Should we use combination therapy for all advanced renal cell carcinoma?

The treatment landscape in advanced renal cell carcinoma has changed since 2018 with the development of inhibitors of PD-1 and its ligand PD-L1.

CheckMate 214 was the first phase 3 randomised trial[1–3] to show that a combination of the PD-1 inhibitor nivolumab and the CTLA-4 inhibitor ipilimumab led to a statistically significant improvement in overall survival and quality of life over sunitinib as a first-line treatment. In the initial trial report in 2018,[1] the study met two of the co-primary endpoints of improvement in overall survival and objective response rates in the population at intermediate or poor risk according to the International Metastatic Database Consortium (IMDC) criteria. The updated results with extended follow-up, reported by Robert Motzer and colleagues in *The Lancet Oncology*,[3] show that the benefit of nivolumab and ipilimumab was maintained at longer follow-up, with all three co-primary endpoints (overall survival, objective responses, and progression-free survival) now met in intermediate-risk and poor-risk patients. Moreover, the occurrence of complete responses in some patients and the efficacy reported in selected patient populations, including those with sarcomatoid features,[4] add more evidence to support the combination of nivolumab and ipilimumab as a new first-line standard of care for patients with advanced renal cell carcinoma.[1]

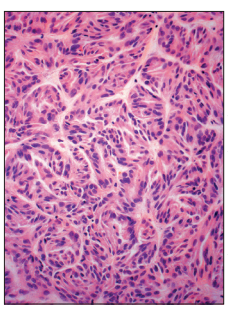
In addition to CheckMate 214, two other randomised phase 3 trials[5,6] have investigated different combinations of PD-1 or PD-L1 inhibitors and angiogenesis inhibitors (immunotherapy and tyrosine-kinase inhibitor combinations) compared with sunitinib. The first trial,[5] JAVELIN Renal 101, showed the superiority of the combination of a PD-L1 inhibitor, avelumab, and a multikinase inhibitor, axitinib, over sunitinib in terms of progression-free survival irrespective of IMDC risk group, although the overall survival data are not yet mature. The second trial,[6] KEYNOTE-426, met the two co-primary endpoints of improved overall survival and progression-free survival with the PD-1 inhibitor pembrolizumab and axitinib versus sunitinib in all-risk prognostic groups. Together, these three studies suggest that combination therapy including a PD-1 or PD-L1 inhibitor should be considered as a first-line standard treatment for patients with advanced renal cell carcinoma.

Previously, another randomised phase 3 trial, IMmotion151,[7] reported that the combination of the angiogenesis inhibitor bevacizumab and the PD-L1 inhibitor atezolizumab was superior to sunitinib in terms of investigator-assessed median progression-free survival. This trial suggests that some additional biological features, including effector T cells, interferon γ, and angiogenesis gene expression signatures, could be used to select patients more responsive to the immunotherapy combinations over tyrosine-kinase inhibitors and vice-versa, but the combination between atezolizumab and bevacizumab was not approved by the regulatory agency (US Food and Drug Administration [FDA] or European Medicines Agency) because of the lack of benefit in overall survival and progression-free survival after central radiological review.

The FDA approval of the three combinations, nivolumab plus ipilimumab (in 2018), avelumab plus axitinib (in 2019), and pembrolizumab plus axitinib (in 2019), opened the door to a shift from monotherapy towards combination therapy for first-line treatment for patients with advanced renal cell carcinoma. Therefore, we consider it useful to focus our attention on several issues.

First, the molecular and metabolic heterogeneity of renal cell carcinoma is well known and the scarcity of predictive biomarkers remains a major issue. Only in the past 5 years, some features, including PD-L1 status, CD8 positivity, an angiogenic gene signature, and several other polymorphisms, have been identified and are moving us towards the identification of a personalised approach.[7]

Second, the main reason for the benefit from the study combination treatments over monotherapy is not completely understood; is the different mechanism of action able to justify a synergistic effect or is the benefit primarily due to an additive effect of the study treatments? Furthermore, most patients with advanced renal cell carcinoma received several treatments in a sequential way, which could consequently modify the



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clinical course of the disease, so the overall survival benefit might partially depend on the subsequent lines of therapy. Practical caveats remain unsolved, including the optimal duration of treatment exposure, the need to continue treatment with both drugs until progressive disease, the timing of the assessment of response, and the criteria used to improve the identification of responses and disease status.

Third, the comparison between the CheckMate 214, JAVELIN Renal 101, and KEYNOTE 426 trials could be done only indirectly and the interpretation of the efficacy between the immunotherapy combinations could be partly confounded; indeed, the patient populations enrolled in the three trials were partially different and the endpoints were similar but not identical. Some key findings need to be highlighted, such as the higher percentage of complete responses with the nivolumab plus ipilimumab combination therapy,[1,3–6] the activity in the immunotherapy and tyrosine-kinase inhibitor combinations irrespective of the risk prognostic group,[5,6] and the time to response being theoretically faster with a treatment combination that includes a tyrosine-kinase inhibitor.[5,6] Therefore, the goal of the treatment and the different safety profiles of these combinations could become key drivers of physicians' choice in clinical practice.

Lastly, we need to identify the best monotherapy to use as a comparator group in randomised trials in this setting. Sunitinib was the most used drug in advanced renal cell carcinoma for a decade, but in 2019 (first results in 2017), CABOSUN, a phase 2 randomised trial,[8] showed that the tyrosine-kinase inhibitor cabozantinib was superior to sunitinib in terms of progression-free survival and response rates in poor-risk or intermediate-risk patients. According to the results of the CABOSUN trial, we cannot consider cabozantinib, which is also approved by the US FDA in poor-risk or intermediate-risk patients, automatically inferior to a combination of immunotherapy drugs. In this regard, some patients might continue to receive monotherapy with a tyrosine-kinase inhibitor as their first-line treatment.

The evolution of this dynamic scenario could change after the release of results of two other clinical trials (CLEAR [NCT02811861] and CheckMate 9ER [NCT03141177]), which are testing other combinations, such as lenvatinib plus pembrolizumab and lenvatinib plus everolimus, and nivolumab plus cabozantinib, respectively.

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Renal cell carcinoma treatment after first-line combinations

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Treatment of metastatic renal cell carcinoma has dramatically changed in the past two decades, moving from cytokine-based immunotherapy, to vascular endothelial growth factor (VEGF) pathway inhibitors, and to combinations of these inhibitors with novel immune checkpoint inhibitors. What was once defined as an "embarassment of riches"[1] has now reached new, unexpected heights.