

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.

The society for immunotherapy of cancer consensus statement on immunotherapy for the treatment of advanced renal cell carcinoma (RCC). Rini BI, Battle D, Figlin RA, et al. *J Immunother Cancer*. 2019;7(1):354. Published 2019 Dec 20. doi:10.1186/s40425-019-0813-8

Abstract: The approval of immunotherapeutic agents and immunotherapy-based combination strategies in recent years has revolutionized the treatment of patients with advanced renal cell carcinoma (aRCC). Nivolumab, a programmed death 1 (PD-1) immune checkpoint inhibitor monoclonal antibody, was approved as monotherapy in 2015 for aRCC after treatment with a VEGF-targeting agent. In April 2018, the combination of nivolumab and ipilimumab, a CTLA-4 inhibitor, was approved for intermediate- and poor-risk, previously untreated patients with aRCC. Then, in 2019, combinations therapies consisting of pembrolizumab (anti-PD-1) or avelumab (anti-PD-ligand (L) 1) with axitinib (a VEGF receptor tyrosine kinase inhibitor) were also approved to treat aRCC and are likely to produce dramatic shifts in the therapeutic landscape. To address the rapid advances in immunotherapy options for patients with aRCC, the Society for Immunotherapy of Cancer (SITC) reconvened its Cancer Immunotherapy Guidelines (CIG) Renal Cell Carcinoma Subcommittee and tasked it with generating updated consensus recommendations for the treatment of patients with this disease.

Results of the ADAPT Phase 3 Study of Rocapuldencel-T in Combination with Sunitinib as First-Line Therapy in Patients with Metastatic Renal Cell Carcinoma. Figlin RA, Tannir NM, Uzzo RG, et al. *Clin Cancer Res*, 2020 (26) (10) 2327-2336; DOI: 10.1158/1078-0432.CCR-19-2427

Purpose: Rocapuldencel-T is an autologous immunotherapy prepared from mature monocyte-derived dendritic cells (DC), coelectroporated with amplified tumor RNA plus CD40L RNA. This pivotal phase III trial was initiated to investigate the safety and efficacy of a combination therapy dosing regimen of Rocapuldencel-T plus sunitinib in patients with metastatic renal cell carcinoma (mRCC).

Results: Between 2013 and 2016, 462 patients were randomized 2:1, 307 to the combination group and 155 to the SOC group. Median OS in the combination group was 27.7 months [95% confidence interval (CI) 23.0-35.9] and 32.4 months (95% CI, 22.5-) in the SOC group HR of 1.10 (95% CI, 0.83-1.40). PFS was 6.0 months and 7.83 months for the combination and SOC groups, respectively [HR = 1.15 (95% CI, 0.92-1.44)]. The ORR was 42.7% (95% CI, 37.1-48.4) for the combination group and 39.4% (95% CI, 31.6-47.5) for the SOC group. Median follow up was 29 months (0.4-47.7 months). On the basis of the lack of clinical efficacy, the ADAPT trial was terminated on February 17, 2017. Immune responses were detected in 70% of patients treated with Rocapuldencel-T, and the magnitude of the immune response positively correlated with OS. No serious adverse events attributed to the study medication have been reported to date.

Conclusions: Rocapuldencel-T did not improve OS in patients treated with combination therapy, although the induced immune

response correlated with OS. Moreover, we identified two potential survival-predictive biomarkers for patients receiving DC based immunotherapy, IL-12 produced by the DC vaccine and higher numbers of T regulatory cells present in the peripheral blood of patients with advanced RCC.

Stool Microbiome Profiling of Patients with Metastatic Renal Cell Carcinoma Receiving Anti-PD-1 Immune Checkpoint Inhibitors. Salgia NJ, Bergerot PG, Maia MC, et al. *Stool Microbiome Profiling of Patients with Metastatic Renal Cell Carcinoma Receiving Anti-PD-1 Immune Checkpoint Inhibitors*. *Eur Urol*. 2020;S0302-2838(20)30543-1. doi:10.1016/j.eururo.2020.07.011

Abstract: Preclinical models and early clinical data suggest an interplay between the gut microbiome and response to immunotherapy in solid tumors including metastatic renal cell carcinoma (mRCC). We sought to characterize the stool microbiome of mRCC patients receiving a checkpoint inhibitor (CPI) and to assess treatment-related changes in microbiome composition over the course of CPI therapy. Stool was collected from 31 patients before initiation of nivolumab (77%) or nivolumab plus ipilimumab (23%) therapy, of whom 58% experienced clinical benefit. Greater microbial diversity was associated with clinical benefit from CPI therapy ($p = 0.001$), and multiple species were associated with clinical benefit or lack thereof. Temporal profiling of the microbiome indicated that the relative abundance of Akkermansia muciniphila increased in patients deriving clinical benefit from CPIs. This study substantiates results from previous CPI-related microbiome profiling studies in mRCC.

Summary: We compared the composition and diversity of the gut microbiome in patients receiving immunotherapy for renal cell carcinoma. We found that higher microbial diversity is associated with better treatment outcomes. Treatment response is characterized by changes in microbial species over the course of treatment.

Clinical Activity of Ipilimumab Plus Nivolumab in Patients With Metastatic Non-Clear Cell Renal Cell Carcinoma. Gupta R, Ornstein MC, Li H, et al. *Clin Genitourin Cancer*. 2019;S1558-7673(19)30363-5. doi:10.1016/j.clgc.2019.11.012

Introduction: Ipilimumab plus nivolumab has been approved for intermediate- and poor-risk metastatic renal cell carcinoma (RCC). However, the activity in non-clear cell RCC (nccRCC) is unknown.

Results: Eighteen patients were identified. The median age was 59 years (range, 32-81 years), 77.8% were men, and the Eastern Cooperative Oncology Group performance status was 0 (38%) or 1 (50%). The median treatment duration was 2.4 months (range, 0.7-12.3 months). The non-clear cell histologic types included 6 papillary, 5 chromophobe, 3 unclassified, 2 adenocarcinoma of renal origin, 1 translocation, and 1 medullary. Most had an intermediate (66%) or poor (22%) International Metastatic Database Consortium risk. The best objective response included 6 partial responses (PRs; 33.3%) and 3 with stable disease (16.7%). Of the patients with a PR, the median time to the best response was 3.0

months, and median duration of the PR was 4.3 months. The median progression-free survival was 7.1 months. All-grade TRAEs were noted in 11 patients (61.1%) and included colitis (22%), hepatotoxicity (16%), rash (11%), and fatigue (11%). Eleven patients (61%) had TRAEs requiring high-dose glucocorticoids (> 40 mg of prednisone equivalent daily).

Conclusions: Ipilimumab plus nivolumab demonstrated objective responses and notable toxicity in patients with nccRCC.

HIF-1a and HIF-2a differently regulate tumour development and inflammation of clear cell renal cell carcinoma in mice. Hoefflin R, Harlander S, Schäfer S, et al. *Nat Commun.* 2020;11(1):4111. 2020. doi:10.1038/s41467-020-17873-3

Abstract: Mutational inactivation of VHL is the earliest genetic event in the majority of clear cell renal cell carcinomas (ccRCC), leading to accumulation of the HIF-1a and HIF-2a transcription factors. While correlative studies of human ccRCC and functional studies using human ccRCC cell lines have implicated HIF-1a as an inhibitor and HIF-2a as a promoter of aggressive tumour behaviours, their roles in tumour onset have not been functionally addressed. Herein we show using an autochthonous ccRCC model that Hif1a is essential for tumour formation whereas Hif2a deletion has only minor effects on tumour initiation and growth. Both HIF-1a and HIF-2a are required for the clear cell phenotype. Transcriptomic and proteomic analyses reveal that HIF-1a regulates glycolysis while HIF-2a regulates genes associated with lipoprotein metabolism, ribosome biogenesis and E2F and MYC transcriptional activities. HIF-2a-deficient tumours are characterised by increased antigen presentation, interferon signalling and CD8+ T cell infiltration and activation. Single copy loss of HIF1a or high levels of HIF2A mRNA expression correlate with altered immune microenvironments in human ccRCC. These studies reveal an oncogenic role of HIF-1a in ccRCC initiation and suggest that alterations in the balance of HIF-1a and HIF-2a activities can affect different aspects of ccRCC biology and disease aggressiveness.

Angiogenic and immune-related biomarkers and outcomes following axitinib/pembrolizumab treatment in patients with advanced renal cell carcinoma. Martini JF, Plimack ER, Choueiri TK, et al. *Clin Cancer Res.* 2020; clincanres.1408.2020. doi:10.1158/1078-0432.CCR-20-1408

Purpose: Combined axitinib/pembrolizumab is approved for advanced renal cell carcinoma (aRCC). This exploratory analysis examined associations between angiogenic and immune-related biomarkers and outcomes following axitinib/pembrolizumab treatment.

Results: Higher baseline tumor levels of CD8 showed a trend toward longer PFS (hazard ratio [HR] 0.4; $P = 0.091$). Higher baseline serum levels of CXCL10 ($P = 0.0197$) and CEACAM1 ($P = 0.085$) showed a trend toward better ORR and longer PFS, respectively. Patients for whom IL-6 was not detected at baseline had longer PFS vs patients for whom it was detected (HR 0.4; $P = 0.028$). At C2D1 and/or EOT, mainly immune-related biomarkers showed any association with better outcomes. The genes CA9 ($P = 0.084$), HIF1A ($P = 0.064$), and IFNG ($P = 0.073$) showed trending associations with ORR, and AKT3 ($P = 0.0145$), DDX58 ($P = 0.0726$), GZMA ($P = 0.0666$), LCN2 (NGAL; $P = 0.0267$),

and PTPN11 ($P = 0.0287$) with PFS.

Conclusions: With combined axitinib/pembrolizumab treatment in patients with aRCC, mostly immune-related biomarkers are associated with better treatment outcomes. This exploratory analysis has identified some candidate biomarkers to consider in future prospective testing. ClinicalTrials.gov identifier: NCT02133742.

A pan-cancer analysis of PBAF complex mutations and their association with immunotherapy response. Hakimi AA, Attalla K, DiNatale RG, et al. *Nat Commun.* 2020;11(1):4168. Published 2020 Aug 20. doi:10.1038/s41467-020-17965-0

Abstract: There is conflicting data regarding the role of PBAF complex mutations and response to immune checkpoint blockade (ICB) therapy in clear cell renal cell carcinoma (ccRCC) and other solid tumors. We assess the prevalence of PBAF complex mutations from two large cohorts including the pan-cancer TCGA project ($n = 10,359$) and the MSK-IMPACT pan-cancer immunotherapy cohort ($n = 3700$). Across both cohorts, PBAF complex mutations, predominantly PBRM1 mutations, are most common in ccRCC. In multivariate models of ccRCC patients treated with ICB ($n = 189$), loss-of-function (LOF) mutations in PBRM1 are not associated with overall survival (OS) (HR = 1.24, $p = 0.47$) or time to treatment failure (HR = 0.85, $p = 0.44$). In a series of 11 solid tumors ($n = 2936$), LOF mutations are not associated with improved OS in a stratified multivariate model (HR = 0.9, $p = 0.7$). In a current series of solid tumors treated with ICB, we are unable to demonstrate favorable response to ICB in patients with PBAF complex mutations.

PBRM1 loss defines a nonimmunogenic tumor phenotype associated with checkpoint inhibitor resistance in renal carcinoma. Liu XD, Kong W, Peterson CB, et al. *Nat Commun.* 2020;11(1):2135. Published 2020 May 1. doi:10.1038/s41467-020-15959-6

Abstract: A non-immunogenic tumor microenvironment (TME) is a significant barrier to immune checkpoint blockade (ICB) response. The impact of Polybromo-1 (PBRM1) on TME and response to ICB in renal cell carcinoma (RCC) remains to be resolved. Here we show that PBRM1/Pbrm1 deficiency reduces the binding of brahma-related gene 1 (BRG1) to the IFN α receptor 2 (Ifngr2) promoter, decreasing STAT1 phosphorylation and the subsequent expression of IFN γ target genes. An analysis of 3 independent patient cohorts and of murine pre-clinical models reveals that PBRM1 loss is associated with a less immunogenic TME and upregulated angiogenesis. Pbrm1 deficient Renca subcutaneous tumors in mice are more resistance to ICB, and a retrospective analysis of the IMmotion150 RCC study also suggests that PBRM1 mutation reduces benefit from ICB. Our study sheds light on the influence of PBRM1 mutations on IFN-STAT1 signaling and TME, and can inform additional preclinical and clinical studies in RCC.