

KIDNEY CANCER UPDATE

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Highlights in Kidney Cancer

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Phase 1/2 Trial of MK-6482 Demonstrates Activity Against Kidney Cancer

The experimental agent MK-6482 is well tolerated, has a favorable safety profile, and demonstrates promising activity in heavily pretreated patients with clear cell renal cell carcinoma (ccRCC), according to a phase 1/2 study. MK-6482 is a first-in-class small molecule inhibitor of hypoxia-inducible factor 2 α , a key oncogenic driver in RCC.

For the study, Dr Toni K. Choueiri of the Dana-Farber Cancer Institute in Boston, Massachusetts, and colleagues enrolled 55 patients (median age, 62 years) with advanced ccRCC who had received at least 1 prior therapy; the median number of prior therapies was 3. Five patients were favorable risk, 40 were intermediate risk, and 10 were poor risk by International Metastatic RCC Database Consortium (IMDC) criteria. Patients received 120 mg of MK-6482 orally once a day.

After a median follow-up of 13 months, the most common adverse events (AEs) were anemia (75%), fatigue (67%), dyspnea (47%), nausea (33%), and cough (31%). Anemia (26%) and hypoxia (15%) were the most common grade 3 AEs, and 2 patients discontinued treatment owing to hypoxia. No grade 4/5 AEs related to MK-6482 were observed.

The overall response rate (ORR) to treatment was 24%. There were 13 confirmed partial responses and 31 patients with stable disease (56%), for a disease control rate of 80%. Although the median duration of response was not reached, 81% of patients had a response lasting at least 6 months by Kaplan-Meier estimate. Treatment continued beyond 12 months in 16 patients (29%).

A partial response occurred in 2 of the 5 patients with favorable-risk disease (ORR, 40%), 10 of the 40 patients with intermediate-risk disease (ORR, 25%), and 1 of the 10 patients with poor-risk disease (ORR, 10%). The disease control rate was 100%, 80%, and

70%, respectively. The median progression-free survival (PFS) for the total population was 11.0 months, and the 12-month PFS rate was 49%. The median PFS for favorable-, intermediate-, and poor-risk disease was 16.5, 11.0, and 6.9 months, respectively. As of May 15, 2019, 30 patients had discontinued treatment owing to progressive disease and 2 patients had discontinued treatment owing to AEs. Sixteen patients continued treatment.

The authors concluded that MK-6482 is well tolerated, with a favorable safety profile, and demonstrates promising single-agent activity in heavily pretreated patients with ccRCC across IMDC risk groups. A phase 3 trial in a similar population recently opened that plans to randomly assign 736 patients to MK-6482 or everolimus (Afinitor, Novartis).

Choueiri EK, Plimack ER, Bauer TM, et al. Phase I/II study of the oral HIF-2 α inhibitor MK-6482 in patients with advanced clear cell renal cell carcinoma (RCC) [ASCO GU abstract 611]. *J Clin Oncol*. 2020;38(6)(suppl).

Long-term Analysis of CheckMate 025 Continues to Show Benefit for Nivolumab

The primary analysis of CheckMate 025 (Study of Nivolumab vs. Everolimus in Pre-Treated Advanced or Metastatic Clear-cell Renal Cell Carcinoma) showed that nivolumab (Opdivo, Bristol-Myers Squibb) improved overall survival (OS) compared with everolimus in patients with previously treated advanced RCC, with superior safety and tolerability. Now, the final analysis of this trial—with a minimum follow-up of 64 months vs the 14 months of the primary analysis—confirms these results.

For the trial, Dr Robert J. Motzer of Memorial Sloan Kettering Cancer Center in New York, New York, and colleagues randomly assigned 821 patients with advanced, pretreated, predominantly ccRCC in a 1:1 ratio to nivolumab at 3 mg/kg intravenously every 2 weeks or

everolimus at 10 mg orally once daily until progression or unacceptable toxicity.

Median OS continued to be longer in the nivolumab group vs the everolimus group at extended follow-up, at 25.8 vs 19.7 months, respectively (hazard ratio [HR], 0.73; 0.62-0.85). The ORR also was higher with nivolumab vs everolimus, at 23% vs 4%, respectively (odds ratio, 6.86; 4.01-11.74). The median PFS was similar initially in the nivolumab and everolimus treatment arms, at 4.2 vs 4.5 months, respectively, but diverged at 6 months, and favored nivolumab with long-term follow-up (HR, 0.84; 0.72-0.99).

The median duration of response also was longer with nivolumab vs everolimus, at 18.2 vs 14.0 months, respectively, but the difference was not statistically significant.

An ongoing response was observed in 28% of the nivolumab patients vs 18% of the everolimus patients. Most patients received subsequent systemic anticancer therapy; 67% of those in the nivolumab arm (most commonly everolimus or axitinib) and 72% of those in the everolimus arm (most commonly axitinib or nivolumab). No new safety signals or treatment-related deaths emerged with long-term follow-up in either arm. Patients in the nivolumab arm were less likely to experience a grade 3/4 AE than those in the everolimus arm (21% vs 37%).

After the primary analysis was reported, the protocol was amended and 65 patients crossed over from the everolimus arm to the nivolumab arm. The median OS was 65.9 months from the date of randomization to the everolimus arm, and the median PFS was 7.4 months from the date of crossover to nivolumab. The ORR was 8%.

Dr Motzer concluded that “nivolumab continues to show significant overall survival benefit, higher objective response rate, and improved progression-free survival over everolimus with long-term follow-up.” He added that a lower proportion of nivolumab-treated patients experienced treatment-related AEs, and that no new safety signals were observed with longer follow-up.

Motzer RJ, Tsykodi SS, Escudier B, et al. Final analysis of the CheckMate 025 trial comparing nivolumab (NIVO) versus everolimus (EVE) with >5 years of follow-up in patients with advanced renal cell carcinoma (aRCC) [ASCO GU abstract 617]. *J Clin Oncol*. 2020;38(6)(suppl).

Addition of Radiation to Checkpoint Inhibition Shows Encouraging Antitumor Activity

The addition of stereotactic body radiation therapy (SBRT) to standard treatment with dual checkpoint inhibition had an acceptable safety and encouraging antitumor activity in metastatic RCC, according to a phase 2 study presented by Dr Hans J. Hammers of the University of Texas Southwestern Medical Center in Dallas, Texas.

The study, called RADVAX (Trial of SBRT in Combination With Nivolumab/Ipilimumab in RCC / Kidney Cancer Patients), examined 25 patients with metastatic ccRCC at the University of Texas Southwestern Medical Center and the Johns Hopkins University School of Medicine in Baltimore, Maryland. Nearly half of patients (44%) had received prior treatment with a tyrosine kinase inhibitor (28%) or interleukin 2 (16%). Eight percent of patients were favorable risk, 80% were intermediate risk, and 12% were poor risk by IMDC criteria. Forty percent of patients required the use of prednisone to treat classic immune-related AEs seen with dual checkpoint inhibition.

Patients received standard treatment with nivolumab (3 mg/kg) plus ipilimumab (Yervoy, Bristol-Myers Squibb; 1 mg/kg) every 3 weeks, followed by nivolumab monotherapy. Patients also received SBRT to 1 or 2 disease sites with a dose of 50 Gy in 5 fractions between the first and the second dose of dual checkpoint inhibition.

After a median of 24 months, the ORR was 56%; all responses were partial. In addition, 24% of patients experienced stable disease. Grade 2 radiation pneumonitis occurred in 2 patients, and responded promptly to oral corticosteroids. The median PFS was 8.2 months. Median OS and duration of response were not reported.

Although Dr Hammers cautioned that this is a small, phase 2 trial, he said that the encouraging antitumor activity with dual checkpoint inhibition plus SBRT warrants further investigation. “We do feel that the treatment template is one that could be used for future prospective trials,” he added.

SBRT is hypothesized to promote response to checkpoint inhibition by activating the stimulator of interferon genes (STING) pathway.

Hammers HJ, Vonmerveldt D, Ahn C, et al. Combination of dual immune checkpoint inhibition (ICI) with stereotactic radiation (SBRT) in metastatic renal cell carcinoma (mRCC) (RADVAX RCC) [ASCO abstract 614]. *J Clin Oncol*. 2020;38(6)(suppl)