Clinical Trial Protocol

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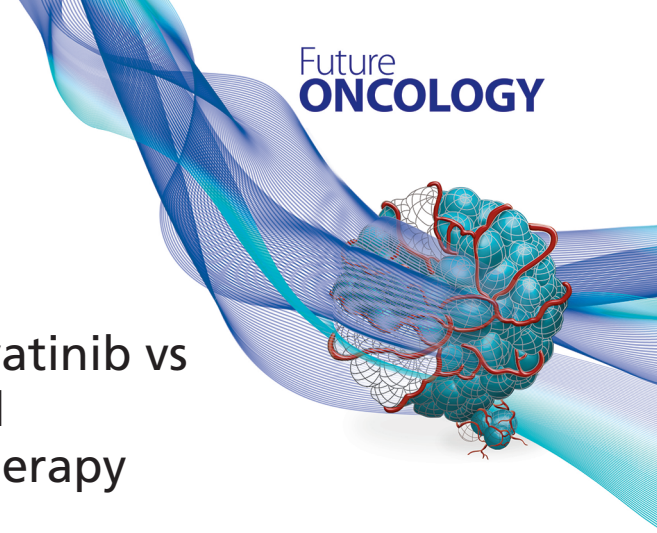

LITESPARK-011:belzutifan plus lenvatinib vs cabozantinib in advanced renal cell carcinoma after anti-PD-1/PD-L1 therapy

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The first-in-class, small molecule HIF-2α inhibitor, belzutifan, has demonstrated promising antitumor activity in previously treated patients with clear cell renal cell carcinoma (RCC). HIF-2α also regulates VEGF expression and is involved in resistance to anti-VEGF therapy. This study describes the rationale and design for a randomized, phase III study evaluating efficacy and safety of belzutifan plus the tyrosine kinase inhibitor (TKI) lenvatinib versus the TKI cabozantinib in patients with advanced RCC progressing after anti-PD-1/PD-L1 therapy in the first- or second-line setting or as adjuvant therapy. Considering the unmet need for effective and tolerable treatment of advanced RCC following immune checkpoint inhibitors, belzutifan plus lenvatinib may have a positive benefit/risk profile.

Clinical Trial Registration: NCT04586231 (ClinicalTrials.gov)

Tweetable abstract: The phase III LITESPARK-011 study will evaluate efficacy and safety of the HIF-2α inhibitor belzutifan plus lenvatinib versus cabozantinib in patients with advanced RCC progressing after anti-PD-1/PD-L1 therapy.

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Keywords: clear cell renal cell carcinoma • HIF-2α inhibitor • immune checkpoint inhibitor • metastatic • PD-1/PD-L1 inhibitor

Renal cell carcinoma (RCC) accounts for approximately 85% of all renal cancers [1], and 2010–2016 US data indicate that about one-third of patients present with regional or distant metastatic disease [2]. Immune checkpoint inhibitors targeted to programmed death 1 (PD-1) or programmed death ligand 1 (PD-L1), administered with cytotoxic T-lymphocyte antigen 4 (CTLA-4) or VEGF-targeted therapies, are widely used first-line treatment for advanced clear cell RCC [1,3,4]. These therapies, evaluated in phase III studies, include nivolumab (PD-1 inhibitor) and ipilimumab (CTLA-4 inhibitor), evaluated in CheckMate 214 [5,6]; avelumab (PD-L1 inhibitor) and axitinib (VEGF inhibitor), evaluated in JAVELIN Renal 101 [7,8]; pembrolizumab (PD-L1 inhibitor) and axitinib, evaluated in KEYNOTE-426 [9,10]; pembrolizumab and lenvatinib (tyrosine kinase inhibitor [TKI]), evaluated in CLEAR/KEYNOTE-581 [11]; and nivolumab and cabozantinib (TKI inhibitor), evaluated in CheckMate 9ER [12]. The primary analyses of these studies demonstrated median progression-free survivals (PFSs) from 11.6 to 23.9 months and objective response rates (ORR) ranging from 42 to 71% [6,7,9,11,12]. Median overall survival (OS) was not reached in these primary analyses [6,7,9,11,12], nor in available extended follow-ups ranging from a median of 19.3 to 32.4 months [5,8,10]. PFS and ORR remained promising [5,8,10].

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No standard-of-care has been established based on randomized and controlled phase III studies for patients with advanced clear cell RCC that has progressed after anti-PD-1/PD-L1-based therapy [1,3,4]. Resistance to VEGF-targeted therapies invariably develops, despite initial responses [13]. Currently, the TKI cabozantinib and the PD-1 inhibitor nivolumab are preferred treatments after first-line combination therapy, and the TKI lenvatinib plus the mammalian target of rapamycin inhibitor everolimus is an alternative option [1,3,4]. Cabozantinib was compared with everolimus in a phase III study (METEOR) that included 658 patients who had progressed after previous TKI therapy [14]. Statistically significant improvements in PFS (7.4 vs 3.9 months), OS (21.4 vs 16.5 months) and ORR (17 vs 3%) were shown for cabozantinib compared with everolimus [14]. In the cabozantinib arm, 71% of participants experienced a grade 3 or 4 adverse event (AE), the most common of which were hypertension (15%), diarrhea (13%), and fatigue (11%) [14]. Nivolumab was compared with everolimus in a phase III study (CheckMate 025) of 821 patients with advanced or metastatic RCC who had progressed on antiangiogenic therapy [15]. Statistically significant improvements in OS (25.0 vs 19.6 months) and ORR (25 vs 5%) were observed for nivolumab compared with everolimus [15]. In the nivolumab arm, 19% of participants experienced a grade 3 or 4 AE, the most common of which were fatigue and anemia (2% each) [15]. In short, the majority of patients (75% or more) do not have an objective response to the current primary recommended therapies after first-line treatment, and there is an urgent unmet need for more efficacious treatment regimens.

LITESPARK-011 study

Herein we describe the rationale and design for the phase III LITESPARK-011 study (NCT04586231), which will evaluate the efficacy and safety of the HIF-2α inhibitor belzutifan (MK-6482) plus the TKI lenvatinib versus cabozantinib alone in patients with advanced clear cell RCC who experienced disease progression on or after anti-PD-1/PD-L1 therapy.

Background & rationale

Approximately 90% of clear cell RCCs result in the loss of function of the Von Hippel-Lindau (VHL) tumor suppressor gene, leading to accumulating HIF-2α and promoting tumor growth [16]. HIF-2α induces genes associated with angiogenesis, invasion, metastasis, resistance to the immune system, and the cell survival mechanism [13]. A phase I, dose-escalation study of the first-in-class oral HIF-2α inhibitor PT2385 in 51 patients with advanced clear cell RCC previously treated with VEGF inhibitor had a manageable safety profile, with 41% of patients experiencing grade 3 or 4 treatment-emergent AEs. The most common grade 3 AEs were anemia (10%), hypoxia (10%) and hypophosphatemia (8%); grade 4 events were lymphocyte count decreased (n = 2) and hypercalcemia (n = 1) and pulmonary embolism (n = 1) [17]. One patient had a complete response (2%), and 6 patients (12%) had a partial response [17]. Plasma erythropoietin levels were decreased at all doses evaluated (100–1800 mg, twice daily) [17]. Although promising, PT2385 had highly variable pharmacokinetics (PK), leaving the potential for underexposure of patients, and thus next-generation inhibitors of HIF-2α were explored [13].

Belzutifan (MK-6482) is an orally available, small molecule inhibitor of HIF-2α that selectively disrupts the heterodimerization of HIF-2α with HIF-1β [13]. Belzutifan was also evaluated in a phase I/II dose-escalation/expansion study LITESPARK-001 (also known as PT2977-101; ClinicalTrials.gov identifier, NCT02974738) [18]. The dose-escalation phase was evaluated in patients with solid tumors (n = 43); the expansion phase was evaluated in previously treated advanced clear cell RCC (n = 52). The maximum tolerated dose was not reached at doses up to 240 mg per day, including 240 mg once daily and 120 mg twice daily. In the dose escalation phase, patients with advanced clear cell RCC received the recommended phase II dose of 120 mg belzutifan orally once daily [18]; this dose choice was supported because exposure to belzutifan did not markedly increase at doses higher than 120 mg once daily [19]. Belzutifan exposure at all dose levels was associated with reductions in erythropoietin [18], a sensitive pharmacodynamic marker of HIF-2α inhibition [20,21]. An RCC cohort (n = 55) consisted of three patients with clear cell RCC in the dose escalation phase treated with belzutifan 120 mg once daily and all 53 patients in the dose expansion phase. In the RCC cohort, the most common grade 3 AEs were anemia (27%) and hypoxia (16%); two patients experienced four grade 4 AEs (sepsis [n = 2], hypercalcemia [n = 1], and respiratory failure [n = 1]), and four patients experienced grade 5 AEs (disease progression, malignant neoplasm progression, acute kidney injury, and cardiac arrest). No grade 4 or 5 AEs were considered related to treatment. These toxicities are expected with treatment using an HIF-2α inhibitor [20–22]; anemia was treated with erythropoiesis-stimulating agent and/or blood transfusion, and hypoxia was managed with supplemental oxygen and treating other concomitant confounding

conditions. The ORR in the RCC cohort was 25% (all partial responses), and median PFS was 14.5 months [18]. Belzutifan demonstrated preliminary antitumor activity in heavily pretreated patients [18], suggesting that HIF-2α inhibition may offer an effective treatment for advanced clear cell RCC.

Lenvatinib inhibits the kinase activities of VEGF receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4) [23,24]. In addition, lenvatinib inhibits FGF receptors FGFR1, 2, 3, and 4; PDGFRα; KIT; and RET [23,24]. This inhibition results in arrest of the neo-vessel assembly and maturation, decreasing vascular permeability of the tumor microenvironment [24]. Lenvatinib is currently approved in combination with everolimus for the treatment of advanced RCC after one antiangiogenic therapy, and in combination with pembrolizumab for the first-line treatment of advanced RCC [23]. Lenvatinib, everolimus, and the combination was evaluated in a phase II, randomized, open-label study of 153 patients with advanced RCC [25]. Per blinded, independent radiologic review, the combination of lenvatinib and everolimus significantly improved median PFS compared with everolimus (12.8 vs 5.6 months) but not lenvatinib (9 months) [26]; ORRs were 35, 0 and 39%, respectively [26]. Participants who received lenvatinib plus everolimus (71%) or lenvatinib alone (79%) reported more grade 3 or 4 AEs compared with everolimus alone (50%); the most common grade 3/4 AEs in recipients of lenvatinib plus everolimus and lenvatinib alone were constipation, diarrhea, proteinuria, hypertension, and fatigue or asthenia [25]. A phase Ib/II study of lenvatinib plus pembrolizumab in 104 participants with advanced RCC who progressed during or after immune checkpoint inhibitor therapy had an ORR of 51%; the most common treatment-related AEs in the entire study were fatigue, diarrhea, proteinuria, hypertension, nausea, dysphonia, stomatitis and arthralgia [27]. Thus, lenvatinib in combination with another targeted therapy appears to increase ORR compared with currently recommended agents [27,28].

Given that HIF-2α activation represents a resistance pathway for anti-VEGF therapy, it is hypothesized that combining belzutifan and lenvatinib will lead to repression of HIF-2α-regulated VEGF production at the level of transcription by belzutifan, and inhibition of VEGF production downstream of HIF-1α by lenvatinib at the growth factor level [29]. An analysis of the phase II study of belzutifan plus cabozantinib in patients with advanced clear cell RCC demonstrated an ORR of 31% with a median PFS of 13.8 months in 52 patients who had ≥1 dose of treatment [30]. For all patients (N = 52), the most common (≥10%) grade 3 treatment-related AEs were hypertension (27%), anemia (15%) and fatigue (12%); two patients experienced grade 3 hypoxia (4%) [30]. No grade 4 or 5 treatment-related AEs were reported [30]. Therefore, the combination of belzutifan plus lenvatinib is an attractive therapeutic intervention for patients with advanced RCC.

Design

This is a phase III, open-label, multicenter, international, randomized, active-controlled study in patients with advanced clear cell RCC. The study will enroll approximately 708 adults with advanced clear cell RCC who experienced disease progression on or after an anti-PD-1/PD-L1 therapy as either first- or second-line treatment for locally advanced/metastatic RCC or as adjuvant treatment with progression on or within 6 months of the last dose. The immediately preceding line of treatment must have been an anti-PD-1/PD-L1 therapy, with no more than two prior systemic regimens permitted. Also, no more than one anti-PD-1/PD-L1 therapy for adjuvant or locally advanced/metastatic clear cell RCC is allowed.

Patients

Eligible patients (Table 1) will be randomly assigned 1:1 to receive either 120 mg oral belzutifan plus 20 mg oral lenvatinib once daily or 60 mg oral cabozantinib once daily; 354 patients will be included in each treatment arm (Figure 1). At randomization, patients will be stratified based on International Metastatic RCC Database Consortium (IMDC) prognostic scores (0 vs 1–2 vs 3–6) [31,32], line of treatment in which anti-PD-1/PD-L1 therapy was given (1 [adjuvant, neoadjuvant/adjuvant, or first-line] vs 2 [second-line]), and geographic region (North America, Western Europe or rest of world). Study treatment will continue until documented disease progression, start of a new anticancer treatment, unacceptable toxicity or patient withdrawal.

Outcomes

The dual primary end points of this study are to evaluate the efficacy of belzutifan plus lenvatinib compared with cabozantinib for the treatment of advanced RCC as assessed by PFS as determined by blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1), and by OS. A meta-analysis of 31 studies (including 10,943 patients) evaluated the relationship between PFS and OS in

Table 1. Patient eligibility criteria.

Key inclusion criteria	Key exclusion criteria
• Age ≥18 years	• CNS metastases and/or carcinomatous meningitis
• Locally advanced or metastatic clear cell RCC (with or without sarcomatoid features)	• Moderate to severe hepatic impairment (Child–Pugh B or C)
• Measurable disease per RECIST v1.1 as assessed by the local site investigator/radiology	• Prior treatment with belzutifan or another HIF-2α inhibitor, lenvatinib, or cabozantinib
• Disease progression on or after an anti-PD-1/PD-L1 therapy as either first- or second-line treatment for locally advanced/metastatic RCC or as neoadjuvant/adjuvant treatment with progression on or within 6 months of the last dose	• Having received any type of small molecule kinase inhibitor ≤2 weeks before randomization
• Has not received >2 prior systemic regimens, including 1 anti-PD-1/PD-L1-containing adjuvant or neoadjuvant/adjuvant regimen with progression on or within 6 months from the last dose of that regimen OR 1 or 2 regimens for locoregional/advanced disease – No more than 1 anti-PD-1/PD-L1 therapy for adjuvant, neoadjuvant/adjuvant, or locally advanced/metastatic clear cell RCC permitted	• Having received any systemic cancer antibody ≤4 weeks before randomization
• KPS score ≥70% assessed within 10 days before randomization	• Active infection necessitating systemic therapy • History of HIV infection • History of hepatitis B virus or active hepatitis C virus infection

KPS: Karnofsky Performance Status Scale; PD-1: Programmed death 1; PD-L1: Programmed death ligand 1; RCC: Renal cell carcinoma. RECIST 1.1: Response Evaluation Criteria in Solid Tumor, version 1.1.

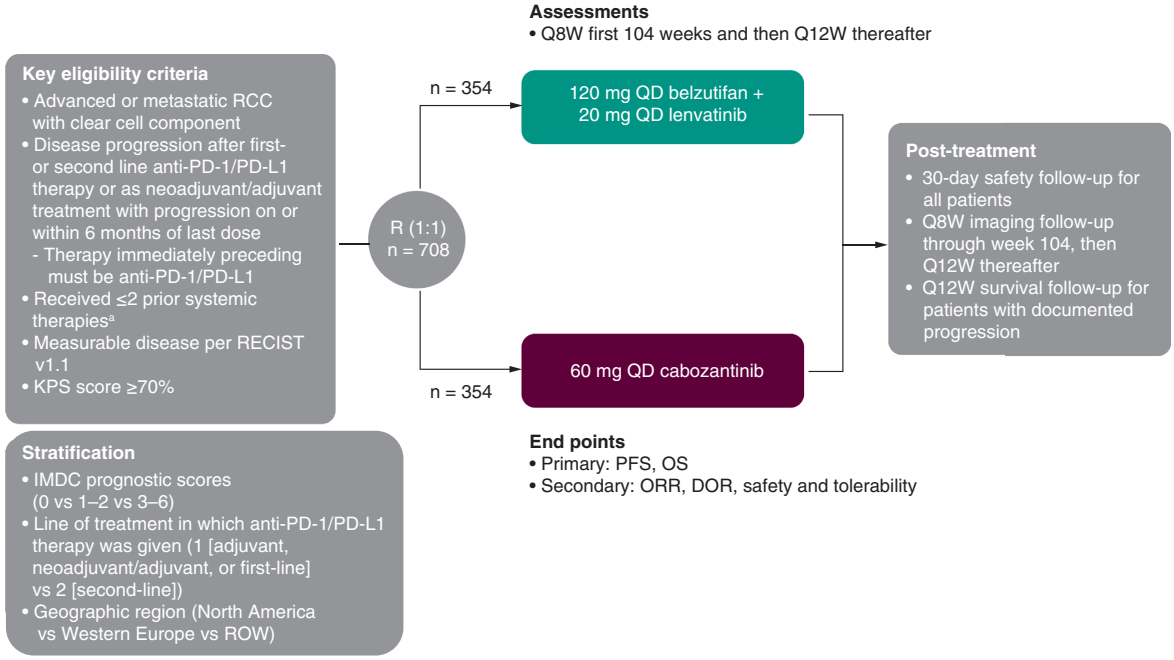

Figure 1. Study design.
[a]Including 1 anti-PD-1/PD-L1-containing adjuvant or neoadjuvant/adjuvant regimens with progression on or within 6 months from the last dose of that regimen OR 1 or 2 regimens for locoregional/advanced disease.
DOR: Duration-of-response; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; KPS: Karnofsky Performance Status Scale; ORR: Objective response rate; OS: Overall survival; PD-1: Programmed death 1; PD-L1: Programmed death ligand 1; PFS: Progression-free survival; Q8W: Every 8 weeks; Q12W: Every 12 weeks; QD: Once daily; R: Randomization; RCC: Renal cell carcinoma; RECIST 1.1: Response Evaluation Criteria in Solid Tumors, version 1.1; ROW: Rest of world.

metastatic RCC and concluded that in RCC, the treatment effects on PFS are strongly associated with treatment effects on OS [33]. To ensure that PFS is rigorously evaluated, PFS will be determined by a BICR that will review all radiographic studies. The BICR will be blinded to study treatment. Safety and tolerability end points include but are not limited to the incidence of, causality, and outcome of AEs/serious AEs and changes in vital signs and laboratory values. AEs will be assessed as defined by Common Terminology Criteria for Adverse Events (CTCAE) v5.0. The open-label study design enables appropriate dose modifications for AEs in both study intervention

treatment groups. Belzutifan, lenvatinib and cabozantinib each have unique safety profiles that may result in the participants experiencing different AEs that could disclose the treatment intervention received if the study were blinded.

Secondary end points include ORR and duration-of-response, as evaluated by RECIST 1.1, and safety and tolerability.

PK and pharmacodynamic end points include analysis of plasma concentrations of belzutifan. The PK of lenvatinib will not be analyzed in this study because a drug–drug interaction effect is not anticipated from belzutifan on lenvatinib PK, and lenvatinib dose modification will be based on observed toxicity. The effect of belzutifan on erythropoietin levels will be assessed using descriptive statistics.

Exploratory end points including health-related quality of life and disease-related symptoms will be investigated among all participants using the Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index-Disease Related Symptoms (FKSI-DRS), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), and EuroQoL EQ-5D-5L questionnaires. Exploratory biomarker analyses include biospecimen (including blood components and tumor material) collection to support analysis of cellular components (e.g., protein, DNA, RNA and metabolites) and other circulating molecules.

Procedures

In the treatment phase, all patients will have weekly visits for the first 3 weeks, then visits will be every 2 weeks through week 9, and then every 4 weeks thereafter. In addition to those visits, approximately the first 15 patients randomly assigned to each arm and treated (30 total) will have a visit at week 4, day 1 for safety assessments. The data from this visit will be reviewed by an external Data Monitoring Committee to provide recommendations on the conduct of the study should significant and/or new safety signals potentially associated with belzutifan plus lenvatinib be identified. These participants will be included in the intention-to-treat population for efficacy analyses.

Radiologic evaluation by computed tomography (CT) or MRI of the abdomen and pelvis with IV contrast (unless medically contraindicated) will occur every 8 weeks for 80 weeks, after which imaging will continue every 12 weeks for patients who remain on the study drug until week 104. If the patient has a positive baseline bone scan at screening, after randomization bone imaging will be performed at week 16 and will continue every 16 weeks through week 80, then every 24 weeks to week 104 until disease progression is verified by BICR. A brain scan (MRI or CT) will be performed during screening for participants with brain metastases to ensure the participant's condition is stable. After randomization, brain imaging will be performed as clinically indicated and to confirm complete response in patients with brain metastases at baseline.

AEs will be monitored during the study and graded in severity per CTCAE, version 5.0. AEs will be reported for 30 days after cessation of study treatment. Serious AEs will be reported for 90 days after cessation of study treatment or for 30 days if the patient begins a new anticancer therapy regimen (whichever is earlier). A post-treatment safety follow-up visit will occur within 30 days after discontinuation of study treatment.

Patient-reported outcomes (PRO) questionnaires will be administered every 2 weeks during treatment up to week 13, when they will shift to every 4 weeks. Every effort will be made to administer PRO surveys on site before dosing and before other assessments and procedures. The electronic PRO assessments will continue for up to 2 years from randomization (week 105) or until safety follow-up after end-of-treatment.

Blood for PK analyses will be drawn from participants randomly assigned to the belzutifan plus lenvatinib arm at weeks 1, 2, 3 and 5. Blood draws for pharmacodynamic analyses and experimental biomarker analyses will be drawn before dose at weeks 1, 3 and 5 and at time of discontinuation; serum biomarker analyses in patients randomly allocated to belzutifan plus lenvatinib will also have postdose collections at 1, 2 and 4 h following week 1 dose.

Statistics

This study is ongoing and the planned sample size is approximately 708 patients. The efficacy analyses will be performed in the intention-to-treat population (all randomly assigned patients). The primary end points of PFS and OS will be evaluated using a stratified log-rank test and will be controlled for family wise type 1 error. The hazard ratio will be estimated using a stratified Cox proportional hazard model, and survival probabilities over time will be estimated within each treatment group using the Kaplan–Meier method. The secondary end point of ORR will be analyzed using the stratified Miettinen and Nurminen method [34], with strata weighted by sample size.

The safety analysis will be performed for the all-patients-as-treated population (all randomly assigned patients who receive ≥1 dose of study treatment). The safety results will be summarized by treatment group and number and percentage of AEs. The Miettinen and Nurminen method will be used to perform analyses in which 95% CIs will be provided for between-treatment differences in the percentages of patients who experienced events.

Conclusion

Here we described a phase III, open-label, multicenter, randomized, active-controlled study (LITESPARK-011; NCT04586231) designed to compare the efficacy and safety of belzutifan plus lenvatinib with that of cabozantinib alone in patients with advanced clear cell RCC who experienced disease progression on or after anti-PD-1/PD-L1 therapy. Given the high risk of disease progression in patients with advanced clear cell RCC, there is an unmet medical need for more effective and tolerable treatment options; a positive benefit/risk profile is expected for belzutifan across various tumor types.

Executive summary

- Effective treatment options are limited for patients with advanced clear cell renal cell carcinoma (RCC) whose disease progresses after anti-programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) therapy.

Rationale

- By combining the HIF-2α inhibitor belzutifan and the VEGF inhibitor lenvatinib, it is hypothesized that VEGF production regulated by HIF-2α will be repressed at the level of transcription by belzutifan, and production of VEGF downstream of HIF-1α will be inhibited by lenvatinib at the growth factor receptor level.
- In addition, as HIF-2α drives tumor cell expression of several oncogenes in clear cell RCC, *VEGF* being just one of them, the combination could inhibit multiple oncogenic signaling pathways involved in initiation, progression and metastasis.

LITESPARK-011 study design & eligibility criteria

- The LITESPARK-011 study is a randomized, phase III study evaluating efficacy and safety of belzutifan plus the VEGF inhibitor lenvatinib versus the tyrosine kinase inhibitor cabozantinib in patients with advanced clear cell RCC whose disease progresses after anti-PD-1/PD-L1 therapy.
- Approximately 708 patients will be randomly assigned 1:1 to receive either 120 mg oral belzutifan plus 20 mg oral lenvatinib once daily or 60 mg oral cabozantinib once daily.
- Randomization will be stratified based on International Metastatic Renal Cell Carcinoma Database Consortium prognostic scores (0 vs 1–2 vs 3–6), line of treatment in which anti-PD-1/PD-L1 therapy was given (1 [adjuvant, neoadjuvant/adjuvant, or first-line] vs 2 [second-line]), and geographic region (North America, Western Europe or rest of world).

Outcomes measures/end points

- The dual primary end points are progression-free survival as determined by blinded independent central review per RECIST 1.1, and by overall survival; secondary end points include objective response rate, duration-of-response, and safety and tolerability.

Conclusion

- Results from this study may indicate more effective treatments for advanced clear cell RCC following treatment with immune checkpoint inhibitors.

Author contributions

RJ Motzer: conception, design or planning of the study and drafting the manuscript. M Schmidinger: acquisition of the data, interpretation of the results and drafting the manuscript. M Eto: acquisition of the data. C Suarez: conception, design or planning of the study, analysis and acquisition of the data and interpretation of the results. R Figlin: conception, design or planning of the study, analysis of the data, interpretation of the results and drafting of the manuscript. Y Liu: conception, design or planning of the study and acquisition of the data. R Perini: conception, design or planning of the study, analysis and acquisition of the data and interpretation of the results. Y Zhang: conception, design or planning of the study, analysis of the data and interpretation of the result. DYC Heng: conception, design or planning of the study. All authors critically reviewed and/or revised the manuscript for important intellectual content and approved the final manuscript for submission.

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Ethical conduct of research

The investigator or medically qualified designee (consistent with local requirements) will obtain documented consent from each potential participant or each participant's legally acceptable representative prior to their participation in the study. MSD clinical trials are conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

Data sharing statement

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