# Nivolumab May Improve Survival in Advanced Renal-Cell Carcinoma

Nivolumab, a PD-1 inhibitor, shows improved overall survival as compared to everolimus as second-line treatment for renal-cell carcinoma, as evidenced by results of a recent study.

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January 14, 2015 – In patients experiencing treatment failure with first-line kinase inhibitor therapy for renal-cell carcinoma, the PD-1 inhibitor nivolumab showed improved overall survival as compared to the mTOR everolimus as second-line treatment in a recent randomized, open-label, phase 3 study.

Robert J. Motzer, MD, with Memorial Sloan Kettering Cancer Center, in New York, New York, and colleagues reported their findings in the September 25, 2015 issue of the *New England Journal of Medicine.*

Nivolumab is a human monoclonal antibody which acts as a PD-1 inhibitor thereby blocking evasion of tumor cells from natural immune response. Previous phase 2 trials showed overall survival with nivolumab treatment ranging from 18.2 to 25.5 months. Everolimus is a mTOR inhibitor that blocks antibody production. Everolimus was FDA approved for the treatment of advanced renal-cell carcinoma in 2009.

The current study, spanning 24 countries on 5 continents, enrolled a total of 803 patients with previously treated, metastatic renal-cell carcinoma measurable by RECIST 1.1. After enrollees were randomized, 406 patients received nivolumab and 397 patients received everolimus. Based on pre-treatment samples, 92% of total enrollees had measurable tumor PD-L1 expression. Patients received nivolumab every 2 weeks by intravenous infusion at 3 mg per kilogram of body weight. Patients received everolimus daily as a 10 mg oral dose.

The overall survival from randomization to date of death served as the primary endpoint for this study. Overall survival in the nivolumab group was 25.0 months (95% CI, 21.8 to not estimable) compared to 19.6 months (95% CI, 17.6 to 23.1) with everolimus.

Multiple secondary endpoints were evaluated including tumor response, progression-free survival, and the relationship between overall survival and PD-L1 expression. In the nivolumab group, 24% showed partial response as compared to 5% in the everolimus group. A similar initial progression-free survival was noted in the two groups with nivolumab 4.6 months (95% CI, 3.7 to 5.4) and everolimus 4.4 months (95% CI, 3.7 to 5.5). However, a subgroup of patients surviving without progression after 6 months was further evaluated and showed a progression-free survival of 15.6 months (95% CI, 11.8 to 19.6 ) with nivolumab and 11.7 months (95% CI, 10.9 to 14.7) with everolimus. According to the authors, this indicates that nivolumab provides a delayed benefit in progression-free survival. Results show that overall survival was improved in patients with lower levels of PD-L1 expression in both the nivolumab and everolimus groups.

Adverse events (AE) occurred in 319 (79%) of participants treated with nivolumab and 349 (88%) of participants treated with everolimus. The most common AE's were fatigue, pruritis, and nausea with nivolumab and fatigue, stomatitis and anemia with everolimus. No treatment related deaths were reported with nivolumab while 2 treatment related deaths were reported with everolimus. This safety profile is consistent with previous reports of nivolumab and documented AE's with everolimus.

The researchers “observed consistently prolonged survival with nivolumab, as compared to everolimus” and reported that this benefit was observed “irrespective of PD-L1 expression”. The authors concluded that study results, specifically median overall survival of 25.0 months with nivolumab, “provide evidence of benefit in patients who have already undergone treatment and have advanced renal-cell carcinoma”.

This study was sponsored by Bristol-Myers Squibb. Collaborative effort from Bristol-Myers Squibb and the authors produced the study design as well as manuscript preparation.

N Engl J Med. 2015 Nov 5;373(19):1803-1813. doi: 10.1056/NEJMoa1510665. Epub 2015 Sep 25.