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Frontline immunotherapy treatment with nivolumab and ipilimumab in metastatic renal cell cancer: a new standard of care

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ABSTRACT

Nivolumab is a programmed death 1 (PD-1) inhibitor currently approved as second-line treatment for advanced renal cell carcinomas (RCC) after failure of standard antiangiogenic treatment. Motzer et al. have recently published in the *New England Journal of Medicine* the findings of CheckMate 214 trial, using nivolumab and ipilimumab, a cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitor, versus sunitinib in previously untreated advanced RCC. The combination demonstrated a higher 18-month overall survival rate of 75% versus 60%, and a higher objective response rate of 42% versus 27%, for the combination in favor over sunitinib monotherapy. These results herald the rapidly changing role of immune checkpoint inhibitor therapy as first-line treatment for metastatic RCC.

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In 2018, there will be an estimated 65,000 new cases of renal cancer in the United States, with an estimated 15,000 deaths.[1] Advanced RCC have been historically treated with Interferon-α and high-dose Interleukin-2, and more recently with vascular endothelial growth factor (VEGF) pathway inhibitors and mammalian target of rapamycin (mTOR) inhibitors, which comprise the current standard of care for first-line treatment in favorable/intermediate-risk and poor-risk metastatic renal cell cancers, respectively.[2]

Nivolumab is a fully human IgG4 monoclonal antibody that selectively blocks the binding of programmed death 1 (PD-1) on T cells with its ligands, programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2) on tumor cells, to prevent PD-1 mediated T cell inhibition, and nivolumab monotherapy was granted approval by the FDA for the second-line treatment of advanced RCC after failure of treatment with antiangiogenic therapy after demonstrating an overall survival benefit compared to everolimus in the CheckMate 025 trial.[3] Ipilimumab is a humanized monoclonal antibody that blocks the inhibitory cytotoxic T-lymphocyte antigen 4 (CTLA-4) on T cells, allowing for an increase in T cell activation and proliferation and in antigen-specific immunity.[4] Motzer et al. published the results of a phase III randomized clinical trial, CheckMate 214, which investigated the combination of nivolumab and ipilimumab in intermediate- and poor-risk patients with previously untreated clear-cell RCC.[5]

The study was a multi-site, international trial that included 1096 patients who received treatment with nivolumab plus ipilimumab (n = 547) or sunitinib (n = 535). Of the two treatment groups, 77% and 78% of patients, respectively, were categorized as having intermediate- or poor-risk disease according to the validated prognostic model developed by the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC). Patients were predominantly male (74%) with a median age of 62 years, with a majority having undergone previous nephrectomy (81%). The most common sites of metastasis were lung (68%), followed by lymph nodes (47%), bone (21%), and liver (19%). Patients were administered nivolumab (3 mg/kg) plus ipilimumab (1 mg/kg) intravenously every 3 weeks for four doses, followed by nivolumab (3 mg/kg) every 2 weeks, or sunitinib 50 mg orally once daily for 4 weeks (out of a 6-week cycle). The co-primary end points were overall survival (OS), objective response rate (ORR), and progression-free survival (PFS) among all treated patients. Secondary end points included the ORR, PFS, and OS in the intention-to-treat population, and the incidence rate of adverse events (AE's) among all treated patients. Exploratory end points included ORR, PFS, and OS among patients with favorable-risk disease, outcomes according to the level of PD-L1 expression, and health-related quality of life scores in intermediate- and poor-risk patients.

The combination of nivolumab plus ipilimumab demonstrated a significant overall survival benefit of 80% compared to 72% with sunitinib at 12 months, and 75% versus 60%, respectively at 18 months. The death rate was 37% lower in the nivolumab plus ipilimumab group (Hazard ratio Median overall survival was not reached in the nivolumab plus ipilimumab group but was 26.0 months in the sunitinib group.

Among intermediate- and poor-risk patients, the objective response rate was 42% with nivolumab plus ipilimumab (with complete responses in 9% of patients) compared to 27% with sunitinib (with complete responses in 1% of patients). While median time to response did not differ between the two

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groups (2.8 months vs. 3.0 months, respectively), median duration of response was not reached in the nivolumab plus ipilimumab group compared to 18.2 months in the sunitinib group. The higher objective response rate with nivolumab plus ipilimumab was observed among all subgroups regardless of cohorts of gender, baseline PD-L1 expression, and both intermediate- and poor-risk disease.

Median PFS was longer with nivolumab plus ipilimumab at 11.6 months compared to 8.4 months with sunitinib, but the difference did not meet prespecified criteria for statistical significance. However, there was a delayed benefit seen at 6 months after randomization, similar to that seen in the trial comparing nivolumab versus everolimus as second-line treatment in advanced renal-cell cancer.3

The median duration of treatment were similar at 7.9 months and 7.8 months, respectively, for the nivolumab/ipilimumab and sunitinib arms. 79% of patients in the nivolumab plus ipilimumab group received all four doses of treatment. However, dose delays occurred with nivolumab in 58% of patients and in ipilimumab at 27% of patients. In those treated with sunitinib, dose delays occurred in 53% of patients, and dose reductions occurred in 53% of patients. The protocol allowed for treatment beyond initial investigator-assessed, RECIST-defined progression if they were deemed to have clinical benefit. 29% of patients in the nivolumab plus ipilimumab group and 24% of patients in the sunitinib group were treated beyond RECIST-defined progression.

Fewer adverse events of any grade occurred in the nivolumab plus ipilimumab group (93%) compared to the sunitinib group (97%). Grade 3 or grade 4 events were also less common in the nivolumab plus ipilimumab group (46%) versus the sunitinib group (63%). The most common adverse events in the nivolumab plus ipilimumab group were fatigue (37%), pruritus (28%), and diarrhea (27%), while the most common adverse events in the sunitinib group were diarrhea (52%), pruritus (49%), and palmar-plantar erythrodysesthesia (43%). However, there were 8 treatment-related deaths in the nivolumab plus ipilimumab group, primarily involving pulmonary and hematologic complications. The four treatment-related deaths in the sunitinib group were primarily cardiac-related. Changes in health-related quality of life scores from baseline favored the nivolumab plus ipilimumab group.

In conclusion, the combination of nivolumab and ipilimumab in intermediate- and poor-risk patients as front-line therapy for metastatic RCC has already emerged as a new standard of care, with US FDA approval of this approach on April 16, 2018. The results of this trial has changed the landscape of treatment of metastatic RCC and has now established role of immune checkpoint inhibitor therapy as first-line treatment for advanced kidney cancers. The search for continued improvement in response in the form of combination therapies with immune checkpoint blockade along with VEGF-TKI are underway.

Conflict of interest

AN has no conflict to disclose. JAC serves on the Speakers' Bureau of Bristol Myers Squib (BMS).

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References

1. Kidney and Renal Pelvis Cancer - Cancer Stat Facts [Internet]. [accessed 2018 Jun 23]. https://seer.cancer.gov/statfacts/html/kidrp.html.
2. Motzer RJ, Jonasch E, Agarwal N NCCN guidelines: kidney cancer (Version 4.2018) [Internet]; 2018 [accessed 2018 Jun 23]. https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf.
3. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, Tykodi SS, Sosman JA, Procopio G, Plimack ER, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med. 2015;373:1803–1813. doi:10.1056/NEJMoa1510665.
4. Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. J Clin Oncol. 2015;33:1974–1982. doi:10.1200/JCO.2014.59.4358.
5. Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, Plimack ER, Barthélémy P, Porta C, George S, et al. Nivolumab plus Ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med. 2018;378:1277–1290. doi:10.1056/NEJMc1711583.