



Retrospective comparison of the different immune combinations in metastatic renal cell carcinoma

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The advent of immune combinations has recently advanced the treatment landscape in metastatic renal cell carcinoma (mRCC). While tyrosine kinase inhibitors (TKI) dominated the medical treatment in mRCC during the past decade, such as sunitinib and cabozantinib (1), immune combinations received approval for first line treatment, recently. This shift of the treatment paradigm occurred based on the survival benefit that was associated with such therapies in comparison to sunitinib treatment. Today, nivolumab plus ipilimumab (intermediate- and poor-risk patients, only) (2) axitinib + pembrolizumab (all comers) are immune combinations, which reported overall survival (OS) benefit over sunitinib. Other combinations, such as bevacizumab + atezolizumab and axitinib + avelumab, conveyed positive results on efficacy endpoints. However, bevacizumab + atezolizumab did not improve OS and data for the combination of axitinib + avelumab remains immature for a valid conclusion. While axitinib + avelumab or pembrolizumab pushed the objective response rate to 55–59%, their complete response (CR) rate remains in the range of 3–6%, which is distinct from the activity of ipilimumab + nivolumab (42% objective response rate, including 11% CR). Differences in toxicity, health-related quality of life (HR-QoL) and follow-up time exist and are the basis for the current debate on which immune-combination remains the gold standard in first line

treatment in mRCC.

While the treatment landscape in mRCC evolved to a new level of activity with the current treatment options in hands, it lacks direct comparison of the different immune combinations. This leaves physicians and patients without solid evidence about the differential benefit between such combinations and a road map when to prefer one over the other.

Dudani and colleagues (3) used the International Metastatic renal cell carcinoma Database Consortium (IMDC) dataset to address this question in retrospective fashion. Treatment outcomes of first-line ipilimumab and nivolumab (IPI-NIVO) were compared to the combination of checkpoint + vascular endothelial growth factor (VEGF) inhibitors (IOVE).

The major limitation of the analysis is its retrospective nature. Although the IMDC database collects treatment outcome from different institutions on a global level, it is prone to selection bias for a given immune combination as part of the treatment decision process. While known IMDC risk factors remained balanced between IPI-NIVO and IOVE groups, numerical differences existed. Furthermore, unknown predictive factors may exist and impact clinical outcome. As an example, sarcomatoid features defines a group of tumors with an explicit susceptibility to immune combinations.

Although the analysis reports the largest sample size to compare immune combinations so far, the total sample size remains rather small. Given these limitations, efficacy parameters were reported without significant differences between both treatment groups. Interestingly, the objective response rate (ORR) did not favor IOVE, which does not confirm expectations raised from the pivotal trials and may be caused by the heterogeneity of agents used in this group of patients.

Immune-mediated CRs are increasingly recognized as a putative surrogate for long-term benefit and was reported in 2% and 5% for IOVE and IPI-NIVO, respectively. These findings do not suggest major differences between both treatment approaches, although a numerical advantage for IPI-NIVO can be noted. These results are in line with the clinical outcome, which did not show a major difference between IOVE and IPI-NIVO. However, the first-line choice clearly determined the efficacy of the subsequent line, which reported a lower ORR in patients after failure of IOVE (15% vs. 45%).

Can IOVE and IPI-NIVO be interchangeably used in the real world? This question cannot be sufficiently answered with the data in hands today. While comparative data remains limited, the current clinical read-out is limited to early and mid-term outcomes. However, a major denominator in the treatment decision process is most likely determined by long-term outcome and the fraction of patients alive after 5 years or more in the patients journey. Ideally, a proper comparison between both treatment approaches should be performed in order to identify differences in a fair comparison of both strategies. However, given the speed of current development and the competitive landscape it remains unclear whether such an endeavor will succeed. More importantly it is time to develop proper biomarkers, which rationalize the treatment decision in the clinic and maximize treatment benefit for our patients.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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