ABOUT THE COVER
A graphical illustration of tivozanib molecule, a selective potent VEGFR TKI exerting its actions by selectively inhibiting the phosphorylation of vascular endothelial growth factor receptors: VEGFR-1, VEGFR-2 and VEGFR-3. Tivozanib suppresses tumor angiogenesis by being selectively inhibitory against VEGFRs in Renal Cell Carcinoma.

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KCJ Editor's Memo

Novel Drug Combinations Gain Traction Across Therapeutic Landscape


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More than a year since the COVID-19 crisis upended the face of health care in the United States, its impact on cancer clinical trials has continuously been seismic. Right now, it seems likely to be a while before we enroll newly designed studies and start gathering trial data at the rate they once were. While there is only a limited capacity for bringing in new trials or launching new therapies into clinical practice, the oncology community certainly moved quickly with a concerted effort to get the halted cancer trials back up and running. This year's ASCO Genitourinary Cancers Symposium sessions offered tantalizing preview of clinical breakthroughs and practice-changing research updates in GU cancers landscape despite the pandemic's impact on clinical trials space worldwide.

As highlighted in the recent *Kidney Cancer Journal* online edition, GU ASCO21 abstracts provided snapshots of the most important trends, foremost research and key strategies from latest clinical trials that impact the current standard of care in renal cancer. Certainly, looming on the horizon are the new IO/IO and IO/TKI combinations, which generated a lot of buzz at this year's ASCO in the renal cancer therapeutics space. Least to say, while targeted agents and immune monotherapies are still moving the needle to some extent, combination regimens comprised of IO/IO, IO/TKI, or other molecularly targeted agents are gaining momentum in evolving RCC landscape.

Let's have a quick snapshot of the latest data from the GU21 sessions. In the pivotal phase 3 CLEAR study (KEYNOTE-581), lenvatinib plus pembrolizumab demonstrated statistically significant and clinically meaningful improvements in progression-free survival, overall survival and objective response rate versus sunitinib, supporting the regimen as a potential first-line treatment for advanced RCC. Also, improvement in ORR and PFS, but not OS was observed for lenvatinib at 2 different starting doses in combination with everolimus vs sunitinib. Other related abstract presented quality of life outcome data from a phase II trial of lenvatinib plus everolimus in patients with RCC. Investigation by

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Choueiri and colleagues was the first to report efficacy of combining the novel HIF-2alpha inhibitor plus cabozantinib (a VEGF TKI) in 118 patients with advanced clear-cell RCC. Belzutifan in combination with cabozantinib demonstrated promising antitumor activity and better tolerability in previously treated patients with metastatic ccRCC. CheckMate 9ER (NCT03141177), a phase III open-label trial has shown that nivolumab + cabozantinib demonstrated statistically significant HRQoL benefits and superior efficacy versus sunitinib. Also, nivolumab + cabozantinib demonstrated improved efficacy and prolonged survival vs sunitinib in previously untreated aRCC patients regardless of sarcomatoid status. In a phase II SWOG 1500 study by Pal and colleagues that put cabozantinib, crizotinib, or dacomitinib to the test, the small molecule inhibitor cabozantinib was found most effective in treating 180 patients with metastatic papillary RCC following progression. The exploratory analysis by Plimack and colleagues provide an update of phase III KEYNOTE-426 study which demonstrates that a significant proportion of patients in the pembrolizumab and axitinib arm were able to complete 2 years of pembrolizumab with ongoing clinical benefit. In previous reports of KEYNOTE-426, investigators showed that pembrolizumab plus axitinib prolonged OS and PFS vs sunitinib in patients with treatment-naive advanced RCC.

Emerging data from these trials will position such IO/IO or IO/TKI combination regimens as the new standards of care for patients with renal cell carcinoma. There were several useful additions to the repertoire of currently approved therapies, which should prompt further conversations. As oncologists gear up to gauge the potency of newly available combination regimens in a real-world perspective, significant challenges remain in regard to management of overlapping toxicities, while maintaining quality of life in patients. Ultimately, the rationale for optimal treatment selection for a given combination regimen depends on multi-factorial elements including safety/efficacy, tolerability, cancer progression, comorbidities, drugs cost etc.

This edition of *Kidney Cancer Journal* provides a stimulating roundtable discussion which I chaired, participated by expert panelists Drs. Brian I Rini and Thomas E. Hutson. This discussion shed light into the robust safety/tolerability portfolio of VEGF-TKIs especially tivozanib which could potentially carve out a space within the area of unmet need : third- or fourth-line therapy for heavily pretreated RCC population. The discussion also integrated new concepts emerging from the phase-3 TIVO-3 trial and analyze the potential impact of novel data. On the heels of the recent US FDA approval of tivozanib (Fotivda) in the relapsed/refractory RCC setting based on data from phase 3 TIVO-3 trial, tivozanib is now being investigated in combination with the PD-1 inhibitor nivolumab (Opdivo) in the phase 3 TiNivo-2 trial in patients with relapsed/refractory RCC. A case study by Russo's team in this edition describes the cytoreductive partial nephrectomy (cPN) approach in a patient with metastatic disease in the context of a small renal mass and pre-existing chronic kidney disease and discusses a framework for patient selection. A review article by Rathmell and colleagues summarizes how glycogen, lipid, and cholesterol metabolism which has long been recognized as a differentiating feature of ccRCC play key roles in ccRCC tumor growth. This review also provides key insights about therapeutic potential of targeting bioenergetic metabolism pathways.

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