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.

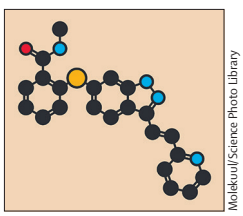
Improvements in overall survival have been mainly achieved by means of sequential treatment, rather than by a single treatment. However, in the past 2 years, two first-line combinations have been approved on the basis of their superior overall survival compared with sunitinib (ipilimumab plus nivolumab and axitinib plus pembrolizumab).[2,3] Nonetheless, efficacious strategies for subsequent treatment lines need validation.

In *The Lancet Oncology*, Ornstein and colleagues[4] report on the results of a multicentre, phase 2 trial of individualised axitinib dose titration in patients in whom an immune-checkpoint-inhibitor-based treatment failed, irrespective of the treatment line in which it had been used.[4] Despite recruiting just 40 patients and not meeting the prespecified threshold for progression-free survival to be significant, the strength of this study is its prospective design, which differentiates it from various retrospective case series published earlier. The question arises as to whether this study is supported by a scientific and molecular rationale; one might argue that it is just an attempt to generate prospective data on an established agent in a new therapeutic setting. According to the results of an elegant paper by Pal and colleagues,[5] renal cell carcinoma biology changes with the ongoing course of the disease, with the number of mutations increasing from first-line to later lines. For example, genetic alterations to the *VHL* tumour suppressor gene, the key genetic hallmark of clear cell renal cell carcinoma, were reported to increase between treatment lines.[5] This finding clearly suggests that angiogenesis, the direct molecular consequence of *VHL* gene alterations, remains key throughout the natural history of renal cell carcinoma. Therefore, axitinib appears to be a reasonable strategy after failure of immune checkpoint inhibitors.

At this point, a second key question arises: why axitinib, and not other VEGF receptor (VEGF-R)-targeting drugs? Axitinib has three theoretical advantages over other anti-angiogenics: its potency and selectivity for the three VEGF-Rs, its safety profile with less off-target adverse events, and the possibility of using individualised dose-titration to exploit its full potential. From preclinical models[6] to randomised controlled, phase 3 studies,[7] the potency of axitinib in suppressing angiogenesis has been well established. Moreover, its selectivity for VEGF-Rs results in a predictable and usually manageable safety profile, meaning it might be better tolerated by patients receiving later lines of therapy, who might be less willing to accept side effects. Dose titration allows for individualisation of treatment, which could lead to increased activity, although not necessarily to increased efficacy.[8]

Reasonable treatment options after failure of axitinib plus immune-checkpoint inhibitor combinations remain purely speculative. None of the patients reported by Ornstein and colleagues[4] had received axitinib in combination with either avelumab or pembrolizumab. In patients in whom such combinations fail, resistance to VEGF-inhibitors might have occurred. However, resistance to VEGF-targeting agents and the corresponding epithelial-to-mesenchymal transition were shown to be temporary;[9] thus, a certain responsiveness to axitinib or to other potent and selective VEGF-Rs inhibitor, such as tivozanib, might be expected in patients in whom combination treatments have failed. Nevertheless, targeting drivers of resistance to anti-VEGF-R therapies (eg, *MET* and *AXL*) appears more promising in this setting, making cabozantinib a sensible drug choice. Similar considerations might also be made for the combination of lenvatinib and everolimus.

What are the options after first-line immune checkpoint inhibitor-based combinations have failed? Should we stop thinking in treatment lines at all? One aspect worthy of academic study is the timing and duration of tyrosine kinase inhibitor treatment within such combinations. Upfront VEGF-R-tyrosine kinase inhibitor-immune checkpoint inhibitor combinations might make sense, because tyrosine kinase inhibitors were shown to modify the immune system, increasing the likelihood of an immune response. However, whether continuous tyrosine kinase inhibitor dosing is necessary is unknown.[10] Withholding axitinib or intermittent dosing in the case of progression could spare the patients relevant toxicities, without necessarily hampering treatment activity.[10] More academic—and less marketing-driven—studies are strongly warranted to answer these key questions and to optimise treatment outcomes for patients with metastatic renal cell carcinoma.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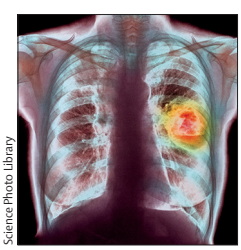
Immune checkpoint inhibitors: a game changer for metastatic non-small-cell lung cancer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Immune checkpoint inhibitors have become pivotal for the treatment of non-small-cell lung cancer (NSCLC). PD-L1 inhibitors as monotherapy are the standard for second-line therapy (atezolizumab or nivolumab, or pembrolizumab when PD-L1 expression is at least 1%), and even for front-line therapy when PD-L1 expression is at least 50% (pembrolizumab). Front-line administration of standard chemotherapy plus pembrolizumab has been shown to increase survival compared with standard chemotherapy alone, regardless of PD-L1 status and in both squamous and non-squamous histologies.[1,2] Thus, in less than 5 years, immune checkpoint inhibitors have taken centre stage in metastatic disease treatment.

The CheckMate 017 and 057 trials[3,4] benefited from fast-track publication because of the magnitude of the results in favour of nivolumab, which was subsequently approved as a second-line (and beyond) treatment. The analysis by Scott J Antonia and colleagues[5] in *The Lancet Oncology* brings new and very interesting mature data on the long-term results of the four trials assessing second-line nivolumab in NSCLC.[3,4,6,7] The main finding of their pooled analysis is that 4-year overall survival was 14% after second-line and subsequent-line nivolumab therapy was started. Additionally, in the trial with the longest follow-up (CheckMate 003),[6] 6-year overall survival was 15%. Notably, Antonia and colleagues' findings are consistent with the long-term effects of pembrolizumab in the KEYNOTE-001 trial (n=550),[8] in which 5-year overall survival was 16% in previously treated patients (n=449) and 23% in treatment-naive patients (n=101).

Put in perspective with historical data in this setting (5-year survival of <5% in stage 4 disease[9]) and the control groups of the CheckMate trials (4-year overall survival of 5%), these results give hope for a long-term plateau in overall survival of around 15%, which is three-times higher than survival values before the immunotherapy era. These findings are a true game changer for patients diagnosed with metastatic NSCLC.

Objective response at 6 months appeared to be a surrogate marker for predicting overall survival in the pooled analysis of the CheckMate trials: 4-year overall survival was 58% for patients with objective response, compared with 4% for those who had progression. This finding remained consistent when calculating overall survival from inclusion, time of response, or time of progression after best overall response. Furthermore, and similar to the long-term results of KEYNOTE-001,[8] a positive PD-L1 status (PD-L1 expressed in at least 1% of tumour cells in immunohistochemistry) was a prognostic factor, given that 4-year overall survival almost doubled in PD-L1-positive compared with PD-L1-negative patients.

Finally, the study by Antonia and colleagues provides interesting data on late toxicity. Although the majority of treatment-related adverse events