Essential Peer-Reviewed Reading in Kidney Cancer

The peer-reviewed articles summarized in this section were selected by the Editor-in-Chief, Robert A. Figlin, MD, for their timeliness, importance, relevance, and potential impact on clinical practice or translational research.

Molecular Subsets in Renal Cancer Determine Outcome to Checkpoint and Angiogenesis Blockade. Motzer RJ, Rini B, et al. Cancer Cell. 2020;S1535-6108(20)30542-0. PMID: 33157048 DOI: 10.1016/j.ccell.2020.10.011

Abstract: Integrated multi-omics evaluation of 823 tumors from advanced renal cell carcinoma (RCC) patients identifies molecular subsets associated with differential clinical outcomes to angiogenesis blockade alone or with a checkpoint inhibitor. Unsupervised transcriptomic analysis reveals seven molecular subsets with distinct angiogenesis, immune, cell-cycle, metabolism, and stromal programs. While sunitinib and atezolizumab + bevacizumab are effective in subsets with high angiogenesis, atezolizumab + bevacizumab improves clinical benefit in tumors with high T-effector and/or cell-cycle transcription. Somatic mutations in PBRM1 and KDM5C associate with high angiogenesis and AMPK/fatty acid oxidation gene expression, while CDKN2A/B and TP53 alterations associate with increased cell-cycle and anabolic metabolism. Sarcomatoid tumors exhibit lower prevalence of PBRM1 mutations and angiogenesis markers, frequent CDKN2A/B alterations, and increased PD-L1 expression. These findings can be applied to molecularly stratify patients, explain improved outcomes of sarcomatoid tumors to checkpoint blockade versus antiangiogenics alone, and develop personalized therapies in RCC and other indications.

Prognostic significance and immune correlates of CD73 expression in renal cell carcinoma. Tripathi A et al. J Immunother Cancer. 2020 Nov;8(2):e001467. doi: 10.1136/jitc-2020-001467.

BACKGROUND: CD73-adenosine signaling in the tumor microenvironment is immunosuppressive and may be associated with aggressive RCC. We investigated the prognostic significance of CD73 protein expression in RCC leveraging nephrectomy samples. We also performed a complementary analysis using The Cancer Genome Atlas (TCGA) dataset to evaluate the correlation of CD73, CD39 and A2AR transcript levels with markers of angiogenesis and antitumor immune response.

METHODS: Patients with RCC with available archived nephrectomy samples were eligible for inclusion. Tumor CD73 protein expression was assessed by immunohistochemistry and quantified using a CS. Samples were categorized as CD73negative (CS=0), CD73low or CD73high. Multivariable Cox regression analysis compared disease-free survival DFS and OS between CD73 expression groups. In the TCGA dataset, samples were categorized as low, intermediate and high NT5E, ENTPD1 and ADORA2A gene expression groups. Gene expression signatures for infiltrating immune cells, angiogenesis, myeloid inflammation, and effector T-cell response were compared between NT5E, ENTPD1 and ADORA2A expression groups.

RESULTS: Among the 138 patients eligible for inclusion, 'any' CD73 expression was observed in 30% of primary tumor samples. High CD73 expression was more frequent in patients with M1 RCC (29% vs 12% M0), grade 4 tumors (27% vs 13% grade 3 vs 15% grades 1 and 2), advanced T-stage (≥T3: 22% vs T2: 19% vs T1: 12%) and tumors with sarcomatoid histology (50% vs 12%). In the M0 cohort (n=107), patients with CD73high tumor expression had significantly worse 5-year DFS (42%) and 10-year OS (22%) compared with those in the CD73negative group (DFS: 75%, adjusted HR: 2.7, 95% CI 1.3 to 5.9, p=0.01; OS: 64%, adjusted HR: 2.6, 95% CI 1.2 to 5.8, p=0.02) independent of tumor stage and grade. In the TCGA analysis, high NT5E expression was associated with significantly worse 5-year OS (p=0.008). NT5E and ENTPD1 expression correlated with higher regulatory T cell (Treg) signature, while ADORA2A expression was associated with increased Treg and angiogenesis signatures.

CONCLUSIONS: High CD73 expression portends significantly worse survival outcomes independent of stage and grade. Our findings provide compelling support for targeting the immunosuppressive and proangiogenic CD73-adenosine pathway in RCC.

Randomized trial assessing impact of probiotic supplementation on gut microbiome and clinical outcome from targeted therapy in metastatic renal cell carcinoma. Nazli Dizman Cancer Med. 2020. https://doi.org/10.1002/cam4.3569

Abstract: Studies suggest a link between the gut microbiome and metastatic renal cell carcinoma (mRCC) outcomes, including evidence that mRCC patients possess a lower abundance of Bifidobacterium spp. compared to healthy adults. We sought to assess if a Bifidobacterium-containing yogurt product could modulate the gut microbiome and clinical outcome from vascular endothelial growth factor-tyrosine kinase inhibitors (VEGF-TKIs). mRCC patients initiating VEGF-TKIs, regardless of the line of therapy, were randomized to probiotic-supplemented (two 4 oz. servings of the probiotic yogurt product daily) or probiotic-restricted arms. Stool samples were collected prior to therapy and at weeks 2, 3, 4, and 12. Microbiome composition was assessed using whole-metagenome sequencing. A total of 20 patients were randomized. Bifidobacterium animalis, the active ingredient of the probiotic supplement, reached detectable levels in all patients in the probiotic-supplemented arm versus two patients in the probiotic-restricted arm. Clinical benefit rate was similar in probiotic-supplemented versus probiotic-restricted arms (70% vs. 80%, p = 0.606). Linear discriminant analysis (LDA) effect size analysis of MetaPhIAn2 abundance data predicted 25 enriched species demonstrating an LDA score >3 in either clinical benefit or no clinical benefit. In patients with clinical benefit (vs. no clinical benefit), Barnesiella intestinihominis and Akkermansia muciniphila were significantly more abundant ($p = 7.4 \times 10\text{-}6$ and $p = 5.6 \times 10\text{-}3$, respectively). This is the first prospective randomized study demonstrating modulation of the gut microbiome with a probiotic in mRCC. Probiotic supplementation successfully increased the Bifidobacterium spp. levels. Analysis of longitudinal stool specimens identified an association between B. intestinihominis, A. muciniphila, and clinical benefit with therapy. Trial Registration: NCT02944617.

Grading Chromophobe Renal Cell Carcinoma: Evidence for a Four-tiered Classification Incorporating Coagulative Tumor Necrosis. Avulova S et al. Eur Urol. 2020 Nov 7;S0302-2838(20)30784-3. doi: 10.1016/j.eururo.2020.10.007.

Background: Although grading systems have been proposed for chromophobe renal cell carcinoma (ChRCC), including a three-tiered system by Paner et al (Paner GP, Amin MB, Alvarado-Cabrero I, et al. A novel tumor grading scheme for chromophobe renal cell carcinoma: prognostic utility and comparison with Fuhrman nuclear grade. Am J Surg Pathol 2010;34:1233–40), none have gained clinical acceptance, and the World Health Organization (WHO) currently recommends against grading ChRCC.

Objective: To validate a previously published grading scheme and propose a scheme that includes tumor necrosis.

Design: A total of 266 patients who underwent nephrectomy for nonmetastatic ChRCC between 1970 and 2012 were reviewed for ChRCC grade according to the Paner system and coagulative tumor necrosis. Outcome measurements and statistical analysis: Associations with cancer-specific survival (CSS) were evaluated using Cox proportional hazard regression models and summarized with hazard ratios (HRs).

Results and limitations: Twenty-nine patients died from RCC; the median follow-up was 11.0 (interquartile range 7.9–15.9) yr. ChRCC grade according to the Paner system was significantly associated with CSS, including the difference in outcome between grade 1 and 2 tumors. Among patients with grade 2 tumors, the presence of tumor necrosis helped delineate patients with worse CSS. As such, the Paner system was expanded to four tiers separating grade 2 into those with and without tumor necrosis. HRs for associations of the proposed grade 2, 3, and 4 tumors with CSS were 4.63 ($p = 0.007$), 17.8 ($p < 0.001$), and 20.9 ($p < 0.001$), respectively. The study is limited by the lack of multivariable analysis including additional pathologic features.

Conclusions: The expansion of a previously reported ChRCC grading system from three to four tiers by the inclusion of tumor necrosis helps further delineate patient outcome and can, therefore, enhance patient counseling following surgery. It also aligns the number of ChRCC grades with the WHO/International Society of Urologic Pathology four-tiered grading systems for clear cell and papillary RCC.

Stereotactic Radiotherapy for the Treatment of Patients With Oligo-progressive Metastatic Renal Cell Carcinoma Receiving Vascular Endothelial Growth Factor Receptor Tyrosine Kinase Inhibitor: Data From the Real World. Vittorio Gebbia, Andrea Girlando, Alfio DI Grazia et al., Anticancer Res. 2020 Dec;40(12):7037-7043. DOI: 10.21873/anticanres.14730

Aim: This retrospective observational study evaluated the role of hypo-fractionated stereotactic radiotherapy (SRT) in patients with oligo-progressive metastatic renal cell carcinoma (mRCC) treated with first-line oral tyrosine kinase inhibitors (TKI). Data on local control, delay of further progression, and safety are reported.

Patients and methods: Between January 2010 and December 2016, 28 patients with mRCC who showed oligo-progressive disease while receiving first-line pazopanib were treated with hypofractionated SRT to progressive metastatic sites to delay the change of systemic therapy. First and second progression-free survival (PFS-1 and PFS-2) were recorded, as well as objective response and toxicity.

Results: After pazopanib therapy, nine partial remissions (32%), 12 stable disease (43%) and seven progressions (25%) were recorded. The median time to progression from first-line pazopanib until oligo-progression was 9.45 months (PFS-1 range=2-30 months). Seventeen patients (61%) showed progression at pre-existing tumor sites, and 11 patients (39%) showed the appearance of new metastases. Progression-free survival after radiation therapy was 4.55 months (PFS-2 range=1-11 months). PFS-1 plus PFS-2 was 14.0 months (range=3-41 months). Severe grade 3-4 toxicities were seen only occasionally.

Conclusion: Patients with oligo-progressive mRCC treated with first-line pazopanib may benefit from hypo-fractionated high-dose SRT at progressing sites achieving a further increase in median progression-free survival. Further studies and prospective validation are required to establish if this minimally invasive approach may have a positive impact on overall survival and reported outcomes.

An Italian, multicenter, real-world, retrospective study of first-line pazopanib in unselected metastatic renal-cell carcinoma patients: the 'Pamerit' study. Mosca A et al. Front Pharmacol., Jpn J Clin Oncol. 2020;hyaa193. doi: 10.1093/jjco/hyaa193.

Objective: The aim of this study is to add information about efficacy and safety of pazopanib as first-line treatment in metastatic renal cell cancer patients not enrolled into clinical trials.

Methods: Retrospective analysis (the PAMERIT study) of first-line pazopanib in real-world metastatic renal cell cancer patients among 39 Centers in Italy. Outcomes were PFS, OS, OSR and treatment-related AEs. Kaplan-Meier curves, log-rank test and multivariable Cox's models were used and adjusted for age, histology, previous renal surgery, International Metastatic RCC Database Consortium score and pazopanib initial dose.

Results: Among 474 patients, 87.3% had clear cell metastatic renal cell cancer histology. Most of them (84.6%) had upfront renal surgery. Median progression-free survival and overall survival were 15.8 and 34.4 months, respectively, significantly correlating with International Metastatic RCC Database Consortium's good prognosis ($P < 0.001$), ECOG PS 0 ($P < 0.001$), age (<75 years, $P = 0.005$), surgery ($P < 0.001$) and response to pazopanib ($P < 0.001$). After 3 months of pazopanib, overall disease control rate have been observed in 76.6% patients. 57/121 (47%) showed complete/partial response. No unexpected AEs emerged.

Conclusions: In this real-world study, mRCC patients treated with first-line pazopanib reached greater progression-free survival and overall survival than in pivotal studies and had high response rates, without new toxicities. Pazopanib has been confirmed a valid first-line option for IMRCC Database Consortium's good prognosis mRCC patients who cannot be submitted to immunotherapy.