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Clinical Trials Corner: Adding up in Adjuvant

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Dear Readers,

The Clinical Trials Corner of *Kidney Cancer* highlights planned or ongoing high-impact studies in renal cell carcinoma (RCC). In this issue, we highlight the LITESPARK-022 trial, a study evaluating the addition of belzutifan to pembrolizumab for patients having undergone a nephrectomy.

In the future, if you feel that you would like to draw attention to a specific trial, please feel free to email us at mbparikh@ucdavis.edu or kca@iospress.com.

Sincerely,

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A Multicenter, Double-Blind, Randomized Phase 3 Study to Compare the Efficacy and Safety of Belzutifan (MK-6482) Plus Pembrolizumab (MK-3475) Versus Placebo Plus Pembrolizumab, in the Adjuvant Treatment of Clear Cell Renal Cell Carcinoma (ccRCC) Post Nephrectomy (MK-6482-022)

Status: Recruiting

Clinicaltrials.gov identifier: NCT05239728

Sponsor: Merck Sharp & Dohme LLC

Enrollment: 1600

Rationale: The KEYNOTE-564 study, a Phase 3 study evaluating the efficacy of pembrolizumab versus placebo in the adjuvant treatment of clear cell RCC post nephrectomy, extended disease-free survival (DFS) and has thus become an option for adjuvant therapy. Belzutifan, a small molecule hypoxia-inducible factor 2-alpha inhibitor, is a current treatment for patients with RCC associated with von Hippel-Lindau disease. It is possible that the combination of belzutifan and pembrolizumab may provide additive benefit to patients who are candidates for adjuvant therapy after nephrectomy.

Study design: This Phase 3 study enrolls patients with clear cell RCC (with or without sarcomatoid features) with no evidence of disease (NED) after complete resection of primary tumor, if pathology confirms intermediate-

high risk (pT2, Grade 4 or sarcomatoid, N0, M0; pT3, any grade, N0, M0), high risk (pT4, any Grade N0, M0; pT any stage, any Grade, N+, M0), or M1 NED (complete resection of a soft tissue metastasis at time of nephrectomy or < 2 years from nephrectomy). Eligible patients must have an Eastern Cooperative Oncology Group performance status of 0 to 1 within 10 days before randomization, must have undergone nephrectomy and/or metastasectomy < 12 weeks prior to randomization, and must have adequate organ function. Patients cannot have had a prior systemic treatment or radiotherapy for RCC, have pulse oximetry of <92% at rest or require supplemental oxygen. Following enrollment, patients are randomized to receive either belzutifan (120 mg orally once daily) for up to 54 weeks plus pembrolizumab (400 mg intravenously every 6 weeks) for up to 9 administrations or placebo plus pembrolizumab for the same duration. Patients will continue to be followed after the time of treatment discontinuation or completion.

Endpoints: The primary endpoint of this trial is disease-free survival (DFS). Key secondary outcomes include overall survival (OS), disease recurrence-specific survival, rate of study treatment discontinuation and rate of participants with one or more adverse events (AEs).

Comments: Pembrolizumab has recently become an option for adjuvant therapy for patients with intermediate to high-risk RCC after nephrectomy, based on establishing a disease-free survival benefit when compared to placebo. As with previous adjuvant trials in RCC with other systemic agents, overall survival benefit has not been demonstrated to date with pembrolizumab compared to placebo. Nevertheless, there remains interest in improving outcomes and preventing recurrences in patients with surgically resectable RCC. Combining pembrolizumab with belzutifan may provide additional benefit in adjuvant treatment as compared to pembrolizumab alone, which will be addressed in this clinical trial. The other important consideration in this study will be the additional toxicity that comes with addition of belzutifan, including development of hypoxia. Trials involving oral VEGF tyrosine kinase inhibitors in the adjuvant setting have been plagued with treatment discontinuation due to toxicity. Thus, the rate of discontinuation, a secondary endpoint, will be a meaningful finding. Ultimately, identifying patients most likely to benefit from adjuvant therapy should be an emphasis of all trials in resectable RCC, especially trials considering significant duration of multiple therapies. Thus, hopefully, correlative work will ensue from this trial to address that.

CONFLICT OF INTEREST

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Consultant: AstraZeneca, Janssen, Exelixis, Seagen, Oncocyte