighting by sample size – DOR will be evaluated in responders (patients who achieved CR or PR) and will be summarized descriptively using the Kaplan-Meier method – OS and PFS will be estimated using the Kaplan-Meier method, and the magnitude of treatment difference (hazard ratio and 95% CI) between arms will be assessed using a stratified Cox proportional hazard model with the Efron method of tie handling

Status

Sites of enrollment for LITESPARK-024

- Australia
- Israel
- United States
- Additional countries in Europe and Latin America will be added

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Acknowledgments

The authors thank the patients and their families and investigators and site personnel. Palbociclib was provided by Pfizer. Medical writing and/or editorial assistance was provided by Robert Steger, PhD, and Matthew Grzywacz, PhD, of ApotheCom (Yardley, PA, USA). This assistance was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Funding for this research was provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

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Presented at the 2023 Kidney Cancer Research Summit (KCRS); Boston, Massachusetts; July 13-14, 2023