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Commentary

The Trouble with Doublets: Making Sense of Combination Strategies in Advanced Kidney Cancer

Primo N. Lara, Jr.[a,*] and Sumanta K. Pal[b]
[a]*University of California Davis Comprehensive Cancer Center, Sacramento, CA, USA*
[b]*City of Hope Comprehensive Cancer Center, Duarte, CA, USA*

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On November 10, 2020, the topline results of the Phase III CLEAR/Keynote 581 trial were announced in a press release [1]. In that trial, the combination of pembrolizumab, a PD-1 immune checkpoint inhibitor, plus lenvantinib, a multi-targeted receptor tyrosine kinase inhibitor (TKI), as well as the combination of lenvantinib plus the mTOR inhibitor everolimus, were evaluated versus sunitinib for the first-line treatment of patients with metastatic renal cell carcinoma (mRCC). Both combinations were reported to demonstrate enhanced efficacy when compared to sunitinib. The pembrolizumab/lenvantinib arm met the trial's primary endpoint of significantly prolonging progression-free survival (PFS). In addition, there was statistically significant improvement in the secondary endpoints of overall survival (OS) and response rate (ORR). The lenvantinib/everolimus doublet also met the trial's primary endpoint of PFS and the secondary endpoint of ORR.

These results came on the heels of the Checkmate 9ER topline data which were reported at the virtual European Society of Medical Oncology Annual Meeting in September 2020 [2]. In that trial, the combination of the PD-1 inhibitor nivolumab with the multi-targeted TKI cabozantinib also showed superiority over sunitinib by doubling PFS, doubling the ORR, and significantly improving OS in patients with mRCC.

These new immunotherapy-based doublets now join a growing list of highly active combination regimens in the frontline mRCC setting, including pembrolizumab/axitinib, avelumab/axitinib, and nivolumab/ipilimumab [3, 4]. Most of these combinations appear to have activity across all pre-defined prognostic risk categories, with the exception of nivolumab/ipilimumab which is only approved for intermediate and poor risk patients.

The availability of new systemic therapy options is reflective of the incredible success and increased efficiencies of recent drug development efforts in mRCC. But one must also ask: are these results really an advance? Or are these recently reported positive phase III trials simply a reflection of a de-risked "me-too" drug development strategy that has proven effective time and again?

In some respects, we have seen this movie before. When VEGF-targeted TKIs were shown to have remarkable single agent activity in mRCC begin-

*Correspondence to: Primo N. Lara Jr, University of California Davis Comprehensive Cancer Center, Sacramento, CA, USA. E-mail: pnlara@ucdavis.edu.

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ning with sorafenib, there was an expected stream of "me-too" TKIs that followed. Granted, each new TKI had notable differences in its spectrum of molecular targets; but by-and-large, the principal common target was VEGFR. Clinical activity and toxicity profiles also varied across the many TKIs, but after years of clinical trials, one can safely conclude that there have really been no spectacular leaps in survival or cure rates seen with newer generation TKIs.

It now appears that the same "me-too" process that had dominated TKI drug development is unfolding with immune checkpoint inhibitor-based doublets, most of which now include a TKI partner. (Only nivolumab/ipilimumab remains the "all immunotherapy" doublet within its more limited intermediate/poor risk indication). The same clinical issues that confounded the TKI era will again be raised with modern immunotherapy doublets. Which doublet is best for the patient sitting in front of you? Is there a predictive biomarker that can select who receives what? What is the optimal sequence of therapies? What is the optimal duration of therapy? What are the mechanisms of resistance? What are the economic considerations? The list of questions is longer than our collective patience.

In our view, the recent lessons of mRCC drug development could not be ignored. In order for the next major advance to be achieved, we must look beyond "me-too" drug development. Instead, we should collectively leverage the highly efficient clinical trials infrastructure built in the last decade to diversify the therapeutic armamentarium beyond TKIs and PD1/PDL1 targeted therapies. The ongoing development of new agents that target HIF, adenosine, and cancer metabolism is particularly promising. How these new agents would be accommodated into the universe of frontline doublets will require robust preclinical modeling and carefully designed clinical trials that include relevant translational studies. In the meantime, we simply have to use our best clinical judgment, individualizing therapy as appropriate until more precise and transformative evidence becomes available.

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CONFLICT OF INTEREST

PNL and SKP have no conflicts of interest to report.

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