KIDNEY CANCER UPDATE

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Highlights in Kidney Cancer From the 2015 American Society of Clinical Oncology Annual Meeting

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Biomarkers Associated With Improved Clinical Outcomes With Nivolumab in Metastatic Renal Cell Carcinoma

Biomarkers indicating the presence of adaptive immune activity were associated with improved clinical outcome in nivolumab (Opdivo, Bristol-Myers Squibb)-treated patients with metastatic renal cell carcinoma, according to a prospective study presented by Dr Toni K. Choueiri at the 2015 American Society of Clinical Oncology (ASCO) annual meeting.

This study examined 91 patients at baseline and during treatment with nivolumab. Of these patients, 56 had evaluable biopsies that were used to investigate potentially predictive biomarkers for response to nivolumab, including programmed death ligand 1 (PD-L1) expression, soluble factors, gene expression, and T-cell receptor sequencing. Previously untreated patients received 10 mg/kg of nivolumab intravenously (IV), and previously treated patients received 0.3, 2, or 10 mg/kg of nivolumab IV.

The overall survival findings were similar to those of previous studies. The median overall survival was 16.4 months for previously treated patients receiving 0.3 mg/kg of nivolumab, not reached for those receiving 2 mg/kg, 25.2 months for those receiving 10 mg/kg, and not reached for treatment-naive patients. The 1-year and 2-year overall survival rates in the overall population were 75% and 58%, respectively.

Of the evaluable patients, 32% were found to be PD-L1 positive, defined as 5% or greater tumor membrane staining via immunohistochemistry. The 1-year and 2-year survival rates were promising in both PD-L1–positive patients (71% and 64%, respectively) and PD-L1–negative patients (71% and 48%, respectively), though the PD-L1–positive patients appeared to have better responses.

Overall, researchers found an association between adaptive immune activity and improved clinical outcomes. When examining potential biomarkers, researchers found that some cell-mediated immune transcripts were associated with tumor burden response, indicating that infiltrating immune-activating cells may play an important role during nivolumab treatment. Some serum-soluble markers were associated with overall survival, including interferon γ (IFN-γ) and many other cytokines. Other associated serum-soluble markers included those associated with lymphoid and myeloid infiltration, and active checkpoint regulation. Researchers also found that a higher quantity of T cells in the tumor was associated with longer survival. Decreased clonality of T-cell receptors in the tumor and blood appeared to be associated with improved survival, but the results were not significant.

The study also found significant upregulation of cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) and PD-L2 during nivolumab treatment, suggesting that combinations of this drug with other checkpoint inhibitors might be beneficial.

Dr Choueiri noted that "additional investigation in randomized, controlled trials is needed to better understand the potential for predicting outcomes based on these observed changes."

Choueiri TK, Fishman MN, Escudier B, et al. Immunomodulatory activity of nivolumab in metastatic renal cell carcinoma (mRCC): association of biomarkers with clinical outcomes [ASCO abstract 4500]. *J Clin Oncol.* 2015;33(suppl).

Mutations in *PBRM1* and *KDM5C* Associated With Improved Response to Everolimus and Sunitinib in Metastatic Renal Cell Cancer

Mutations in the epigenetic regulators *PBRM1* and *KDM5C* were associated with an improved progression-free survival response in metastatic renal cell cancer to everolimus (Afinitor, Novartis) and sunitinib (Sutent, Pfizer), respectively, according to the results of the RECORD-3 study presented at the 2015 ASCO annual meeting by Dr James J. Hsieh.

This phase 2 randomized trial enrolled 471 previously untreated patients with metastatic renal cell cancer. In the overall results of the study, published in 2014 in the *Journal of Clinical* Oncology by Dr Robert J. Motzer, patients treated with sunitinib followed by everolimus had a longer progression-free survival than those treated with everolimus followed by sunitinib (10.7 months vs

7.9 months, respectively). Because the progression-free survival had a wide range within both arms, researchers used next-generation sequencing to investigate a potential correlation between somatic mutations and the treatment efficacy of first-line everolimus vs first-line sunitinib. Samples from 260 patients were examined in this study.

Frequently mutated genes found in this study were similar to those in previously published data, and included *VHL*, *PBRM1, SETD2, BAP1, KMD5C,* and *PTEN*.

Among patients treated with everolimus, those with *PBRM1* mutations had a longer median progression-free survival than those with wild-type *PBRM1* (11.5 months vs 5.3 months, respectively; *P*=.0031). Patients with and without *PBRM1* mutations responded similarly to sunitinib (progression-free survival, 11.0 months vs 8.3 months, respectively; *P*=.413).

Among patients treated with sunitinib, those with *KDM5C* mutations had a trend toward a longer median progression-free survival compared with those with wild-type *KDM5C* (20.6 months vs 8.4 months, respectively; *P*=.0511). No difference was found between genotypes in patients treated with everolimus (9.8 months vs 8.1 months, respectively; *P*=.424).

Among patients treated with everolimus, those who were wild-type for *BAP1* had improved progression-free survival compared with those who had *BAP1* mutations (10.2 months vs 5.3 months, respectively; *P*=.018). There was a similar nonsignificant trend in patients treated with sunitinib (11.3 months vs 8.1 months, respectively; *P*=.068).

The results showed no difference in progression-free survival response in patients with or without *SETD2* mutations for everolimus (wild-type, 8.1 months; mutation, 8.1 months; *P*=.247) or sunitinib (wild-type, 10.9 months; mutation, 10.9 months; *P*=.417). The study also found *SETD2* mutations in 29% of the 227 patients with clear cell renal cell cancer, a higher percentage than in previous studies of the overall population (10%). The authors suggest that this indicates a role for *SETD2* in renal cell cancer metastasis.

Dr Hsieh mentioned that these biomarkers "should be validated and could be considered as molecular entry criteria for prospective clinical studies."

Hsieh J, Chen D, Wang P, et al. Identification of efficacy biomarkers in a large metastatic renal cell carcinoma (mRCC) cohort through next generation sequencing (NGS): results from RECORD-3 [ASCO abstract 4509]. *J Clin Oncol.* 2015;33(suppl).

Dose Reductions in Adjuvant Sunitinib or Sorafenib Do Not Reduce Disease-Free Survival in Renal Cell Cancer

A reduction in the dose of adjuvant sunitinib or sorafenib (Nexavar, Bayer/Onyx) successfully decreased rates of discontinuation, but none of the doses or treatments affected disease-free survival for patients with completely resected locally advanced renal cell cancer who have a high risk for recurrence, as shown in the ASSURE randomized phase 3 trial presented by Dr Naomi B. Haas at the 2015 ASCO annual meeting.

In this trial, 1943 patients received sunitinib (50 mg daily for four of 6 weeks), sorafenib (400 mg twice daily), or placebo; however, midway through the trial, the researchers noted a large discontinuation rate of patients in the treatment arms. Therefore, the original regimens were revised to reduce patient dose (sunitinib, 37.5 mg daily; sorafenib, 400 mg once daily) and potentially reduce discontinuation of therapy. Drug dosing, toxicity, and outcome were analyzed, with a primary endpoint of disease-free survival.

Dose reduction successfully decreased the 3-month rate of discontinuation from adverse events or refusal from 25% to 17% with sunitinib and from 30% to 11% with sorafenib. The rates of grade 3 adverse events also were decreased by dose reduction for sunitinib (from 62% to 47%) and sorafenib (from 72% to 59%), but were still high. Less than half of patients received the entire dose that was originally intended for the sunitinib group (full dose, 40.2%; reduced dose, 44.5%) or sorafenib group (full dose, 27.9%; reduced dose, 37.0%). The most common grade 3 or higher adverse events were hypertension, hand-foot reaction, rash, and fatigue.

Despite the successful dose reduction, the study found no difference between overall treatment groups in median disease-free survival (sunitinib, 5.8 years; sorafenib, 5.8 years; placebo, 6.0 years) or 5-year overall survival rate (76.9%, 80.7%, and 78.7%, respectively). There also were no differences in the 5-year disease-free survival rate between the reduced and full dose for the sunitinib-treated group (56.0% vs 55.1%, respectively) or placebo-treated group (55.8% vs 55.0%, respectively). However, patients receiving a reduced dose of sorafenib had a smaller 5-year disease-free survival rate than those receiving the full dose (29.2% vs 56.6%, respectively). The study found no differences in disease-free survival based on the amount of time the patients received treatment. Interestingly, the study found that women had significantly longer disease-free survival than men (83.0 months vs 62.1 months, respectively; *P*=.002).

The researchers concluded that patients with locally advanced renal cell cancer should not receive adjuvant sorafenib or sunitinib. The authors also mention that this study "raises concern about the differential effects of multi-kinase inhibitors across a range of doses."

Haas NB, Manola J, Flaherty K, et al. Dose analysis of ASSURE (E2805): Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma, an ECOG-ACRIN-led, NCTN phase 3 trial [ASCO abstract 4508]. *J Clin Oncol.* 2015;33(suppl).