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Commentary

Enhancing Antitumor Immunity with Antiangiogenic Therapy: A Clinical Model in Renal Cell Carcinoma?

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Disclosures of potential conflicts of interest may be found at the end of this article.

Therapeutic options for advanced renal cell carcinoma (RCC) have expanded significantly in recent years and continue to evolve at a rapid pace. Since 2005, the Food and Drug Administration (FDA) has approved a dozen systemic therapies targeting four broad mechanistic pathways—angiogenesis, mechanistic target of rapamycin, immune checkpoint proteins, and cytokine signaling [1]. Although these contemporary therapies have improved clinical outcomes for many patients with advanced RCC, most patients still do not derive optimal long-term benefit from any one specific therapy, and metastatic RCC remains a lethal diagnosis.

New to the therapeutic landscape are combinations of antiangiogenic therapies plus immune checkpoint inhibitors poised to transform the treatment paradigm in advanced RCC. Preclinical studies have suggested that abnormal tumor vasculature promotes immunosuppression in the tumor microenvironment, an effect that may be reversed with antiangiogenic therapies targeting vascular endothelial growth factor (VEGF) signaling [2]. Furthermore, antiangiogenic therapies and immune checkpoint inhibitors have independently demonstrated clinical efficacy as monotherapies in advanced RCC [3–8]. Combining these treatments in the frontline setting was therefore a rational next step. Initial phase I studies showed encouraging signs of clinical activity with such combinations, including objective response rates (ORRs) ranging from 40% with bevacizumab plus atezolizumab to 73% with axitinib plus pembrolizumab [9, 10] These preliminary data led to the launch of five large randomized phase III studies to evaluate various combinations of VEGF or VEGF receptor (VEGFR) inhibitors plus immune checkpoint inhibitors targeting either programmed cell death protein 1 (PD-1) or its ligand PD-L1: bevacizumab plus atezolizumab, axitinib plus avelumab, axitinib plus pembrolizumab, lenvatinib plus pembrolizumab, and cabozantinib plus nivolumab [11].

Data from the phase III studies of bevacizumab plus atezolizumab (IMmotion151) [12], axitinib plus avelumab (JAVELIN Renal 101) [13], and axitinib plus pembrolizumab (KEYNOTE-426) [14] have been presented to date. IMmotion151 demonstrated improved investigator-assessed progression-free survival (PFS) with bevacizumab plus atezolizumab compared with sunitinib in patients with PD-L1+ tumors (median, 11.2 vs. 7.7 months; hazard ratio [HR], 0.74; 95% confidence interval [CI], 0.57–0.96; $p = .02$) and in the intention-to-treat (ITT) population (median, 11.2 vs. 8.4 months; HR, 0.83; 95% CI, 0.70–0.97) [12]. Benefit from the combination was seen across prognostic risk groups. PD-L1+ patients had ORRs of 43% versus 35% and complete response (CR) rates of 9% versus 4%, both favoring bevacizumab plus atezolizumab. In the ITT population, bevacizumab plus atezolizumab resulted in an ORR of 37% and 5% CR, compared with an ORR of 33% and CR of 2% with sunitinib. Grade ≥3 treatment-related adverse events (TRAEs) occurred in 40% of patients treated with bevacizumab plus atezolizumab versus 54% of those receiving sunitinib. Similarly, JAVELIN Renal 101 showed improved PFS with the combination of axitinib plus avelumab compared with sunitinib in patients with PD-L1+ tumors (median, 13.8 vs 7.2 months; HR, 0.61; 95% CI, 0.47–0.79; $p < .001$) and in the ITT population (median, 13.8 vs. 8.4 months; HR, 0.69; 95% CI, 0.56–0.84; $p < .001$) [13]. PD-L1+ patients has ORRs of 55.2% versus 25.5%, with CR rates of 4.4% versus 2.1%, both in favor of axitinib plus avelumab. In the overall population, axitinib plus avelumab resulted in an ORR of 51.4% and CR of 3.4%, compared with ORR of 25.7% and CR of 1.8% with sunitinib. The frequencies of grade ≥3 TRAEs were similar for axitinib plus avelumab (71.2%) versus sunitinib (71.5%). Overall survival (OS) data remain immature for both IMmotion151 and JAVELIN Renal 101, although preliminary results from both studies suggest promising trends toward survival benefit with combination therapies.

Most recently, data from KEYNOTE-426 showed that the combination of axitinib plus pembrolizumab achieved both coprimary endpoints of improved OS (HR, 0.53; 95% CI, 0.38–0.74; $p < .0001$) and PFS (median, 15.1 vs. 11.1 months; HR, 0.69; 95% CI, 0.57–0.84; $p < .001$) compared with sunitinib in the ITT population [14]. Importantly, KEYNOTE-426 was the first of the combination studies to demonstrate an OS benefit over sunitinib. Objective response was also significantly improved with axitinib plus pembrolizumab compared with sunitinib (59.3% vs. 35.7%; $p < .0001$). Complete response was seen in 5.8% versus 1.9% of patients, favoring

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Treatment Setting		Preferred Therapy	Alternative Therapies to Consider in Certain Circumstances
First-Line Therapy	Favorable risk	Axitinib + Pembrolizumab	Sunitinib[a] Pazopanib[a] Cabozantinib[a]
	Intermediate/Poor risk	Nivolumab + Ipilimumab Axitinib + Pembrolizumab	Cabozantinib[a] Sunitinib[a] Pazopanib[a]
Second-Line Therapy	Prior Nivolumab + Ipilimumab	Preferred therapy is unclear May consider clinical trial	Cabozantinib Axitinib Lenvatinib + Everolimus
	Prior Axitinib + Pembrolizumab		Cabozantinib Lenvatinib + Everolimus Nivolumab + Ipilimumab

Figure 1. Systemic treatments to consider for first- and second-line therapy for advanced renal cell carcinoma (RCC). Due to the rapidly changing standard-of-care systemic treatment landscape for advanced RCC, this proposed treatment algorithm may be subject to change based on the expected FDA review of axitinib + avelumab and results of the ongoing phase III studies involving lenvatinib + pembrolizumab (CLEAR) and cabozantinib + nivolumab (CheckMate 9ER).
[a]If immunotherapy is contraindicated due to comorbidities.

axitinib plus pembrolizumab. The superiority of the axitinib plus pembrolizumab combination extended across risk groups and PD-L1 expression status. The frequencies of grade ≥3 TRAEs were similar with axitinib plus pembrolizumab (62.9%) versus sunitinib (58.1%). Although longer-term follow-up and detailed analyses of the ongoing phase III studies will be helpful in assessing axitinib plus pembrolizumab in the treatment algorithm for advanced RCC, the results from KEYNOTE-426 led to the FDA approval of the combination as first-line therapy for advanced RCC in April 2019.

How will the combinations of antiangiogenic therapies plus immune checkpoint inhibitors stack up against the dual checkpoint immunotherapy combination of nivolumab plus ipilimumab? The latter combination has gained approval from the FDA and European Medicines Agency for frontline treatment of patients with intermediate- or poor-risk advanced RCC based on improved OS (HR, 0.66; 95% CI, 0.54–0.80; $p < .0001$) compared with sunitinib [15, 16]. Although nivolumab plus ipilimumab was associated with an ORR of 42% and an impressive CR rate of 11.3% in intermediate- or poor-risk patients, immune-related TRAEs led to high-dose corticosteroid use in 27.8% of patients assigned to the combination [15]. Therefore, details regarding the long-term survival outcomes and adverse event profiles associated with the various immune checkpoint inhibitor-based combinations will be critical in evaluating their place in the RCC treatment algorithm. One potential advantage of the nivolumab plus ipilimumab combination is the existence of more robust data on the durability of response, in both RCC and melanoma [17, 18]. Furthermore, because the dual immune checkpoint inhibitor combination allows for use of nivolumab monotherapy long-term after the initial four doses of combination therapy, long-term safety and toxicity data may be superior to the antiangiogenic therapy plus immune checkpoint inhibitor combinations that require continued use of both medications. Future clinical studies comparing antiangiogenic therapy plus immune checkpoint inhibitor combinations versus nivolumab plus ipilimumab may shed light on the added value of VEGF/VEGFR-targeted therapies. In the meantime, based on available evidence to date, one potential treatment algorithm is shown in Figure 1.

Although the enhanced efficacy of antiangiogenic therapy plus immune checkpoint inhibitor combinations may simply reflect patient-to-patient variability in response to each individual agent [19], one exciting possibility is that the combination results in synergistic antitumor activity. Such synergy may result from combining two effective therapies in a disease known to have diverse intratumor genetic heterogeneity [20]. More intriguing, however, is the possibility that antiangiogenic therapy may provide beneficial immunomodulatory effects that augment the efficacy of immune checkpoint inhibition. Following the initial successes of checkpoint inhibitors across a variety of cancer types, a multitude of clinical trials have evaluated combination therapies with the goal of enhancing antitumor activity. To date, the only combination to gain regulatory approval is the dual immune checkpoint inhibitor combination of nivolumab plus ipilimumab [15, 18]. Unfortunately, numerous other therapies have failed to show enhanced clinical activity when combined with currently approved immune checkpoint inhibitors, most notably the combination of the indoleamine 2,-3-dioxygenase inhibitor epacadostat plus pembrolizumab that initially showed promising results in phase I/II studies [21]. The angiogenesis and immune checkpoint inhibitor combinations in RCC have thus far demonstrated the most promising signs of synergistic activity, consistent with preclinical data suggesting that angiogenic signaling may modulate anticancer immune trafficking and activity within the tumor microenvironment [2]. Correlative studies from a phase I trial of bevacizumab plus atezolizumab have also demonstrated increases in intratumoral CD8+ T lymphocytes and number of unique T cell clones with combination therapy [9], suggesting that antiangiogenic therapy may facilitate antitumor immunity in patients with RCC.

Correlative studies will be vital to better our understanding of the interactions between VEGF/VEGFR-targeted therapy and immune checkpoint inhibition. Comprehensive whole-transcriptome profiling studies via RNA sequencing in pre-treatment tumor specimens have already been carried out as part of the phase II and III studies involving bevacizumab plus atezolizumab, revealing distinct molecular subtypes that may predict for response to combination therapy [22, 23]. Additional studies of pre-, on-, and post-treatment tumor and blood samples may further dissect the immunomodulatory effects of

antiangiogenic therapies and provide insight into novel therapeutic targets that could further improve clinical outcomes.

If longer-term follow-up of the phase III studies in RCC shows improved CR rates, deep partial responses, and durable responses with antiangiogenic therapy plus immune checkpoint inhibitor combinations, there may be vast-ranging implications for the treatment of other advanced solid tumors. All ongoing phase III combination studies in RCC are evaluating patients with clear cell histology, which constitutes approximately 90% of metastatic kidney cancers and is characterized by dysfunctional angiogenesis and high degrees of antitumor immunogenicity. Whether the enhanced efficacy in combining antiangiogenic therapy and immunotherapy is specific to the innate biology of clear cell RCC is an important question. Angiogenesis and immune checkpoint inhibitor combinations are being evaluated in small single-arm studies of patients with non-clear cell RCC and have demonstrated evidence of antitumor activity [24].

Finally, combination regimens targeting angiogenesis and immune checkpoint proteins have also shown evidence of activity in a number of other advanced malignancies including nonsquamous non-small cell lung cancer [25], hepatocellular carcinoma [26], endometrial cancer [27], head and neck cancer [28], and anaplastic thyroid cancer [29], providing some further support for the tantalizing possibility that the combination may lead to at least additive antitumor immunity across multiple types of solid tumors. While we eagerly await additional follow-up from the ongoing phase III studies in RCC, the promising results thus far provide hope that combination therapies targeting angiogenesis and immune checkpoints will improve outcomes for patients with kidney cancer and perhaps patients with other advanced solid tumors.

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