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https://doi.org/10.1016/j.eururo.2018.12.033

Re: Preliminary Results for Avelumab Plus Axitinib as First-Line Therapy in Patients with Advanced Clear-cell Renal-cell Carcinoma (JAVELIN Renal 100): An Open-label, Dose-finding and Dose-expansion, Phase 1b Trial

Choueiri TK, Larkin J, Oya M, et al

Lancet Oncol 2018;19:451–60

Experts' summary:

Axitinib is a second-generation tyrosine kinase inhibitor (TKI) with a reported objective response rate (ORR) of 32% without any complete responses (CRs) in treatment-naïve metastatic renal cell carcinoma (mRCC) [1]. JAVELIN 100 tested whether the combination of axitinib and the PD-L1 inhibitor avelumab could improve clinical activity in treatment-naïve mRCC with clear cell histology [2]. The study focused on evaluating the safety and tolerability of the combination. Both drugs were given at full doses either with or without a 7-d lead-in period. As a secondary objective, clinical activity was recorded. Overall, the combination boosted efficacy (ORR 58.2%; CR 5.5%) and treatment remained safe and very well tolerated, warranting further development.

Experts' comments:

Checkpoint inhibitors (CPIs) have changed the treatment landscape for mRCC. While TKIs offer a great deal for palliation, CPIs may benefit a subgroup of patients in the long term. The augmentation of both mechanisms of action in one combined treatment regimen has been thought to increase efficacy in mRCC. JAVELIN 100 has reported unprecedented clinical activity, including a 5.5% CR rate at median follow-up of 52 wk. This observation led to the recently presented randomized controlled JAVELIN 101 study, which confirmed the ORR (51%) and CR (3%) rates in an unselected patient population with median follow-up of 10.8 mo [3]. Additional evidence comes from the combination of axitinib and pembrolizumab, which was tested in an early clinical trial. This TKI-CPI combination achieved an ORR of 65% and a CR rate of 8% [4]. In contrast to the previous studies, the median follow-up was 20.4 mo, possibly indicating that more mature data are needed to make a proper judgment on the true CR rate of a given regimen.

The CA209-214 study recently set a new standard of care in treatment-naïve mRCC with intermediate or poor risk [5]. The fraction of patients who achieved a CR was 9%, which improved with longer follow-up to 11% [6]. In this study, the quality of response differed between TKI- and CPI-treated patients (2-yr progression-free survival 60% vs 41%), underscoring the relevance of an immune-mediated response in mRCC.

Taken together, this exciting body of evidence is leading to a paradigm shift in mRCC towards long-term response and cure as the main target for current drug development. Dissecting the target population and offering the optimal combination for an individual patient is the next step in therapy optimization.

Conflicts of interest: Viktor Grünwald reports grants, personal fees, and nonfinancial support from BMS and MSD; personal fees and nonfinancial support from Roche, Novartis, and Ipsen; grants and personal fees from Pfizer and AstraZeneca; and personal fees from Eisai, EUSA Pharma, and Cerulean. Boris Hadaschik reports grants from German Cancer Aid, German Research Foundation, and Profound Medical; grants, personal fees, and nonfinancial support from Janssen; personal fees and nonfinancial support from Astellas, Bayer, BMS, Lightpoint Medical, and Sanofi; and grants and personal fees from Uromed.

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https://doi.org/10.1016/j.eururo.2018.12.018