KIDNEY CANCER UPDATE

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Nivolumab Provides Long-Term Benefit in Advanced Renal Cell Carcinoma

Nivolumab (Opdivo, Bristol-Myers Squibb) has been shown to extend overall survival (OS) more than everolimus (Afinitor, Novartis) in patients with previously treated advanced renal cell carcinoma (RCC). Now, follow-up from phase 1 and 2 trials reveals that approximately one-third of patients continue to benefit from the programmed death 1 (PD-1) inhibitor more than 4 years later.

"This represents the longest follow-up with any anti–PD-1 agent to date in RCC," said Dr David F. McDermott of the Beth Israel Deaconess Medical Center in Boston, Massachusetts, presenting his team's research.

Both the phase 1 and phase 2 studies were conducted in pretreated patients with advanced RCC, and nivolumab treatment continued until confirmed progression or unacceptable toxicity. The 34 patients in the phase 1 trial were more heavily pretreated than the 167 patients in the phase 2 trial. Although the dose and treatment schedule differed between the 2 groups, this did not affect clinical outcomes. If patients were clinically stable on nivolumab, treatment continued for 96 weeks in the phase 1 trial and until progression or toxicity in the phase 2 trial.

The median OS was longer than 22 months in both groups. Median OS at more than 4 years was 38% in the phase 1 group and 29% in the phase 2 group. At 5 years, it was 34% in the phase 1 group.

In the phase 2 group, long-term survival was possible for patients at favorable risk, intermediate risk, and poor risk (median OS, 35.5, 22.1, and 12.6 months, respectively) by Memorial Sloan Kettering Cancer Center (MSKCC) risk criteria. Long-term survival also occurred in patients with both excellent and reduced Karnofsky performance status (median OS, 27.2 and 14.6 months, respectively). Long-term survival also was achievable for patients whose best response was complete or partial response, stable disease, or progressive disease.

The phase 3 CheckMate 025 study (Study of Nivolumab vs. Everolimus in Pre-Treated Advanced or Metastatic Clear-cell Renal Cell Carcinoma) revealed that nivolumab produced an 18.7% rate of grade 3 or 4 adverse events and a 7.6% rate of adverse events leading to discontinuation. With more than 4 years of follow-up in the current phase 1 and 2 trials, the rate of grade 3 or 4 adverse events was less than 20%, and the rate of treatment-related adverse events leading to discontinuation was less than 10%. "These results are notable because they remain similar to the safety outcomes in the larger phase 3 study, even with an additional 3 years of follow-up," said Dr McDermott.

Nivolumab was well tolerated in both groups, and most side effects were reversible with treatment. Approximately 40% of patients in the phase 2 trial experienced endocrine, gastrointestinal, hepatic, pulmonary, renal, or skin adverse events. Most adverse events occurred within 6 months of the start of treatment. For example, all grade 3 or 4 endocrine toxicities resolved with treatment, but half of the patients with grade 1 or 2 toxicity required hormonal replacement therapy. Some patients required 2 to 3 months of immune-modulating therapy to resolve side effects such as gastrointestinal problems.

The objective response rate in the phase 2 trial was 21.6%, with a short median time to response of 2.8 months. The median duration of response was 23 months. A subset of patients experienced durable responses even after treatment was discontinued.

The 48 patients in the phase 2 trial who were alive for more than 4 years came from all patient subgroups: favorable, intermediate, and poor MSKCC risk. More than half the patients who experienced long-term survival had a best overall response of stable or progressive disease rather than complete or partial response, and 15 of the 48 patients did not require treatment besides nivolumab.

Dr McDermott concluded by saying that future investigation should focus on identification of predictors of long-term survival, determination of optimal treatment duration, and trial designs that evaluate the clinical impact of sequential, adjuvant, and combination approaches.

"We look forward to examining whether nivolumab produces similar long-term survival in the phase 3 trial," he said.

McDermott DF, Motzer RJ, Atkins MB, et al. Long-term overall survival (OS) with nivolumab in previously treated patients with advanced renal cell carcinoma (aRCC) from phase I and II studies [ASCO abstract 4507]. *J Clin Oncol.* 2016;34(15)(suppl).

Continued Nivolumab After Progression May Benefit Patients With Advanced RCC

Patients with advanced clear cell RCC who develop resistance to nivolumab may continue to benefit from treatment with the agent after disease progression, according to a new analysis of data from the CheckMate 025 study. Dr Bernard J. Escudier of the Institut Gustave Roussy in Villejuif, France, presented the results as a poster.

In CheckMate 025, researchers randomly assigned 821 patients with advanced clear cell RCC who had received prior treatment to either nivolumab 3 mg/kg intravenously every 2 weeks or everolimus 10 mg orally per day.

For the new analysis, researchers looked just at the 406 patients who had received nivolumab. Of these, 38% had received treatment beyond progression (TBP) and 36% had not received treatment beyond progression (NTBP). (The remaining patients either received treatment only briefly beyond progression or did not progress.) The baseline characteristics were similar between the 2 groups with the exceptions of Karnofsky performance status of at least 90, which was significantly higher in the TBP group than in the NTBP group (72% vs 62%), and the presence of bulky tumor burden, which was less common in the TBP group than in the NTBP group (18% vs 26%). The median duration of treatment was 8.8 months in the TBP group and 2.3 months in the NTBP group.

The researchers found that the objective response rate was 20% in the TBP group and 14% in the NTBP group, with a median time to response of 1.9 and 3.7 months, respectively. The duration of response was 5.6 months in the TBP group and 7.0 months in the NTBP group. The median duration of treatment after first progression was 3.4 months.

Median OS was 28.1 months in the TBP group and 14.0 months in the NTBP group. Of 140 patients with TBP who had tumor measurements taken before and after progression, 14% had at least a 30% reduction in tumor burden from first progression.

The researchers concluded that treatment beyond progression with nivolumab can be associated with additional tumor shrinkage.

Escudier BJ, Motzer RJ, Sharma P, et al. Treatment beyond progression with nivolumab (nivo) in patients (pts) with advanced renal cell carcinoma (aRCC) in the phase III CheckMate 025 study [ASCO abstract 4509]. *J Clin Oncol.* 2016;34(15)(suppl).

Cabozantinib Improves Overall Survival in Advanced Renal Cell Carcinoma

The tyrosine kinase inhibitor (TKI) cabozantinib (Cometriq, Exelixis) has been shown to improve OS significantly more than everolimus in patients with previously treated advanced RCC, according to final results from the phase 3 METEOR trial (Cabozantinib Versus Everolimus in Advanced Renal Cell Carcinoma). Interim results from the trial showed a significant improvement in progression-free survival (PFS) and a trend toward improved OS with cabozantinib.

Cabozantinib is an oral inhibitor of such tyrosine kinases as MET, AXL, and vascular endothelial growth factor receptor (VEGFR).

Dr Toni K. Choueiri of the Dana-Farber Cancer Institute in Boston, Massachusetts, explained that the METEOR study included 658 patients with advanced RCC that had progressed after treatment with a prior VEGFR inhibitor. Patients were randomly assigned 1:1 to treatment with cabozantinib 60 mg or everolimus 10 mg until loss of clinical benefit or intolerable toxicity. No crossover was allowed.

As Dr Bernard J. Escudier reported at the 2015 annual meeting of the American Society of Clinical Oncology, median PFS was significantly higher with cabozantinib (7.4 months) than with everolimus (3.9 months). The objective response rate also was significantly higher with cabozantinib (17%-24%) than with everolimus (3%-4%). "Notably, the rate of patients with progressive disease as best response—indicating primary refractory disease to cabozantinib treatment—was remarkably low," said Dr Choueiri, at 9% to 12%.

Median OS at follow-up of at least 13 months was significantly higher with cabozantinib than with everolimus, at 21.4 months vs 16.5 months (hazard ratio [HR], 0.66; 95% CI, 0.53-0.83; *P*=.0003). The benefit in OS with cabozantinib occurred across all subgroups, regardless of MSKCC risk group, number of prior VEGFR inhibitors used, duration of first VEGFR inhibitor, location of metastases, and MET expression level. PFS was highly predictive of OS.

The safety profile of cabozantinib was similar to that seen in the previous results. The most common adverse events with cabozantinib were diarrhea (75%), fatigue (59%), decreased appetite (47%), palmar-plantar erythrodysesthesia (43%), hypertension (37%), weight loss (34%), and vomiting (34%). Dose modifications were

used to manage side effects, and just 12% of patients in the cabozantinib group and 11% in the everolimus group discontinued their medication owing to adverse events.

Dr Choueiri concluded that cabozantinib is "a new treatment standard for patients with advanced RCC after prior antiangiogenic therapy."

Choueiri TK, Escudier B, Powles T, et al; METEOR Investigators. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial [published online June 3, 2016]. *Lancet Oncol*. doi: 10.1016/S1470-2045(16)30107-3.

Choueiri TK, Powles T, Escudier BJ, et al. Overall survival (OS) in METEOR, a randomized phase 3 trial of cabozantinib (Cabo) versus everolimus (Eve) in patients (pts) with advanced renal cell carcinoma (RCC) [ASCO abstract 4506]. *J Clin Oncol*. 2016;34(15)(suppl).

Hypoxia-Inducible Factor 2α Inhibitor Safe, Well Tolerated in Phase 1 Trial

A phase 1 trial of PT2385, the first inhibitor of hypoxia-inducible factor 2α (HIF-2α), suggests that the agent is safe and well tolerated in patients with heavily pretreated advanced clear cell RCC. In addition, the agent shows early signs of clinical activity in these patients.

HIF-2α is a key oncogenic driver of clear cell RCC that regulates the expression of VEGF, cyclin D1, and CXCR4, all of which play a role in tumor cell survival, growth, and metastasis. PT2385 is a selective inhibitor of HIF-2α that impairs heterodimerization with HIF-1β but does not block HIF-1α.

Dr Kevin D. Courtney of the University of Texas Southwestern Medical Center in Dallas, who presented the results, said that the investigators began by studying 26 patients with locally advanced or metastatic clear cell RCC that had progressed during treatment with at least 1 prior VEGF inhibitor. Following a 3 + 3 study design, the dose level was increased by 100% until the first drug-related grade 2 or higher toxicity occurred, after which the dose was increased by 50%.

Although one grade 4 pulmonary embolism occurred in a patient treated with 800 mg twice daily of PT2385, it occurred outside the dose-limiting toxicity window, and no dose-limiting toxicity was observed at any dose level up to 1800 mg twice daily. A rapid reduction of erythropoietin was observed at all doses, but there was no further reduction in erythropoietin at doses higher than 800 mg twice daily.

"Based on the safety, pharmacokinetic, and pharmacodynamic data, 800 mg twice daily was selected as the recommended phase 2 dose of PT2385," said Dr Courtney. An additional 25 patients received this dose in an expansion cohort.

PT2385 was well tolerated among the group of 51 patients, with the most common adverse events being anemia, peripheral edema, and fatigue, which were grade 1 and 2 in most cases. Hypoxia occurred in 20% of patients.

To date, 1 patient has experienced a complete response, 3 patients have experienced a partial response, and 16 patients have had stable disease for at least 16 weeks. Five patients have been in the study for at least 1 year.

Dr Courtney said that researchers are continuing to develop PT2385 for clear cell RCC in combination with nivolumab or a TKI. It is also being developed for use in von Hippel-Lindau disease and glioblastoma.

Courtney KD, Infante JR, Lam ET, et al. A phase I dose escalation trial of PT2385, a first-in-class oral HIF-2a inhibitor, in patients with advanced clear cell renal cell carcinoma [ASCO abstract 2506]. *J Clin Oncol*. 2016;34(15)(suppl).