Newsworthy, late-breaking information from Web-based sources, professional societies, and government agencies

Latest Outcomes from the Phase 3 JAVELIN Renal 101 Trial (N = 886; NCT02684006) were Published.

Biomarker analyses of baseline tumor samples from the phase 3 JAVELIN Renal 101 trial (NCT02684006) demonstrated that first-line avelumab + axitinib versus sunitinib significantly prolonged progression-free survival (PFS) in advanced renal cell carcinoma (aRCC). In this retrospective analysis of the large (n = 886), controlled, exploratory clinical biomarker dataset, authors have provided evidence to confirm the immunomodulatory role of anti-angiogenic therapy, defined molecular features that differentiate therapy-specific outcomes in first-line aRCC and highlighted previously unappreciated biologically and clinically significant determinants of PFS benefit with an ICI + VEGFR TKI combination versus VEGFR TKI alone according to the results published in *Nature Medicine*.

The investigators in this study identified important biological features associated with differential PFS between the treatment arms, including new immunomodulatory and angiogenesis gene expression signatures (GESs), previously undescribed mutational profiles and their corresponding GESs, and several HLA types. Similar to findings in KEYNOTE-426 (pembrolizumab + axitinib versus sunitinib), these observations suggest that PD-L1 expression (on TCs or ICs) may have limited positive-predictive value in RCC and are in contrast with findings from the CheckMate 214 (ipilimumab + nivolumab versus sunitinib) and IMmotion 150 (atezolizumab + bevacizumab vs sunitinib) trials. These findings provide insight into the determinants of response to combined PD-1/PD-L1 and angiogenic pathway inhibition and may aid in the development of strategies for improved patient care in aRCC. This research outcome may inform personalized therapeutic strategies for patients with aRCC and other tumor types.

Reference: Motzer, R.J., Robbins, P.B., Powles, T. et al. Avelumab plus axitinib versus sunitinib in advanced renal cell carcinoma: biomarker analysis of the phase 3 JAVELIN Renal 101 trial. Nature Medicine (2020). Published online. https://doi.org/10.1038/s41591-020-1044-8

AVEO Oncology Announces FDA Acceptance for Filing of a New Drug Application for Tivozanib as a Treatment of Relapsed or Refractory Renal Cell Carcinoma

BOSTON - AVEO Oncology recently announced that the US FDA accepted for filing its New Drug Application (NDA) seeking approval for tivozanib, the Company's next-generation VEGFR-TKI, as a treatment for relapsed or refractory renal cell carcinoma (RCC).

"The acceptance of our NDA filing marks yet another important milestone for AVEO, as we pursue our goal of providing RCC patients whose disease has relapsed or become refractory to multiple lines of therapy with a meaningful new treatment option," said Michael Bailey, president and chief executive officer. "We look forward to working closely with the FDA over the coming months during their review of our application. In parallel, we continue to focus on commercial-readiness to ensure we are well positioned to support the potential launch of tivozanib, subject to approval."

The NDA submission is based on AVEO's pivotal Phase 3 study, TIVO-3, comparing tivozanib to sorafenib in 3rd and 4th line RCC, including results recently presented at the American Society of Clinical Oncology 2020 Virtual Scientific Program. As previously announced, the TIVO-3 trial met the primary endpoint of progression free survival (PFS) (HR=0.73; p=0.02) and the secondary endpoint of overall response rate (ORR) (18% vs. 8%; p=0.02). The final OS hazard ratio (HR), which assesses the overall relative risk of death, was 0.97 (95% CI: 0.75-1.25; p=0.82), favoring tivozanib and improving from the previously reported interim HR of 0.99. Updated median OS, representing a single point in time in the OS curve, was 16.4 months for tivozanib (95% CI: 13.4-22.2) and 19.2 months for sorafenib (95% CI: 15.0-24.2). These OS HR results are similar to those of prior VEGFR TKI vs. VEGFR TKI studies in RCC. The application is also supported by three additional trials, including an active comparator-controlled Phase 3 study, TIVO-1, comparing tivozanib to sorafenib in first line RCC, and two Phase 2 studies, Study 902, the open-label, crossover clinical study of tivozanib for patients who progressed on sorafenib in TIVO-1, as well as placebo-controlled Study 201 in first line RCC. TIVO-3 provides the first positive superiority study to help guide this important treatment decision and, furthermore, offers this highly refractory patient population a favorable tolerability profile as indicated by fewer dose reductions, interruptions and discontinuations over a less selective VEGFR TKI in sorafenib." Said Dr. Sumanta Pal, MD, co-director, Kidney Cancer Program, at City of Hope Comprehensive Cancer Center.

19th Annual Meeting of the IKCS 2020

The 19th annual meeting of the International Kidney Cancer Symposium (IKCS 2020) organized by Kidney Cancer Association (KCA) is scheduled on November 6th and 7th virtually. This annual event is an opportunity for physicians, researchers, academics, and industry professionals from across the globe to join together and exchange ideas which will direct the future of kidney cancer research and treatment in the ultimate pursuit of a cure. The hot topics include (i) immunotherapy and emerging therapies for rcc discussion and round table, (ii) metabolism as a target for rcc discussion, (iii) multimodality therapy for metastatic rcc and an international considerations panel, (iv) non-clear cell trial design round table, (v) health disparities and crisis management: lessons from covid-19 (vi) the woodfire tumor board. Registration and full details on the agenda is available online through the Association's website, kcameetings.org/ikcs. Submission deadline is September 18, 2020 at 11:59 p.m. CST. All accepted abstracts will be published in our Kidney Cancer Journal.

The 2020 ASTRO Annual Meeting

The 2020 ASTRO Annual Meeting has transitioned from a live meeting to an enhanced virtual educational experience.

The meeting will include all of the programming you are accustomed to, only this year it will be in an interactive online format including a robust program of educational and scientific sessions, live SA-CME opportunities, a poster hall with narration from poster presenters, and a virtual Exhibit Hall where you can visit booths to learn and connect with industry colleagues. The meeting opens on October 25 and will be available for 30 days to ensure you have access to all the presentations and materials. This year's Annual Meeting will be uniquely redesigned to ensure that attendees from around the globe continue to access timely scientific and education session. The PRO and ARRO programs will provide curated content addressing issues specific to community practitioners and residents.

Liquid Biopsy Shows High Accuracy in Detecting Early-Stage Renal Cell Carcinoma

A novel plasma DNA assay has shown remarkable accuracy in identifying patients with renal cell carcinoma (RCC) across all stages of disease, making it easier to detect at early-stage, according to the recent report published in Nature Medicine. If validated, this assay could potentially be used initially as a screening test for people who have a family history of kidney cancer or who previously had kidney cancer. This is especially very important as currently, no FDA-approved or recommended screening method is available for the early detection of RCC in the general population.

Of all extracranial tumors, RCC sheds the least amount of cell-free DNA (cfDNA) so cfDNA-based methods alone are insufficient for detecting RCC. Therefore, Cell-free methylated DNA immunoprecipitation and high-throughput sequencing (cfMeDIP-seq), could be potentially efficient in identifying RCC. The investigators in this study used a cfMeDIP-seq approach on plasma and urine cfDNA to detect RCC, which was the first such application of cfMeDIP-seq on urine cfDNA for cancer detection and demonstrated for the first time that this assay can accurately detect RCC by measuring urine cfDNA

Testing was performed on 148 samples, including 99 from cases of stage I to IV RCC, 21 samples of stage IV urothelial bladder cancer, and 28 samples from healthy, cancer-free controls. Across the training test sets, RCC samples had a higher median methylation score than control samples and had a mean area under the receiver operating characteristic (AUROC) curve of 0.990 (95% CI, 0.985-0.995). Among urine cfDNA samples, the mean AUROC for patients with RCC compared with healthy controls was 0.858 (95% CI, 0.831-0.885).

The authors noted that following further validation, this screening method, alone or in combination with imaging, could transform clinical management by enabling early detection of RCC and reducing unnecessary kidney biopsies and nephrectomies.

Reference: Nuzzo PV, Berchuck JE, Korthauer K, et al. Detection of renal cell carcinoma using plasma and urine cell-free DNA methylomes. *Nature Med*. Published online June 22, 2020. doi:10.1038/s41591-020-0933-1

EDITOR'S MEMO *(continued from Page 66)*

It is exciting to see the promising results from KEYNOTE-426, KEYNOTE-146, COSMIC-313 and PDIGREE that highlighted optimal strategies for combining and sequencing treatment modalities of targeted and immunotherapies. The initial results of the open-label phase 2 study of MK-6482 that targets hypoxia inducible factor signaling has opened up an avenue of a new class of therapy for treatment of VHL-associated ccRCC. Some other hot topics especially new approaches exploiting PARP inhibitors, glutaminase inhibitors, newer personalized medicine around immunotherapies, and new tyrosine kinase inhibitor strategies were also presented in ASCO20 plenary sessions.

Despite revolutionary approaches in the RCC treatment, it is apparent that intra-tumoral heterogeneity poses a significant problem for cancer management. Precision oncology approaches harnessing knowledge of heterogeneous tumor is crucial to tailor those therapies to ultimately target and improve prognosis and outcomes for patients. The article in this issue by Payal Kapur and James Brugarolas *et al* present an intriguing molecular genetic and morphologic evolutionary model especially focusing on prototypical model of tumor heterogeneity in renal cell carcinoma. This systematic and comprehensive ontology that captures the breath of ccRCC morphologies has profound implications both for understanding the biology of tumor progression, and for the ability to stratify patients in the clinic. Undoubtedly, this knowledge sets a paradigm for de-convoluting phenotypic complexity and establishes a comprehensive morphologic ontology of ccRCC. The other article by Ritesh Kotecha dicusses the mechanistic insights into the potential mechanisms underlying the counter-intuitive phenomenon known as obesity paradox in clear cell renal cell carcinoma. Emerging trends discussed in this article highlight that differences in the tumour microenvironment could hold the key to apparent survival advantage of obese patients with clear cell RCC versus patients at a normal weight and also emphasize such studies merit careful consideration for designing clinical trials in the future. In the *Letter to the Editor* column, Nirmish Singla and Shyamli Singla illustrate that the deep machine learning may be harnessed to inform clinical prognosis and therapeutic responsiveness using clear cell renal cell carcinoma as a prototype and also envision that such artificial intelligence approach may effectively shape the future of precision oncology.

Robert A. Figlin, MD
Editor-in-Chief