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Commentary

Vorolanib and everolimus: Lenvatinib and everolimus part deux, or something new?

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The landscape of systemic treatment for metastatic clear-cell renal cell carcinoma (mRCC) has recently undergone considerable change. In the wake of JAVELIN Renal 101, CheckMate-214, and KEYNOTE-426, frontline strategies have now fully embraced multimodal combination therapy in the form of programmed death-1/programmed death ligand-1 (PD-1/PD-L1) inhibition with either a tyrosine-kinase inhibitor (TKI) or a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor. However, multimodal combination regimens have yet to achieve commensurate success beyond the first line setting of mRCC.

In a Phase I dose-finding study, Sheng et al. assess the safety, tolerability, and efficacy of vorolanib when used in conjunction with everolimus for the treatment of mRCC patients who have progressed through at least one previous line of TKI therapy [1]. Vorolanib is novel, highly potent vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) TKI with activity against Flt3 and c-Kit that does not exhibit an inhibitory effect on RET or AMPK. A staple following first-line therapy for over a decade, everolimus is an inhibitor of mammalian target of rapamycin (mTOR), which is a component of an intracellular signaling pathway regulating cell growth and proliferation, and metabolism [2]. In the target dose cohort, vorolanib plus everolimus was generally well tolerated and all 14 of 22 patients who experienced grade 3 or higher treatment-related toxicity were effectively managed with dose adjustments or supportive medication [1].

Due in large part to their mutually exclusive pathways for down-regulating tumor angiogenesis, the combination of mTOR-targeted and VEGF-targeted agents has been an area of active mRCC research for more than a decade. Unfortunately, early enthusiasm was tempered by four negative frontline phase II and phase III trials, all of which demonstrated increased toxicity without significantly improving efficacy versus their comparator arms [3–6]. These lackluster results underscored the need to address tumor resistance mechanisms that attenuate multimodal combination therapy.

The first and only combination of mTOR-targeted and VEGF-targeted agents to achieve a significant clinical benefit was everolimus plus lenvatinib in patients who progressed after first line TKI therapy. Lenvatinib is a multitarget VEGFR-TKI with inhibitory activity against fibroblast growth factor receptors (FGFR), PDGFR, RET, and KIT. At that time, clinical practice guidelines in the second-line setting favored everolimus, axitinib, cabozantinib, or nivolumab. In their Phase II trial of lenvatinib plus everlomius versus lenvatinib versus everolimus, Motzer et al. demonstrated that lenvatinib plus everlomius dramatically prolonged progression-free survival and overall survival compared with everolimus monotherapy [7]. Lenvatinib's heightened efficacy is owed in part to its inhibition of FGFR, which has been shown to play a crucial role in metastasis and may account for tumor resistance to VEGF-targeted therapy [8]. The FDA subsequently awarded breakthrough therapy designation to lenvatinib in combination with everolimus for the treatment of advanced renal cell carcinoma following one prior TKI therapy.

However, one of the challenges faced by practitioners was where to position lenvatinib plus everolimus in their treatment paradigm. Most consider cabozantinib and nivolumab's level of evidence to be higher because they were approved on the basis of overall survival benefit from randomized phase III trials that involved many more patients. Moreover, many oncologists favored nivolumab for patients who suffered from treatment-related toxicity as grade 3 or 4 adverse events occurred in 19% of nivolumab compared to 68% of cabozantinib and 71% of lenvatinib plus everolimus. Although preferred to everolimus alone, lenvatinib plus everolimus has struggled to receive much attention prior to the fourth-line setting. The ultimate fate of lenvatinib plus everolimus rests on the phase III CLEAR trial (NCT02811861), which juxtaposes this regimen against lenvatinib plus pembrolizumab and sunitinib. However, with very compelling data for lenvatinib plus pembrolizumab in the refractory setting (and with the aforementioned studies supporting a TKI plus PD-1/PD-L1 combination), it is likely this will emerge as the victor [9].

As evidenced by lenvatinib plus everolimus, the combination of mTOR-targeted and VEGF-targeted agents is a viable treatment modality for mRCC. However, vorolanib plus everolimus faces a similar uphill battle in terms of clinical application. Perhaps the only way forward is to harness the small but not insignificant population of patients with mTOR pathway alterations. Data suggest that alterations in *MTOR, TSC1* and *TSC2* may confer sensitivity to everolimus

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[10]. Focusing on a biomarker-driven population may be the only way to claim territory in a crowded landscape of therapies.

Declaration of Competing Interest

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