The 19th Annual Meeting of

The International Kidney Cancer Symposium

Supplement Issue
**EDITORIAL MISSION**

The purpose of Kidney Cancer Journal is to serve as a comprehensive resource of information for physicians regarding advances in the diagnosis and treatment of renal cell carcinoma. Content of the journal focuses on the impact of translational research in oncology and urology and also provides a forum for cancer patient advocacy. Kidney Cancer Journal is circulated to medical oncologists, hematologist-oncologists, and urologists.

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From Chair’s Desk

This year we celebrated the 30th anniversary of The Kidney Cancer Association and 19th International Kidney Cancer Symposium. This year we pivoted to a virtual format to help everyone stay safe in these challenging times. On behalf of the Scientific Program Committee, we are delighted to see the outstanding abstracts presented at the first virtual IKCS meeting published in the Kidney Cancer Journal. While the 2019-2020 academic year has been full of challenges, the tireless effort of the kidney cancer community to advance treatment options, enhance our understanding of tumor biology, strengthen advocacy efforts, and support patients and their families has continued unabated.

The Kidney Cancer Association was founded in 1990 by Eugene P. Schonfeld and a small group of patients and doctors in Chicago, Illinois and has grown into an international non-profit organization. The KCA promotes scientific advances through two annual research symposiums and a robust grant program, participates in legislative advocacy, and seeks to be a source of education and resources for patients, caregivers, and anyone impacted by kidney cancer. In 2020, the Kidney Cancer Association has awarded $1.3 million to support novel and innovative research in RCC in the form of 4 Young Investigator Awards and 2 Advanced Discovery Awards.
This year, we are proud to have featured the 2019 Nobel Prize winner in Physiology or Medicine Dr. William G. Kaelin, Jr., who gave the IKCS 2020 keynote address, as well as two KCA career awardees – Dr. Steven Campbell of the Cleveland Clinic, who delivered the Andrew C. Novick Memorial Lecture, and Dr. Axel Bex of the Royal Free NHS Foundation Trust in London, who gave the Pieter de Mulder Memorial Lecture.

Merit Award recipients for outstanding abstracts include:

1st place: **Arnav Srivastava**, MD, MPH for “Delaying Surgery for Clinical T1b–T2bN0M0 Renal Cell Carcinoma: Oncologic Implications in the COVID-19 Era and Beyond”

2nd place: **Jack Gleeson**, MBBCh, MRCPI for “Response to Systemic Therapy in Patients with Metastatic Fumarate Hydratase (FH) Deficient Renal Cell Carcinoma”

3rd place: **Alex Chehrazi-Raffle**, MD for “Associations between Serum Cytokine Levels and Gut Microbiota Composition in Metastatic Renal Cell Carcinoma”

We hope you enjoy reading the following abstracts as much as we did hearing about their exciting work first hand. Please mark your calendars for IKCS 2021 from November 5-6, 2021 in Austin, TX.

Sincerely,

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NEW ABSTRACT SUBMISSION

NAS101. Associations between serum cytokine levels and gut microbiota composition in metastatic renal cell carcinoma

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Background: Plasma cytokines and the gut microbiome have been shown separately to influence the response to systemic therapy in mRCC. We sought associations between serum cytokines and gut microbial composition in patients (pts) with mRCC.

Methods: Eligibility requirements included histologically proven mRCC and an intent to receive either vascular endothelial growth factor-tyrosine kinase inhibitor (VEGF-TKI) or immune checkpoint inhibitor (ICI). Blood samples were collected prior to treatment initiation and immunologic profiles were evaluated using a Human Cytokine 30-plex protein assay (Invitrogen). Stool was collected at baseline and shotgun metagenomic sequencing was performed to quantify gut microbial populations using previously published methods (Salgia et al Eur Urol 2020).

Results: A total of 50 pts were studied (36:14 M:F) with a median age of 67 (range, 32-85). Twenty pts and 30 pts had subsequent initiation of VEGF-TKI and ICI therapy, respectively. Levels of Akkermansia spp were significantly higher in pts who were IL-6 low (P=0.023). In contrast, pts who were IL-6 high had higher levels of enteric pathogens, including Salmonella spp and Enterococcus spp. Both Akkermansia spp and Bacteroides spp levels were higher in pts who were IL-8 low. Associations between cytokine levels, microbiome composition, and treatment response will be presented.

Conclusions: Given studies suggesting the role of Akkermansia spp in enhancing ICI response (Routy et al Science 2018), our data provide a critical link between the gut microbiome and systemic immunomodulation.

NAS102. Distinct cytokines predict response to immunotherapy and targeted therapy in metastatic renal cell carcinoma (mRCC)

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Background: Previous studies have suggested a link between plasma cytokines and mRCC outcomes with systemic therapy. In a prospective study, we assessed whether plasma cytokines could separately predict outcome with immunotherapy or targeted therapy.

Methods: Eligible patients (pts) had histologically proven mRCC with intent to receive a vascular endothelial growth factor-tyrosine kinase inhibitor (VEGF-TKI) or immune checkpoint inhibitor (ICI). Immunologic profiles were evaluated using a Human Cytokine 30-plex protein assay (Invitrogen). Clinical benefit (CB) was defined as complete response, partial
response, or stable disease ≥ 6 months. Progression-free survival (PFS) was assessed per RECIST 1.1.

**Results:** A total of 56 pts (40:16 M:F) were enrolled; 23 pts and 33 pts received VEGF-TKI and ICI, respectively. The most common VEGF-TKI was cabozantinib; the most common ICI was nivolumab. Most patients had clear cell histology (86%). CB was similar between VEGF-TKI and ICI arms (70% vs 76%). Pts with CB from ICI had higher levels of IL-13 (p=0.03) and VEGF (p=0.03). Pts without CB from VEGF-TKI had lower levels of IL-6 (p=0.008). Median PFS was significantly longer for ICI patients with lower baseline IL-13 values as well as for VEGF-TKI patients with higher baseline IL-6 values. Major shifts in plasma cytokines were seen as early as 1 month; these data will be presented.

**Conclusions:** Distinct plasma cytokines predict benefit with VEGF-TKIs and ICIs. Ongoing work will incorporate analysis of pts receiving VEGF-TKI and ICI combination therapy.

NAS103. **Reassuring RECIST v1.1 defined progression by Dynamic Contrast-Enhanced Computed Tomography in metastatic renal cell carcinoma.**

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**Background:** Evaluation of response using RECIST1.1 has limitations. Recently, dynamic Contrast-Enhanced CT (DCE-CT) identified Blood Volume (BV) and Blood Flow (BF) have shown promising results in mRCC. We assessed DCE-CT to demonstrate progressive disease (PD) as an enhancement to RECIST v1.1.

**Methods:** BV and BF were prospectively quantified using the deconvolution (deconv) and patlak (patlak) methods. PD risk was assessed at RECIST v1.1 defined PD (PDtimepoint) and the scan timepoint prior to PDtimepoint (PDminustimepoint). Compared with baseline values, the relative changes in BV (ΔBV) and BF (ΔBF) were assessed at each scan timepoint as categorical (≥ 20% cut-off) and continuous variables (20-percent-point increasements). Adjusted for IMDC features and treatments, hazard ratios (HR) with 95% confidence intervals (CI) were estimated using Cox proportional hazard models with time to progression as endpoint.

**Results:** 65 and 63 patients had technically analyzable DCE-CT scans at PDminustimepoint and PDtimepoint, respectively. Increased ΔBVpatlak and ΔBVdeconv (continuous) were associated with increased risk of PD at PDtimepoint (HR=1.06, 95% CI: 1.03-1.08, P<0.001 and HR=1.13, 95% CI: 1.002-1.27, P=0.043, respectively). Increased ΔBVpatlak (categorical) was associated with increased risk of PD at PDtimepoint (HR=2.60, 95% CI: 1.62-4.16, P<0.001). ΔBFdeconv was not associated with PD.

**Conclusions:** DCE-CT identified BV is a new feature to identify unequivocal PD and may serve as a helping tool to RECIST v1.1.

NAS104. **An alternative to Open Data: Federated Machine Learning for Rare Kidney Cancer Across Data Silos While Enforcing Local Control.**

Anne Kim, Secure AI Labs anne@secureAILabs.com; Bill Paseman, Patient Advocate https://www.linkedin.com/in/paseman/; Dianbo Liu, McGill University, Harvard Medical School, MIT; Shifa Zhang: The Broad Institute, NorthEastern University; JingWei Zhang, Secure AI Labs.

**Background:** Papillary Renal Cell Carcinoma Type 1 (P1RCC) is a rare but debilitating cancer with a dearth
of therapies under development. Exacerbating the scarcity of P1RCC therapies and other resources is the fact that most of the data necessary for innovative breakthroughs is siloed amongst disparate hospital electronic health record (EHR) databases, academic institutions, and biobanks. Hesitations preventing data sharing include HIPAA/GDPR liabilities, and commercial concerns (P1RCC data is scarce and therefore valuable). These perverse alignments have siloed P1RCC data and restricted the most innovative research to meager datasets. In this paper we explore methods of linking these datasets without sharing or exposing personally identifiable information (PII) to unlock the potential for accelerated discoveries in P1RCC research. These methods enable all rare disease stakeholders: patients, researchers and institutions, to contribute to and benefit from collective research without the risk or liability of sharing patient data.

Methods: The authors have demonstrated three unique privacy-preserving architectures for performing clinical research collaborations in Alzheimer's, microbiome, and molecular research using a combination of federated machine learning and secure enclave technology to securely share algorithmic models between datasets instead of sharing raw patient data. To further demonstrate the application of this technology, the authors reproduced gene co-expression network (GCN) results using federated Gaussian Mixture Models (Ficklin et al; Hahn et al) using the same privacy-preserving architecture.

Results: The results are traditional analysis can be reproduced and even enhanced by these methods with small exceptions of certain edge cases and speed penalties within an order of magnitude.

Conclusions: Extending the methods of this technology holds promise for not only P1RCC but other rare cancers with similar data sharing dynamics fraught with adversarial relationships and misaligned incentives that don’t necessarily foster collaboration and innovation.


NAS105. Delaying Surgery for Clinical T1b-T2bNoMo Renal Cell Carcinoma: Oncologic Implications in the COVID-19 Era and Beyond.

Arnav Srivastava, Rutgers Cancer Institute of New Jersey arnavsrivastava.md.mph@gmail.com; Hiren V. Patel, Sinae Kim, Brian Shinder; Joshua Sterling; Alexandra L. Tabakin; Charles F. Polotti; Biren Saraiya; Tina Mayer, Isaac Y. Kim, Saum Ghodoussipour; Hiten D. Patel, Thomas L. Jang; Eric A. Singer.

Purpose: During COVID-19, many operating rooms were reserved exclusively for emergent cases. As a result, many elective surgeries for renal cell carcinoma (RCC) were deferred, with an unknown impact on outcomes. Since surveillance is commonplace for small renal masses, we focused on larger, organ-confined, RCCs. Our primary endpoint was pT3a upstaging and our secondary endpoint was overall survival (OS).

Methods: We retrospectively abstracted cT1b-cT2bNoMo RCC patients from the National Cancer Database (NCDB), stratifying them by clinical stage and time from diagnosis to surgery. We selected only those patients who underwent surgery. Patients were grouped by having surgery within <1 month, 1-3 months, or >3 months after diagnosis. Logistic regression models measured pT3a upstaging risk. Kaplan Meier curves and Cox proportional hazards models assessed OS.

Results: 29,746 patients underwent partial or radical nephrectomy. Delaying surgery >3 months after diagnosis did not confer pT3a upstaging risk among cT1b (OR=0.90; 95%CI: 0.77–1.05, p = 0.170), cT2a (OR=0.90; 95%CI: 0.69–1.19, p=0.454), or cT2b (OR=0.96; 95%CI:0.62–1.51, p=0.873) masses (Table
1). In all clinical stage strata, non-clear cell RCCs were significantly less likely to be upstaged (p<0.001). A sensitivity analysis, performed for delays of <1, 1-3, 3-6, and >6 months, also showed no increase in upstaging risk.

Conclusions: Delaying surgery up to, and even beyond, 3 months does not significantly increase risk of tumor progression in clinically localized RCC. However, if deciding to delay surgery due to COVID-19, tumor histology, growth kinetics, patient comorbidities, and hospital capacity/resources, should be considered.

NAS 106. Radiomic features of renal cell carcinoma metastatic sites can predict BAP1 mutation

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\textsuperscript{a} Department of Medical Oncology & Experimental Therapeutics, City of Hope Comprehensive Cancer Center, Duarte, CA, USA; \textsuperscript{b} Department of Radiology, City of Hope Comprehensive Cancer Center, Duarte, CA, USA; \textsuperscript{c} Integrated Cancer Genomics Division, Translational Genomics Research Institute, Phoenix, AZ; \textsuperscript{d} Genetic Basis of Human Disease Division, Translational Genomics Research Institute, Phoenix, AZ

Background: BAP1 mutations are associated with poor clinical outcome in patients (pts) with metastatic renal cell carcinoma (mRCC). In this study we explore radiogenomics as a non-invasive method to identify this alteration.

Methods: Pts with mRCC who had genomic testing in the course of routine clinic care were included in the current analysis. Pts were assessed with the GEM Extra\textsuperscript{®} assay, a CAP-accredited, CLIA-certified test encompassing paired tumor-normal whole exome sequencing (WES) and tumor whole transcriptome sequencing (TGen; Phoenix, AZ). Pts underwent CT imaging; radiomic analysis was performed on the segmented metastatic and primary lesions. Features were correlated with BAP1 mutation status to generate Pearson correlation values (PCVs).

Results: 88 pts (63:25 M:F) were included in the analysis; of these, the majority of pts (73; 83\%) had clear cell histology. 9 pts had BAP1mt with 5 detected in primary tumor and 4 in metastatic sites. Analysis of primary tumor imaging yielded no significant associations between radiomic features and BAP1mt. However, out of approximately 1500 radiomic features noted in metastatic sites, 111 features correlated with BAP1mt with a PCV ≥ 0.2. Of these, 15 features correlated with a PCV ≥ 0.3. The radiomic features with the highest correlation with BAP1mt were gray level dependence matrix and gray level co-occurrence.

Conclusions: By identifying a correlation between radiomic features and BAP1mt in metastatic sites, our work may ultimately yield a non-invasive method of discerning mutational status. Efforts are ongoing to validate our findings within The Cancer Imaging Archive.

NAS107. An integrated study of spatial dynamics and genomic alterations in renal cell carcinoma evolution

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**Background:** The multi-center prospective longitudinal cohort study, TRACERx Renal (NCT03226886) has revealed the evolutionary features of clear-cell renal cell carcinoma (ccRCC). However, the association of physical spatial location and genetically driven tumor subclones was unclear.

**Methods:** 100 macroscopic tumor images taken at time of surgery were reviewed by a renal pathologist, and following quality control filtering accurate spatial data was available for 79 tumors. From these 79 cases, matched high-depth driver gene panel sequencing data was utilized from 756 individual biopsy regions (mean 9.6 biopsies per tumor). The boundaries between tumor and normal tissues were marked based on macroscopic photos by a renal pathologist, after which the positions of boundaries and biopsy regions were digitally extracted to X- and Y-coordinates. Spatial distances were calculated, with the correlations between spatial characteristics and genomic alterations investigated.

**Results:** We mapped the spatial location of 756 biopsies, across 79 ccRCCs, and integrated these coordinates with sequencing data. This enabled a resolution as to how genetically distinct subclones grew and evolve spatially. Compared with tumor margins, the level of somatic copy number changes was higher in tumor interiors. Moreover, metastasizing clones were found to be more enriched in tumour interiors. The tumor subclones growing to largest physical size were characterized by gains of chromosomes 7q, 1q and losses of chromosome 14q. The degree of discrepancy of genomic alterations across biopsy regions was positively correlated with spatial distances across biopsy regions. Tumor subclone growth was found to be predominantly spatially contiguous, with subclone dispersal a rare event found only in one case, which notably was associated with metastasis.

**Conclusions:** Spatial dynamics is strongly associated with genomic alterations and plays an important role in tumor evolution.

**NAS108. Outcomes based on age in patients with metastatic renal cell carcinoma treated with first line targeted therapy or checkpoint immunotherapy: Older patients more prone to toxicity**

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**Objectives:** Older patients with mRCC were underrepresented in pivotal trials.

**Materials and Methods:** Patients with mRCC treated at Aarhus University Hospital with first line TKI, mTOR inhibitors, or CPI were retrospectively analyzed in age-subgroups; ≥75, 65-74, and <65 years, with OS, PFS and time-to-treatment stop (TTS) as endpoints. Hazards ratios were adjusted (aHR) for IMDC risk factors, histology, and age.

**Results:** Of 838 patients, 159 (19%) were ≥75 years, 324 (39%) 65-74 years, and 355 (42%) <65 years. Treatments were TKI in 729 (87%) patients, mTOR in 43 (5%) and CPI in 67 (8%). Older patients ≥75 years compared with 65-74 years and <65 years had lower toxicity-adjusted median doses of pazopanib, 300 mg vs. 400 mg vs. 600 mg, respectively, (p < 0.001), and sunitinib, 25 mg vs. 37.5 mg vs. 50 mg, respectively (p < 0.001); numerically fewer doses of CPI, median 2 vs. 5 vs. 5, respectively, (p = 0.2); a higher proportion had dose reduction/interruption, 76% vs. 55% vs. 41%, respectively, (p < 0.001); and shorter mean time to dose reduction/interruption, 0.5 months vs. 1.9 months vs. 3.4 months, respectively, (p < 0.001). Age did not
impact OS, TTS or PFS; adjusting for IMDC prognostic factors or histology in multivariate analyses revealed aHR 1.0.

**Conclusion:** Older patients with mRCC were more prone to toxicity, but age did not impact outcomes.

**NAS109. Clinical laboratory values associated with survival in patients with metastatic renal cell carcinoma: a Laboratory Wide Association Study (LWAS) approach**

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**Background:** Current prognostic models of metastatic renal cell carcinoma (mRCC) include tumor characteristics, patient factors, and select laboratory values. However, the literature supporting the use of laboratory values for patients with mRCC is fragmented. To address these issues, we applied a Laboratory-Wide Association Study (LWAS) framework to systematically evaluate common clinical laboratory results associated with survival for patients diagnosed with mRCC.

**Methods:** We identified 3,385 patients with mRCC (N stage >0 or M stage >0) from 2002 through 2017. We identified all common laboratory tests, requiring at least 200 patients with results available. The final laboratory panel included 53 laboratory tests and 641,712 measurements. The outcome measured was the time to death, ascertained using the VA Vital Status File. We randomly split patient records into three data sets. We evaluated associations between each common laboratory test and mortality by fitting proportional hazards (Cox) regression models adjusting for age, sex, race/ethnicity, comorbidity, and receipt of cytoreductive nephrectomy.

**Results:** LWAS validated the association of laboratory values with mortality, including calcium (HR 1.35, 95%CI 1.24-1.48), leukocyte count (HR 1.40, 95%CI 1.30-1.51), platelet count (HR 1.36, 95%CI 1.27-1.51), and hemoglobin (HR 0.79, 95%CI 0.72-0.86). We also identified acute phase reactants associated with mortality not typically included in prognostic models, including serum albumin (HR 0.66, 95%CI 0.61-0.72), ferritin (HR 1.25, 95%CI 1.08-1.45), alkaline phosphatase (HR 1.31, 95%CI 1.23-1.40), and C-reactive protein (HR 1.70, 95%CI 1.14-2.53).

**Conclusions:** LWAS identified routinely measured laboratory tests can help refine current prognostic models, facilitate comparisons across clinical trial cohorts, and match patients with specific systemic therapies.

**NAS110. Analysis of plasma circulating exosomes as a potential prognostic tool in renal cell carcinoma patients with brain metastasis.**

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**Background:** Brain metastasis (BrM) are reported in up to 35-50% of patients with metastatic renal cell carcinoma (mRCC) during disease evolution. BrM is associated with impaired quality of life, limited overall survival and therapeutics. Exosomes are pointed as key elements in tumor biology which could improve the molecular characterization of BrM.

**Methods:** Blood samples from 14 mRCC patients were collected (4 patients with / 10 patients without recently diagnosed BrM). Other clinical variables were well balanced. A cohort of healthy controls was included. Plasma exosomes were isolated by ultracentrifugation, measured by nanoparticle tracking analysis and compared quantitatively by Western blotting of STAT3,
phospho-STAT3 (pSTAT3) and PD-L1. Statistical analyses were performed with GraphPad Prism 8.

**Results:** mRCC patients with BrM presented a decreased number of plasma circulating exosomes compared to the other groups (p=0.02 compared to healthy controls) (Fig1A). We observed increased, although not significant and highly variable, concentration of proteins in exosomes from BrM patients compared to other groups (Fig1B). Analysis of STAT3, pSTAT3 and PD-L1 by Western blot did not report any differences between these groups (Fig1C).

**Conclusions:** Plasma circulating exosomes from patients with mRCC and BrM are reduced in number but with an increased protein cargo. We observed analysis of STAT3, pSTAT3 and PD-L1 expression in circulating exosomes of mRCC is feasible. Despite the absence of differences between these groups, the importance of exosomal PD-L1 in tumor progression / immune evasion warrants further study.

**NAS11. A retrospective study of real-world treatment patterns and outcomes in advanced/metastatic renal cell carcinoma (a/mRCC) patients treated with lenvatinib+everolimus (Len/Eve) in a heavily pretreated population in the United States (US) community oncology setting**

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**Background:** Len/Eve is approved for treating a/mRCC following one prior antiangiogenic therapy. This study aimed to evaluate patient profiles and overall survival (OS) of 2L+ Len/Eve for a/mRCC.

**Methods:** A retrospective observational study was conducted using electronic health record database. Adult patients who initiated 2L+ Len/Eve for a/mRCC from May 13, 2016 to July 31, 2019 were included. Clinical trial Len/Eve participants or those treated for other primary tumors were excluded. OS was estimated from Len/Eve initiation (i.e., index date) using Kaplan-Meier methods.

**Results:** The study population included 152 patients. Approximately 44% of patients received 2L/3L Len/Eve and median prior lines of treatments was 3 (range:1-8). Median age was 63 years, 79% Caucasian, 74% male, and 70% had ECOG performance status 0/1. At initial diagnosis, 66% had stage IV disease, 53% had intermediate/poor, 15% favorable risk and 32% with missing IMDC score. Sixty-five (43%) patients received an immuno-oncology (IO)-based regimen and 49% received tyrosine kinase inhibitors (TKIs) directly before index. Median OS from index date was 13.9 (CI:9.5-16.5) months, 2L/3L and 4L+ were 12.1 (CI:8.4-17.0) and 14.8 (CI:8.9-22.5) months, respectively. Median OS for patients receiving Len/Eve post-IO and post-TKI were 13.9 (CI:8.4-21.3) and 14.8 (CI:7.8-16.5) months, respectively.

**Conclusions:** In this retrospective study, clinical effectiveness of Len/Eve was demonstrated in a/mRCC population in a US community oncology setting.

**NAS12. Real-world clinical effectiveness of lenvatinib+everolimus (Len/Eve) in a heavily pre-treated advanced/metastatic renal cell carcinoma (a/mRCC) population in the US community oncology setting: a retrospective chart review study**

Nicholas J. Vogelzang, MD, FASCO, FACP, US Oncology Comprehensive Cancer Centers of Nevada, Las Vegas, NV 89128; Alisha Monnette, PhD, MPH & Yunfei Wang PhD, MPH, McKesson, Woodlands, TX 77380; Yin Wan, Eisai Inc. Woodcliff Lake, NJ 07677; Nizar M. Tannir,
Background: Few studies have evaluated real-world effectiveness of Len/Eve. This study aimed to evaluate clinical outcomes of 2L+ Len/Eve for a/mRCC.

Methods: A retrospective chart review study was conducted on adult a/mRCC patients who initiated 2L+ Len/Eve (i.e., index date) between May/13/2016 and July/31/2019. Clinical trial Len/Eve participants or those treated for other primary tumors were excluded. Real-world best overall response (BOR), duration of response (DOR), overall survival (OS), time to treatment discontinuation (TTD), and progression-free survival (PFS) were assessed. OS/TTD/PFS/DOR were estimated using Kaplan-Meier methods.

Results: Seventy-nine patients were included; median age was 65 years, 79% Caucasian, 73% male, 79% had ECOG performance score 0/1, median prior lines of treatments was 3(range:1-8) and 29% received 2L/3L Len/Eve. At initial diagnosis, 56% patients were stage IV, 66% had intermediate/poor, 19% favorable risk and 15% missing IMDC score. Thirty-one (39%) patients received an immuno-oncology (IO)-based regimen and 51% received tyrosine kinase inhibitors (TKIs) prior. Median TTD was 5.7(CI:3.3-6.9) months. ORR was 55.7%(1.6% complete response, 54.1% partial response). Median DOR was 9.7(CI:5.8-17.1) months. Landmark OS at 6-months was 71%. Median PFS was 6.1(CI:4.4-9.0) months. Median PFS for patients receiving Len/Eve post-IO and post-TKI were 6.4(CI:4.1-10.8) and 5.7(CI:4.1-10.5) months, respectively.

Conclusions: In this retrospective chart review study, Len/Eve clinical effectiveness in tumor response and PFS were confirmed in clinical practice in a heavily pre-treated a/mRCC population.

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Background: Von Hippel Lindau (VHL) inactivation, which is common in clear cell renal cell carcinoma (ccRCC), leads directly to disruption of oxygen homoeostasis. VHL works through hypoxia-inducible factors (HIFs). Within this VHL-HIF system, prolyl hydroxylases (PHDs) are intermediary proteins that initiate degradation of HIFs. PHD isoform 3’s (PHD3) role in ccRCC growth in vivo is poorly understood.

Methods. Using viral transduction, we knocked down expression of PHD3 in the human ccRCC cell line UMRC3.

Results: Compared with control cells transduced with scrambled vector (UMRC3-SC cells), PHD3-knockdown cells (UMRC3-PHD3KD cells) had increased cell invasion and tumor growth and were more responsive to sunitinib (Tumor Growth Figure). PHD3 knockdown reduced HIF2α expression and increased phosphorylated epidermal growth factor (EGFR) expression in untreated tumor models. However, after sunitinib treatment expression of HIF2α and phosphorylated EGFR in tumor tissue did not significantly differ. In addition, PHD3 knockdown changed the overall redox state of the cell. Concentrations of free glutathione are significantly higher in UMRC3-PHD3KD tumors compared to UMRC3-SC tumors. UMRC3-PHD3KD cells proliferate faster when grown in the presence of 1.5 mM hydrogen peroxide compared to control cells. Conclusions. Our findings illustrate 1) that PHD3’s ability to affect HIF2α expression is variable, 2) reduction of PHD3 expression leads to faster tumor growth in a ccRCC animal model.

NAS113. Prolyl hydroxylase 3 knockdown accelerates VHL-mutant kidney cancer growth in vivo
and 3) PHD3 plays an important role in the redox state of the cell and enhances UMRC3 cells ability to grow in a toxic microenvironment.


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Background: Rare cancers present a pervasive problem to the current paradigm of cohort-based medical research: there is no cohort. The fundamental goal of cancer research is to progress from accurate diagnosis to appropriate treatment, however this is a challenging feat in the case of rare diseases. We address this challenge presented by a lack of generalizable knowledge of rare cancers. We propose a novel deep learning tool (TSPG) which has been used to determine patient-specific transcriptional aberrations inherent in a type 1 papillary renal cell carcinoma patient’s biopsy sample by looking at next generation RNA-sequencing data. With these genetic aberrations, we have begun to identify manipulated transcription pathways via tissue-specific gene regulatory network analysis and have begun the hypothesize which therapeutics might be advantageous in targeting those specific genomic abnormalities. The therapeutics which are being considered are all currently being investigated in randomized clinical trials, so we propose a method of picking targeted clinical trials for patient participation through a computational analysis of genomic sequencing data.

NAS115. Factors Associated With Palliative Care Utilization In Advanced And Metastatic Renal Cell Carcinoma

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Background: Palliative care (PC) offers various benefits for patient with cancer that include, but are not limited to, decrease in disease-specific symptoms and improvement in functional status. Several oncological guidelines have adopted early integration of PC into oncologic care to improve quality of life among patients with advanced malignancies. However, PC utilization patterns and factors associated with its use in advanced renal cell carcinoma (RCC) remain poorly understood.

Methods: Using the National Cancer Database (NCDB), we abstracted patients with Stage III and IV RCC from 2004-2014 and evaluated PC utilization amongst this cohort. Socioeconomic and clinical factors were compared for patient receiving and not receiving PC for advanced RCC. Multivariable logistic regression identified factors that were associated with receipt of PC.

Results: We identified 20,122 and 42,014 patients with Stage III and IV RCC, respectively. Among this cohort, 329 and 9,317 patients received PC for Stage III and IV RCC, respectively. From 2004 to 2014, PC utilization has been stable at ~1% for Stage III RCC and has significantly increased from 17% to 20% for Stage IV RCC. Multivariable analysis demonstrated that Blacks, income >$48,000, regions outside of Northeast, 50-250 miles from facility, Stage III RCC, and patients that received surgery were less likely to receive PC. Patients that were female, with more comorbidities, uninsured or with government insurance, lower educational status, treated at academic or integrated cancer program, with sarcomatoid histology, receiving systemic therapy were more likely to receive PC.

Conclusion: While PC utilization has significantly increased for Stage IV RCC, there are several demographic, socioeconomic, and clinical factors that predict PC usage among patients with advanced RCC. Taken together, this suggests the need for more
equitable and systematic use of PC among patients with advanced RCC.

NAS116. The Impact Of Venous Thromboembolism Presence At The Time Of Nephrectomy For Renal Cell Carcinoma On Complications, Costs, And Survival

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Background: Venous thromboembolism (VTE), defined as pulmonary embolism (PE) or deep vein thrombosis (DVT), are often seen with advanced malignancy. Recent studies have demonstrated that the presence of bland IVC or renal vein thrombus at the time of renal cell carcinoma (RCC) surgery is associated with worse outcomes. However, the impact of VTE at time of RCC surgery remains to be understood, particularly among patients without an IVC or renal vein thrombus. We evaluated the morbidity and mortality associated with having concurrent VTE at the time of surgical resection of a renal mass. Costs of care were also compared.

Methods: We identified 122,342 patients undergoing elective surgical resection for a renal mass from 2013 to 2017 using the Premier Healthcare database, which includes more than 700 non-federal hospitals and translates to over 20% of annual discharges in the United States. The cohort was subdivided based on the presence of VTE at the time of admission for radical nephrectomies (RN) and partial nephrectomies (PN). Patients with renal vein thrombus and/or IVC thrombus were excluded from the analysis. The association of VTE with 90-day non-fatal minor (Clavien 1-2) and major (Clavien 3-4) complication rates, mortality, and direct hospital costs (2019 US dollars) was determined with multivariable logistic regression and quantile regression models, respectively, adjusting for patient, hospital, and surgical characteristics.

Results: Of the total study population, 83,692 patients underwent RN and 38,650 patients had PN. The predicted probability for a non-fatal minor complication in patients with VTE was significantly higher than patients with no VTE undergoing RN and PN (RN: 34.2% vs 21.1%; PN: 36.9% vs 22.5%; p<0.001). The predicted probability for a non-fatal major complication in patients with VTE was significantly higher than patients with no VTE undergoing RN and PN (RN: 10.6% vs 5.2%; PN: 21.5% vs 5.0%; p<0.001). The predicted probability of mortality in patients with VTE was significantly higher than patients with no VTE undergoing RN and PN (RN: 2.6% vs 1.0%; PN: 1.3% vs 0.3%; p<0.001). The 90-day median costs were greater in patients with VTE compared to no VTE undergoing RN and PN (RN: $24,648 vs $13,951; PN: $19,338 vs $13,694; p <0.001).

Conclusions: VTE at the time of renal surgery for suspected RCC is associated with significantly higher rates of major complications, increased mortality, and higher overall costs. Taken together, these findings may
have important implications for the counseling and management of patients with renal masses and VTE.

**NAS117. Retrospective assessment of gastrointestinal tract metastasis from large cohort of metastatic renal cell cancer.**

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**Background:** Digestive metastasis from renal cell cancer is rare. Overall survival of metastatic renal cell cancer (mRCC) has been improved with tyrosine kinase inhibitor (TKI) and immunotherapy. Our aim was to evaluate incidence of gastrointestinal (GI) metastases.

**Methods:** A large monocentric retrospective analysis was performed using data collected from all patients with mRCC between January 2007 and December 2019. A computer search software using artificial intelligence (CONSORÉ) was used to detect the patients and their characteristics.

**Results:** Between January 2007 and December 2019, 11 patients out of 660 (1.6%) with mRCC were identified. The median age was 62 years [range 54-77], 73% were male. Out of 11 patients with GI metastasis, 81.8% were detected by GI bleeding or anemia. Only 2 patients were asymptomatic. Locations were mainly duodenal (50%) and gastric (41.6%). All patients had other metastatic sites. Median time from cancer diagnosis, and from metastatic disease to GI metastasis was 4.3 years [3 months – 19.2 years] and 2.25 years [0 day – 10.2 years] respectively. Local treatment was performed in 38.5% by endoscopy (60%), surgery (20%) or radiotherapy (40%) with success rates of 33%, 100% and 50% respectively. At GI metastases, the systemic treatment was immunotherapy (30.8%), TKI (46.1%) and no treatment (23.1%). The median survival was 1 year from GI metastasis [13 days - 9.4 years].

**Conclusion:** Gastrointestinal metastasis in patients with renal carcinoma is a late event in the course of the disease. Unexplained anemia or persistent digestive symptoms need to be explored by endoscopic investigations.

**NAS118. Response to Systemic Therapy in Patients with Metastatic Fumarate Hydratase (FH) Deficient Renal Cell Carcinoma**

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Introduction: FH-deficient RCC (FHRCC) is characterized by unique pathologic features and lack of FH staining on immunohistochemistry (IHC). Most cases are associated with germline FH mutations and poor prognosis, but there is limited data on the efficacy of systemic therapy.

Methods: Patients with metastatic FHRCC, defined by presence of pathogenic or likely pathogenic (P/LP) FH germline mutation; or somatic P/LP FH mutation with loss of FH by IHC [FH and 2-succino-cysteine], were identified from an institutional database. Clinical and treatment data was obtained from electronic records. The primary outcome was best objective response rate (ORR) to first, second or third-line systemic therapy by blinded investigator RECIST v1.1 assessment.

Results: 32 patients (median age 46; range 20-74; M:F, 20:12) were identified. All patients had evidence of FH-deficiency by IHC. 23 (72%) had germline FH mutations, 5 (16%) had somatic-only FH mutations and 4 (13%) were not assessed for germline FH mutation. Most common sites of metastasis were retroperitoneal lymph nodes (82%), lung (78%) and peritoneal spread (70%); no patients developed brain metastases. Median overall survival (OS) from diagnosis of metastatic disease was 28.1 months (95% CI: 14.9, 33.8). Median follow-up time for survivors is 14.8 months. 26 patients were evaluable for response to first-line therapy, 14 to second-line and 6 to third-line therapy (Table 1). ORR to first, second and third-line therapy was 38.5%, 7% and 17%, respectively, with no complete responses. Combined ORR for all therapies across first-, second- and third-line was 26%.

Conclusion: Patients with FHRCC show distinct patterns of disease progression with primary peritoneal spread. Although there was high ORR to VEGF/mTOR inhibitor combinations, there were limited responses to IO monotherapy.

NAS119. Association of the Neutrophil to Eosinophil Ratio with Response to Ipilimumab/Nivolumab in Metastatic Renal Cell Carcinoma

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Background: Neutrophilia is known to be associated with worse prognosis in metastatic renal cell carcinoma (mRCC); however, less is known about the role of eosinophils in the response to immunotherapy. We investigated the association of the baseline neutrophil to eosinophil ratio (NER) and outcome to combination immunotherapy with ipilimumab and nivolumab.

Methods: Patients with mRCC treated with ipilimumab plus nivolumab from January 2015 to June 2020 at the Vanderbilt-Ingram Cancer Center were retrospectively identified. Baseline NER and association with progression free survival (PFS), overall survival (OS), and objective response rate (ORR) were investigated. Analysis for PFS and OS was performed using the log-rank test and Mantel-Haenszel method, and analysis of the odds ratio for ORR was performed using Fischer’s exact test.

Results: Forty patients were identified: 93% had clear cell histology, 70% prior nephrectomy, 68% were intermediate risk per IMDC, and 60% were treatment
naïve. Patients with baseline NER < median (N=20) had improved clinical outcomes compared to patients with baseline NER > median (N=20) (Table 1). The median baseline NER among patients with PR was significantly lower at 22.5 (95% CI 12.6-43.5) vs. 51.8 (95% CI 22.8-78.0) among those with PD (p= 0.025).

**Conclusions:** In our single center cohort, patients with a low baseline NER treated with ipilimumab plus nivolumab had improved clinical outcomes compared to patients with a high baseline NER. Additional investigation of this parameter in larger cohorts is warranted.

**NAS120.** A pilot study of Tremelimumab with or without cryoablation in patients with metastatic renal cell carcinoma (mRCC): a post hoc analysis of patients with clear cell (cc) versus non-clear cell (ncc) histologies.

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**Background:** The role of single agent anti-cytotoxic T cell lymphocyte antigen 4 (CTLA-4) is not well defined in mRCC. While ncc accounts for 25-30% of patients with RCC, no data is currently available for post treatment tissue (PTT) changes within the tumor microenvironment for patients who receive CTLA-4 based treatment.

**Methods:** NCT02626130 randomized patients to Tremelimumab (CTLA-4) alone or after cryoablation for two doses followed by surgery or biopsy followed by maintenance Tremelimumab. The study was histology agnostic. Tissue based immune monitoring data (IMD) including IHC, CyTOF and Nanostring. A post hoc pooled analysis of patients with ccRCC versus nccRCC was conducted.

**Results:** 18 patients with ccRCC and 11 patients with nccRCC: median progression-free survival (PFS) of 4.3 versus 3.0 months (HR 0.30, 95% CI:0.10-0.91). At 12 months, PFS estimates were 27.8% ccRCC and 9.1% nccRCC, respectively. IMD revealed baseline gene expression differences between ccRCC and nccRCC: enriched IFN-γ signaling pathway in ccRCC. CyTOF analysis revealed a significant increase in CD45+ and CD3+ cells in PTT in ccRCC patients. IHC studies confirmed CD3+granzyme B+PD-1+ T cells were enriched in PTT in ccRCC.

**Conclusion:** Patients with ccRCC had better response to single agent CTLA-4 therapy than nccRCC. Baseline differences in the immune micro-environment may influence the ability to induce an inflamed immune response conducive to benefit with CTLA-4 therapy.

**NAS121.** Real-World Referral and Adjuvant Treatment Patterns in High-Risk Locoregional Renal Cell Carcinoma
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Background: It is unclear whether post-nephrectomy patients with renal cell carcinoma (RCC) are routinely assessed for recurrence risk post-operatively and whether patients at high recurrence risk are seen by providers who can evaluate candidacy for adjuvant systemic therapy (AST) and adjuvant clinical trials.

Methods: We identified all patients with locoregional RCC who underwent nephrectomy within Duke University Health System between 4/1/2015 and 12/31/2019 via an institutional database. Medical records were reviewed to identify patient characteristics, post-nephrectomy referrals, treatment, and follow up. Patients with tumor stage ≥3 and tumor grade ≥2, regional lymph-node metastasis, or both, were classified as high recurrence risk.

Results: Of 618 patients with locoregional RCC who underwent nephrectomy, 136 (22%) had high risk of recurrence. Of those, 25 patients with high risk disease (18%) were referred to a medical oncologist for discussion of AST. Twenty-three (92%) referrals took place ≥2018. Three patients received AST. The decision not to receive AST after referral was primarily made by the oncologist in 10 (46%), patient in 8 (36%), and unrecorded in 4 (18%) of 22 cases for multiple reasons (Figure 1). Individual surgeons referred high risk patients for discussion of AST with varying frequency, ranging from 0 to 100% in 2019.

Conclusions: Despite increasing patients with high-risk locoregional RCC referred to medical oncologists after nephrectomy, few patients received AST. These findings highlight the need for continued identification of effective AST and referral of patients most likely to benefit.

NAS122. Metabolic gene signature as biomarker for recurrence in localized clear cell RCC

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Background: Patients with high risk localized ccRCC have ≥40% risk of recurrence after surgery. As multiple drugs, are being evaluated in the peri-operative setting, there is need to identify biomarkers. A cardinal feature of ccRCC is metabolic reprogramming and downregulation of metabolic genes. Here we present metabolic gene signature analysis of a publically available database.

Methods: Caucasian males with stage III ccRCC in the TCGA cohort for whom recurrence data is available with a minimum follow-up of 2 years were included. The cohort included patients that remained disease free for at least 24 months after surgery (n = 22) and patients whose cancer recurred within 24 months (n = 20). A set of 86 genes encoding members of electron transport chain (ETC) and enzymes of TCA cycle were used.

Results: We identified a signature of 11 significantly changed ETC genes which stratified the 42 patients into three subtypes: significantly enriched for a) recurrence (subtype 1), for b) disease free status (subtype 2) and b) intermediate (subtype 3). Importantly, metabolic genes showed different correlational co-expression patterns associated with prognosis. Work is underway to combine the use of individual gene expression and ratios
of gene expression within the signature to optimize prognostic biomarkers for localized ccRCC.

**Conclusion:** In this analysis, we have identified a metabolic gene signature which can help identify patients with localized ccRCC at high risk of recurrence after surgery to guide aggressive therapy.

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**ENCORE ABSTRACT**

**EA123. Factors associated with clinical trial participation for patients with renal cell carcinoma**

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**Background:** Clinical trials are critical for the development of new treatment paradigms for renal cell carcinoma (RCC). The primary objective of this study was to characterize the factors associated with clinical trial participation for patients with RCC. The secondary objective was to examine survival outcomes in the clinical trial and control cohorts.

**Methods:** The National Cancer Database (NCDB) was queried for patients with RCC who were coded as having enrolled in a clinical trial. Trial patients were matched in a 1:5 ratio to controls from the same institution based on clinical stage. Sociodemographic variables were compared between the two groups and univariate and multivariate logistic regression models evaluated factors associated with clinical trial participation. Kaplan-Meier product limit estimate was used to compare overall survival (OS) between the groups.

**Results:** From 2004-2015, 681 patients enrolled in clinical trials were included for analysis. The mean age of trial patients was 56.4 compared to 62 in the matched cohort (p<0.0001). More patients in the trial group had a Charlson-Deyo comorbidity score of 0 (81.6% vs. 73.9%, p<0.0001). On multivariate analysis, male patients (OR 1.27; 95%CI 1.06-1.54, p=0.012) and white patients (OR 1.88, 95%CI 1.23-2.87; p=0.003) were more likely to participate in a trial. Having Medicaid (OR 0.42; 95%CI 0.27-0.64; p<0.0001) or Medicare (OR 0.6; 95%CI 0.46-0.77; p<0.0001) was negatively associated with clinical trial participation. Median OS was greater among clinical trial participants than that the control cohort (106.61 vs 87.62 months, p<0.0001).

**Conclusions:** In this contemporary analysis of RCC patients from a national hospital registry database, we found that patient sociodemographic factors remain associated with clinical trial participation and that clinical trial participants experienced superior OS. Further work, both qualitative and quantitative, is necessary to identify clinical and non-clinical barriers to research participation in order to improve the validity of RCC trials.

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EA124. Quality-adjusted Time Without Symptoms or Toxicity (Q-TWiST) of Lenvatinib+Everolimus vs Everolimus Monotherapy in Advanced Renal Cell Carcinoma (aRCC)

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Background: Lenvatinib+everolimus (vs everolimus) previously demonstrated significant improvement in progression-free survival in pretreated patients with aRCC (NCT01136733). This post hoc analysis evaluated the impact of lenvatinib+everolimus on Q-TWiST.

Methods: Patients’ survival was partitioned into 3 mutually exclusive health states: time with grade 3/4 toxicity (TOX), time without disease progression and without grade 3/4 toxicity (TWiST), and time post-disease progression (REL). Mean time spent in each state was weighted by health-state utility and summed to calculate Q-TWiST. Base-case utility assumptions for TWiST, TOX, and REL were 1.0, 0.5, and 0.5, respectively. A relative Q-TWiST gain of ≥10% has been established as being clinically important.

Results: Patients receiving lenvatinib+everolimus (n=51) vs everolimus (n=50) had a significantly longer mean time in TWiST (10.9 vs 6.4 months; difference 4.5 [95% CI: 1.4-7.8]), a numerically longer time in TOX (1.9 vs 0.7 months), and a shorter time in REL (5.8 vs 8.5 months). At base-case, lenvatinib+everolimus patients had a significant Q-TWiST gain of 3.7 months (14.7 vs 11.0 [95% CI of difference: 1.3-6.3]), with a relative gain of 24% vs everolimus. In sensitivity analyses using alternative TWiST utility values (range, 0.55-0.9), relative gain ranged from 11.0% to 21.2% (all statistically significant). With TWiST utility set as 1.0, and utility of TOX and REL varying, Q-TWiST relative gain ranged from 11.2% to 37.0%.

Conclusions: Lenvatinib+everolimus resulted in a statistically significant and clinically important gain in Q-TWiST vs everolimus.

EA125. Phase 2 trial of lenvatinib + pembrolizumab for progressive disease after PD-1/PD-L1 immune checkpoint inhibitor (ICI) in metastatic clear cell (mcc) renal cell carcinoma (RCC): results by independent imaging review (IIR) and subgroup analyses

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Background: Lenvatinib + everolimus is approved for advanced RCC following VEGF-targeted therapy. Pembrolizumab + axitinib is approved first-line for advanced RCC. We report phase 2 results of the RCC cohort of a phase 1b/2 trial (Study 111/KEYNOTE-146) of lenvatinib + pembrolizumab in mccRCC.

Methods: This multicenter, open-label study enrolled patients with mccRCC (measurable per irRECIST) who progressed previously per RECIST v1.1 (confirmed ≥ 4 weeks later) during or following ICI therapy. Patients received lenvatinib 20 mg orally daily + pembrolizumab 200 mg IV Q3W. Tumors were assessed Q6W (until week 24), then Q9W. Primary endpoint: objective response rate (ORR) at week 24 (irRECIST per investigator assessment).

Results: 104 Patients were enrolled. Median duration of follow-up for OS was 12.3 months. 65% Of patients had prior anti-PD-1/PD-L1 and anti-VEGF therapy; 37% of patients had prior nivolumab + ipilimumab. ORR week 24 was 53.8% (partial responses: 56/104; 95% CI 43.8–63.7) by investigator assessment (irRECIST). Data by IIR and subgroup analyses are shown in the Table. The most common treatment-related adverse events (TRAEs) were fatigue (55%), diarrhea (46%), and proteinuria (38%). Two grade 5 TRAEs occurred (upper gastrointestinal hemorrhage; sudden death). 14% Of patients discontinued lenvatinib and/or pembrolizumab because of TRAEs.

Conclusions: Lenvatinib + pembrolizumab demonstrated promising antitumor activity in mccRCC after ICI therapy, with no new safety signals.

EA126. Depth of response (DepOR) analysis and correlation with clinical outcomes from JAVELIN Renal 101.

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Background: Avelumab + axitinib (A+Ax) significantly improved progression-free survival (PFS) vs sunitinib (S) in patients (pts) with advanced renal cell carcinoma (HR 0.69; 95% CI, 0.56, 0.84; P<0.001) (Motzer NEJM 2019). We report on the correlation of PFS with DepOR at early imaging timepoints.

Methods: Data from the first interim analysis of JAVELIN Renal 101 (NCT02684006; minimum follow-up of 6.0 mo) were analyzed by blinded independent central review per RECIST 1.1. Tumor shrinkage or growth was categorized by best percent change in target lesions on imaging obtained up to 13 wk: shrinkage ≥ 0% to <30%, ≥30% to <60%, and ≥60% and growth >0% to <20%. Pts without progressive disease and who had not died at or prior to 13 wk after randomization were included in the landmark analysis. PFS data were analyzed for each category. A Cox multivariate
landmark analysis was conducted for PFS for the A+Ax arm, with DepOR as a continuous variable.

Results: The table shows the proportion of pts in each category and PFS outcomes at the 13-wk landmark. After adjusting for prognostic covariates, Cox multivariate analyses showed a meaningful association between DepOR and PFS for the A+Ax arm, consistent with results observed in shrinkage categories.

Conclusion: Greater tumor shrinkage at early imaging timepoints was associated with longer PFS in JAVELIN Renal 101.

EA127. Correlative serum biomarker analyses: lenvatinib (LEN) plus pembrolizumab (PEMBRO) in a phase 1b/2 trial in advanced renal cell carcinoma (RCC)

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Background: In a phase 1b/2 trial (NCT02501096), LEN+PEMBRO had promising efficacy in advanced RCC. We present an exploratory biomarker analysis for LEN+PEMBRO in immune checkpoint blockade-naïve patients with advanced RCC.

Methods: Patients received LEN 20mg orally daily + PEMBRO 200mg intravenously Q3W. Tumors were assessed by investigators per immune-related RECIST. 38 Serum biomarkers were quantified (at baseline, cycle 1 day 15 [C1D15], and C2D1). Baseline biomarker levels were correlated with objective response (OR [complete + partial responses]; via Wilcoxon rank sum test) and PFS (via univariate Cox regression). Associations between composite biomarker scores (CBSs) and PFS were made.

Results: Biomarkers were analyzed in 27 LEN+PEMBRO-treated patients. Levels of 13 biomarkers (eg, CXCL9, CXCL10, VEGF, IFN-γ, FGF-23, and VEGF-D) increased and 5 biomarkers (eg, ANG-2 and VEGFR-2) decreased at both C1D15 and C2D1. ORs occurred in 70.4% patients; ORs were associated with high levels of VEGFR-2 and low levels of VDBP, TNFR2, FGF-21, IL-2RA, CRP, vWF, and IL-18BP at baseline (P<0.05). Longer PFS was associated with low baseline levels of 5 biomarkers (table). CBS data will be presented.

Conclusions: Low baseline levels of FGF-21, IL-2RA, IL-18BP, and TNFR2 were associated with OR and longer PFS in patients with advanced RCC treated with LEN+PEMBRO. Conclusions are limited due to testing multiple variables in a small sample. Further investigation of LEN+PEMBRO in a phase 3 study of advanced RCC (NCT02811861) is ongoing.

EA128. Phase 1/2 Study of the Oral HIF-2α Inhibitor MK-6482 in Patients With Advanced Clear Cell Renal Cell Carcinoma (ccRCC)

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**Background:** MK-6482 is a potent, selective, small-molecule inhibitor of HIF-2α. The expansion cohort of the first-in-human phase 1/2 study (NCT02974738) evaluated safety and antitumor activity of MK-6482 in advanced ccRCC.

**Methods:** Patients with advanced ccRCC who had received ≥1 prior therapy were enrolled. Patients were administered 120 mg of MK-6482 orally once daily. Primary end point: safety. Key secondary end points: ORR, DOR, and PFS.

**Results:** Fifty-five patients enrolled in the dose expansion cohort; 42 were intermediate/poor risk per IMDC criteria. Median number (range) of prior therapies was 3 (1-9); 71% of patients received anti-PD-1 and anti-VEGF agents. Median time from enrollment to data cutoff was 16.7 months; most common all-grade, all-cause AEs >30% were anemia (75%), fatigue (69%), dyspnea (49%), and nausea (36%). Anemia (25%) and hypoxia (16%) were most common grade 3 AEs. No grade 4/5 drug-related AEs were observed. ORR was 24%, with 13 confirmed PRs. Thirty-one patients (56%) had SD, with a disease control rate (CR+PR+SD) of 80%. Median DOR was not reached; in 62% of patients DOR was ≥6 months. Median PFS was 14.5 months (95% CI, 7.3-NR). As of data cutoff, 32 patients (58%) discontinued because of PD and 2 (4%) because of AEs. Treatment was ongoing in 13 patients (24%).

**Conclusions:** MK-6482 was well-tolerated and demonstrated preliminary antitumor activity in heavily pretreated patients, suggesting that HIF-2α inhibition is effective treatment for ccRCC.

**EA129. Nivolumab plus ipilimumab (NIVO+IPI) versus sunitinib (SUN) for first-line treatment of advanced renal cell carcinoma (aRCC) in CheckMate 214: 4-year follow-up and subgroup analysis of patients without nephrectomy**

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**Background:** Four-year (minimum) efficacy and safety results from CheckMate 214 are reported, along with results from a post hoc subgroup analysis in patients without prior nephrectomy.

**Methods:** Patients with clear cell aRCC were randomized to NIVO 3 mg/kg + IPI 1 mg/kg Q3W×4 then NIVO 3 mg/kg Q2W versus SUN 50 mg QD×4 weeks (6-week cycle). Efficacy endpoints: overall survival (OS), objective response rate (ORR), and progression-free survival (PFS) per independent radiology review committee using RECIST v1.1 in IP (primary), ITT (secondary), and favorable-risk (FAV; exploratory) patients.

**Results:** OS remained superior with NIVO+IPI versus SUN in IP and ITT patients, with no significant difference in FAV patients (Table). ORR was higher with NIVO+IPI versus SUN, with more ongoing responses in IP and ITT patients. In FAV patients, ORR was lower with NIVO+IPI versus SUN, yet more responses were ongoing with NIVO+IPI. PFS was consistent with previous reports. No new safety signals emerged. In patients without prior nephrectomy, OS and ORR benefits were observed with NIVO+IPI versus SUN (Table). A ≥30% reduction in target kidney lesion(s) occurred in 35% (NIVO+IPI) versus 20% (SUN) of patients in this subgroup.

**Conclusions:** With longer follow-up, NIVO+IPI continues to demonstrate durable efficacy benefits, inclusive of patients without prior nephrectomy, with no new safety signals.


**Associated Clear Cell Renal Cell Carcinoma (ccRCC)**

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**Background:** MK-6482, a potent, selective, small-molecule HIF-2α inhibitor, was evaluated for treatment of VHL-associated tumors in this open-label phase 2 study (NCT03401788).

**Methods:** Eligible patients were aged ≥18 years and had VHL diagnosis based on germline VHL alteration, ≥1 measurable solid ccRCC tumor, no prior systemic anticancer therapy, and ECOG PS 0 or 1. Patients received MK-6482 120 mg orally once daily until progression, intolerable toxicity, or investigator/patient decision to withdraw. Primary end point: ORR of VHL-associated ccRCC tumors per RECIST v1.1 by independent review committee (IRC). Secondary end points: ORR in non-RCC tumors by IRC and safety.

**EA130. Oral HIF-2α Inhibitor MK-6482 for von Hippel–Lindau Disease (VHL)—**
**Results:** 56 of 61 (92%) enrolled patients remained on treatment with a minimum of 60 weeks’ follow-up. All patients had ccRCC; 100% had pancreatic lesions, 70% had CNS hemangioblastomas, and 26% had retinal lesions evaluable by IRC. For ccRCC, ORR was 36% (95% CI, 24%-49%), and an additional 7 (11%) unconfirmed responses (documented at single time point and pending confirmation at data cutoff) were reported; all were PRs. For non-RCC tumors, ORR was 64% (4 CRs) in pancreatic lesions and 30% (5 CRs) in CNS hemangioblastomas. Of 16 patients with evaluable retinal lesions, 11 (69%) showed improvement. 98% of patients reported treatment-related adverse events (TRAEs); 13% had grade 3 TRAEs, and none had grade 4-5 TRAEs.

**Conclusions:** MK-6482 continued to demonstrate promising antitumor activity against VHL-associated ccRCC and non-RCC tumors and was well tolerated.

**EA131. A phase 2 study of lenvatinib (LEN) plus everolimus (EVE) in patients with advanced non-clear cell renal cell carcinoma (ncRCC)**

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**Background:** nccRCC includes papillary, chromophobe, and unclassified RCC. LEN is a multikinase inhibitor of the VEGF receptor and other targets; EVE is an mTOR inhibitor. LEN + EVE is approved for the treatment of patients with advanced RCC following 1 prior antiangiogenic therapy. This phase 2 study examined the efficacy and safety of LEN + EVE in patients with nccRCC.

**Methods:** This single-arm, multicenter, phase 2 study assessed the efficacy and safety of LEN (18 mg once daily) + EVE (5 mg once daily) in patients with unresectable advanced or metastatic nccRCC and no prior chemotherapy for advanced disease. The primary objective was objective response rate (ORR) by investigators per RECIST v1.1. Secondary objectives included PFS, OS, and safety.

**Results:** At data cutoff (July 17, 2019), 31 patients with nccRCC (papillary, n=20; chromophobe, n=9; unclassified, n=2) were enrolled and treated. The ORR was 25.8% (95% CI: 11.9-44.6%); 8 patients achieved a partial response (papillary, n=3; chromophobe, n=4; unclassified, n=1); and no patients had a complete response. Median PFS was 9.23 months (95% CI: 5.49-not estimable [NE]); median OS was 15.64 months (95% CI: 9.23-NE). The safety profile was consistent with the established profile of LEN + EVE.

**Conclusion:** The combination of LEN + EVE showed promising antitumor activity as a potential first-line therapy in patients with advanced nccRCC. The ORR (25.8%) compares favorably with historical reports of EVE monotherapy.

Clinical trial registration: NCT02915783

**EA132. Clinical IMpact of Early Progression among PAtients (Pts) with Metastatic Renal Cell Carcinoma (mRCC)**
Treated with First-line (1L) Tyrosine Kinase Inhibitors (TKIs): IMPACT RCC Real-world Study

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*Affiliation at the time the analysis was conducted.

**Background:** mRCC pts who progress to second-line (2L) systemic therapy have a high disease burden, suggesting benefits to delaying 1L progression. We examined the clinical impact of early vs delayed disease progression among mRCC pts.

**Methods:** Newly diagnosed mRCC pts treated with 1L TKI monotherapies followed by 2L therapy were identified between OCT2013-MAR2018 within the US Veterans Health Administration database (1L start date = index date). Eligible pts had continuous enrollment ≥6 months post-2L therapy initiation, unless the pt died. Kaplan-Meier (KM)-derived median time to 2L therapy initiation was used to categorize pts into early (=median) and delayed (>median) progression cohorts. KM analysis and Cox proportional hazards models were used to assess the impact of predictive factors on clinical outcomes.

**Results:** Among 289 mRCC pts, the mean age was 67.4 y and the median time to 2L initiation was 6.1 mo. Pt characteristics were similar between the early (n=145) and delayed (n=144) progression cohorts. During follow-up, the delayed progression cohort had better clinical outcomes than the early progression cohort (Table).

**Conclusions:** Early progression is associated with worse clinical outcomes among mRCC pts, confirming the need to adopt for more effective 1L treatment strategies (eg, immuno-oncology–based combinations) that have potential to delay disease progression and reduce disease burden.

EA133. Nivolumab plus cabozantinib (NIVO+CABO) versus sunitinib (SUN) in first-line treatment for advanced renal cell carcinoma (aRCC): the phase 3 CheckMate 9ER trial

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Background: Results from the randomized phase 3 CheckMate 9ER trial evaluating the checkpoint inhibitor NIVO plus the TKI CABO versus SUN for first-line treatment of aRCC are reported.

Methods: Patients were randomized 1:1 (stratified by IMDC risk, tumor PD-L1 expression, region) to NIVO 240 mg IV Q2W + CABO 40 mg PO QD versus SUN 50 mg PO for 4 weeks (6-week cycles) until disease progression/unsatisfactory toxicity (max NIVO treatment, 2 years). Primary endpoint: progression-free survival (PFS; α=0.05 final) by blinded independent central review (BICR). Secondary endpoints (hierarchical testing): overall survival (OS; α=0.011 first interim analysis), objective response rate (ORR; α=0.05 final) by BICR, and safety.

Results: Overall, 651 patients (22.6% favorable, 57.6% intermediate, 19.7% poor risk; 24.9% PD-L1 ≥1%) were randomized to NIVO+CABO (n=323) versus SUN (n=328). With 18.1 months median (10.6 months minimum) study follow-up, all 3 efficacy endpoints were met. NIVO+CABO significantly improved PFS, OS, and ORR compared with SUN (Table), and results were consistent across prespecified subgroups. More patients achieved a complete response and median duration of response was longer with NIVO+CABO versus SUN (Table). Any-grade TRAEs occurred in 96.6% versus 93.1% of patients with NIVO+CABO versus SUN; TRAEs leading to discontinuation are summarized in the Table.


EA134. Phase II Study of Bevacizumab and Erlotinib in Subjects with Advanced Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) or Sporadic Papillary Renal Cell Cancer

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Background: HLRCC is characterized by germline mutations in the fumarate hydratase (FH) gene and predisposes to a type 2 papillary RCC (pRCC) variant. We hypothesized that the combination of bevacizumab and erlotinib would be active in HLRCC and sporadic pRCC.

Methods: Patients with 1) HLRCC and 2) sporadic pRCC were enrolled into parallel, independent cohorts and received bevacizumab 10 mg/kg IV every 2 weeks plus erlotinib 150 mg orally daily. Prior therapy with up to two VEGFR targeted agents was allowed. The primary endpoint was overall response rate (ORR); progression free survival (PFS) was a secondary endpoint.

Results: A total of 83 patients, including 43 with HLRCC and 40 with sporadic pRCC were enrolled. The majority were IMDC intermediate risk (53/83, 64%) and 27 (33%) had at least one prior treatment. The ORR was 54.2% (45/83; 95% CI, 43.6 – 64.5) in all patients, 72% (31/43; 95% CI, 57.2 – 83.4) in the HLRCC cohort, and 35% (14/40; 95% CI, 22.1 – 50.6) in the sporadic pRCC cohort. The median PFS was 14.3 months (95% CI, 11.5 – 21.1). The most common grade ≥3 TRAE was hypertension (34%).

Conclusions: Bevacizumab plus erlotinib is well tolerated and has encouraging activity in advanced pRCC, particularly in patients with FH deficient tumors. This is the first prospective study in HLRCC and provides the basis for considering bevacizumab and erlotinib as a preferred option.

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TRIAL-IN-PROGRESS

TIP135. A Phase 3, Randomized, Placebo-Controlled Trial of Nivolumab or Nivolumab+Ipilimumab in Patients With Localized Renal Cell Carcinoma (RCC) at High Risk of Relapse After Radical or Partial Nephrectomy (CheckMate 914)

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Background: Surgery is standard treatment for nonmetastatic RCC, but patients with stage II-III disease have a high risk of relapse (5-year disease-free survival [DFS]: ~51%-56%); prevention of recurrence is an unmet need. Nivolumab alone and nivolumab+ipilimumab provide clinical benefits in advanced/metastatic RCC, indicating potential for efficacy in early-stage adjuvant settings. The CheckMate 914 study will evaluate nivolumab and nivolumab+ipilimumab versus placebo in patients with high risk of relapse after nephrectomy (NCT03138512).

Trial Design: Key inclusion criteria: radical or partial nephrectomy with negative surgical margins >4 and ≤12 weeks before randomization; predominantly clear-cell histology; pathologic TNM staging (grade) T2a(3/4)NoMo, T2b-T4(any)NoMo, or T(any)N1M0; ECOG performance status ≤1; no macroscopic residual disease or distant metastases post-nephrectomy; tumor tissue obtained ≤3 months pre-enrollment. Key exclusion criteria: conditions requiring corticosteroid/immunosuppressive systemic treatment, autoimmune disease, prior treatment targeting T-cell co-stimulation/checkpoint pathways, prior systemic RCC treatment. Patients are randomized 1:1 to receive nivolumab+ipilimumab or placebo (part A), or 1:1:2 to receive nivolumab+ipilimumab, placebo, or nivolumab (part B), for 24 weeks or until recurrence, unacceptable toxicity, or withdrawal of consent. Patients will be stratified by IMDC prognostic score (0, 1-2, 3-6) and number of prior TKI-containing therapies (0, 1, 2-3). Adverse events will be monitored throughout the study and for 30 days after treatment (90 days for serious AEs). The primary endpoint is ORR per RECIST v1.1 by blinded independent central review (BICR). Secondary endpoints are PFS, DOR, and clinical benefit rate per RECIST v1.1 by BICR, OS, pharmacokinetics, and safety. Enrollment is ongoing (total target, 1600 patients).

TIP136. Open-Label Phase 2 Study of Two Doses of MK-6482 for the Treatment of Advanced Renal Cell Carcinoma Following Progression on Prior Systemic Therapy

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Background: Treatment options for patients with clear cell renal cell carcinoma (ccRCC) after immunotherapy and VEGF-targeted therapy are limited. MK-6482, a small-molecule inhibitor of hypoxia-inducible factor-2α, has shown activity in heavily pretreated advanced ccRCC. This randomized, open-label, phase 2 trial (NCT04489771) evaluates efficacy and safety of 2 doses of MK-6482 in patients with advanced ccRCC who have experienced disease progression after systemic therapy.

Trial Design: Eligible patients are aged ≥18 years with histologically confirmed, locally advanced or metastatic ccRCC (measurable disease per RECIST v1.1) who have experienced progression after first-line systemic treatment comprising an anti–PD-1/anti–PD-L1 agent combined with a VEGF-targeted tyrosine kinase inhibitor (TKI) or an anti–CTLA-4 agent and have undergone no more than 3 prior systemic regimens. Approximately 150 patients will be randomly assigned 1:1 to receive oral MK-6482 120 mg once daily or 200 mg once daily; treatment will continue until progression, unacceptable toxicity, or withdrawal. Patients will be stratified by IMDC prognostic score (0, 1-2, 3-6) and number of prior TKI-containing therapies (0, 1, 2-3). Adverse events will be monitored throughout the study and for 30 days after treatment (90 days for serious AEs). The primary end point is ORR per RECIST v1.1 by blinded independent central review (BICR). Secondary end points are PFS, DOR, and clinical benefit rate per RECIST v1.1 by BICR, OS, pharmacokinetics, and safety. This study is recruiting.
TIP137.  AURORAX-0087A, a multinational diagnostic study for detection of intermediate to high risk clear renal cell carcinoma: Trial in progress report

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**Background:** About 20% of patients who undergo curative surgery for non-metastatic clear cell renal cell carcinoma (ccRCC) recur within 5 years. Current follow-up guidelines using regular interval imaging are not optimized for early detection of recurrence. Blood and urine glycosaminoglycans (GAGs) have emerged as promising metabolic biomarkers of ccRCC. In previous studies, GAG profiling condensed into so-called GAG scores could distinguish any-stage RCC from control subjects with high accuracy. To validate the clinical use of GAGs in the surveillance of ccRCC recurrence after surgery, we initiated the prospective multicenter diagnostic test cohort study AURORAX-0087A (AUR87A; NCT04006405).

**Trial Design:** AUR87A is currently enrolling up to 280 non-metastatic curatively treated ccRCC patients with intermediate or high risk of recurrence (Leibovich points >= 5) across 16 EU and US sites. GAG scores from blood and urine samples, collected preoperatively and every 3 months post-surgery, are compared to standard of care follow-up imaging for recurrence detection. The primary endpoint is GAG score sensitivity and specificity to radiological recurrence.

**Conclusion:** Since first patient enrollment in January 2020, over 90 patients have been screened and 26 are
now enrolled in follow-up. An interim analysis in late 2021 will assess the GAG score sensitivity and specificity estimates. AUR87A aims to validate GAG scores as ccRCC biomarkers and demonstrate that a post-surgery increase in GAG scores can detect recurrence at an earlier or equal time-point compared to imaging. Study completion is expected in mid-2022.

**TIP138. CONTACT-03: Randomized, open-label phase III study of atezolizumab plus cabozantinib vs cabozantinib monotherapy following progression on/after immune checkpoint inhibitor (ICI) treatment in patients with advanced/metastatic renal cell carcinoma (RCC)**

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**Background:** Combining anti-angiogenic drugs with ICIs after progression on ICIs presents a promising therapeutic approach in RCC. Atezolizumab (anti-PD-L1) has shown activity in combination with anti-angiogenic therapy after prior progression with ICI. Cabozantinib promotes an immune-permissive environment, improving OS in second-line RCC, and may enhance atezolizumab activity. In Phase Ib COSMIC-021, cabozantinib+atezolizumab safety and efficacy was favorable in clear-cell(cc)RCC and non-ccRCC (Pal [702O] and McGregor [709P], ESMO2020). The Phase III CONTACT-03 study is further evaluating cabozantinib+atezolizumab vs cabozantinib in second-line/third-line RCC.

**Methods:** CONTACT-03 (NCT04338269; opened July 2020) will enroll ~500 patients globally. Patients must have ccRCC or non-ccRCC (papillary or unclassified); radiographic progression during or following ICI (anti-PD-L1/anti-PD-1) as the immediate preceding therapy (first-line/second-line); measurable disease (RECIST1.1); KPS score ≥70%. Prior cabozantinib or prior adjuvant ICI are exclusionary. Stratification factors are IMDC risk group (0 vs 1–2 vs ≥3); most recent ICI (first-line vs second-line); and histology (dominant cc without sarcomatoid vs dominant non-cc [papillary or unclassified] without sarcomatoid vs any sarcomatoid component [cc or non-cc]). Patients will be randomized 1:1 to receive atezolizumab (1200mg/IV/q3w) plus cabozantinib (60mg/oral/daily) or cabozantinib alone (60mg/oral/daily) until unacceptable toxicity or loss of clinical benefit. Multiple primary endpoints are independent review facility (IRF)-assessed PFS and OS. Additional endpoints include investigator-assessed PFS, IRF- and investigator-assessed ORR and DOR; HRQOL, biomarkers and safety. Efficacy will be assessed per RECIST1.1.

**TIP139. MK-6482, a Hypoxia-Inducible Factor 2α Inhibitor, Versus Everolimus in Heavily Pretreated, Immune Checkpoint Inhibitor–Resistant, Advanced Clear Cell Renal Cell Carcinoma (ccRCC): Phase 3 Study**

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**Background:** In most RCC cases, the Von Hippel-Lindau (VHL) tumor suppressor gene is inactivated, resulting in accumulation and overactivation of hypoxia-inducible factor 2α (HIF-2α). MK-6482 is a
antitumor activity in a phase 1/2 study in pretreated, advanced ccRCC (NCT02974738). This open-label, multicenter, randomized, active-controlled, phase 3 study (NCT04195750) will assess efficacy and safety of MK-6482 versus everolimus in patients with previously treated advanced ccRCC.

**Methods:** Eligible patients are adults with unresectable, locally advanced, or metastatic ccRCC; measurable disease per RECIST v1.1; and a history of ≤3 systemic regimens for locally advanced or metastatic RCC—including at least 2 doses of a PD-1/PD-L1 inhibitor and a VEGF-targeted therapy alone or in combination resulting in progression. Approximately 736 patients will be randomized 1:1 to oral once-daily MK-6482 120 mg or everolimus 10 mg until documented disease progression, withdrawal of consent, or other discontinuation. Randomization will be stratified by IMDC prognostic scores (0 vs 1-2 vs 3-6) and by number of prior anti-VEGF–targeted therapies (1 vs 2-3). Responses will be assessed by CT/MRI per RECIST v1.1 by blinded independent central review at week 8 from date of randomization, then Q8W weeks through week 49, and Q12W thereafter. Dual primary end points are PFS per RECIST v1.1 and OS. Key secondary end points are ORR, duration of response, PROs, and safety.

**Background:** Cabozantinib (C) inhibits tyrosine kinases involved in tumor growth, angiogenesis, and immune regulation, including MET, VEGFR, and TAM kinases (Tyro3, AXL, MER), and may promote an immune-permissive tumor environment, resulting in enhanced response to immune checkpoint inhibitors. C has shown preliminary clinical activity and tolerability in combination with the PD-1 inhibitor nivolumab (N) and as part of a triplet combination with N and the CTLA-4 inhibitor ipilimumab (I) in patients (pts) with advanced renal cell carcinoma (aRCC) (Nadal et al. ASCO 2018). C is approved for pts with aRCC, and N+I is approved as a combination therapy in pts with previously untreated aRCC of intermediate or poor risk. We present the study design of a phase 3 trial of C+N+I vs N+I in previously untreated pts with aRCC of intermediate or poor risk (NCT03937219).

**Methods:** This randomized, double-blind, controlled phase 3 study evaluates the efficacy and safety of C+N+I vs N+I in previously untreated pts with IMDC intermediate or poor risk aRCC. Eligible pts are randomized 1:1 to receive C+N+I or N+I in combination with placebo, stratified by IMDC prognostic score and geographic region. Pts receive C (40 mg oral QD) + N (3 mg/kg IV Q3W) x 4 doses + I (1 mg/kg IV Q3W) x 4 doses, followed by C (40 mg oral QD) + N (480 mg IV flat dose Q4W). Control pts receive C-matched placebo and the same treatment regimen for N+I as the experimental arm. N will be administered for a maximum of 2 years. Eligibility criteria include histologically confirmed metastatic or aRCC with a clear cell component, intermediate or poor risk RCC per IMDC criteria, measurable disease per RECIST 1.1, KPS ≥70%, adequate organ and marrow function and age ≥18 years. Exclusion criteria include prior systemic therapy for aRCC and uncontrolled significant illnesses. The primary endpoint is PFS per RECIST 1.1 by BICR; the secondary endpoint is OS. Additional endpoints include ORR, safety, correlation of biomarkers with outcomes, and pharmacokinetics of C in combination with N+I. The first patient was enrolled in June 2019 and enrollment is ongoing.

**TIP140. A phase 3 study (COSMIC-313) of cabozantinib in combination with nivolumab and ipilimumab in patients with previously untreated advanced renal cell carcinoma of intermediate or poor risk.**

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**Background:** Cabozantinib (C) inhibits tyrosine kinases involved in tumor growth, angiogenesis, and immune regulation, including MET, VEGFR, and TAM kinases (Tyro3, AXL, MER), and may promote an immune-permissive tumor environment, resulting in enhanced response to immune checkpoint inhibitors. C has shown preliminary clinical activity and tolerability in combination with the PD-1 inhibitor nivolumab (N) and as part of a triplet combination with N and the CTLA-4 inhibitor ipilimumab (I) in patients (pts) with advanced renal cell carcinoma (aRCC) (Nadal et al. ASCO 2018). C is approved for pts with aRCC, and N+I is approved as a combination therapy in pts with previously untreated aRCC of intermediate or poor risk. We present the study design of a phase 3 trial of C+N+I vs N+I in previously untreated pts with aRCC of intermediate or poor risk (NCT03937219).

**Methods:** This randomized, double-blind, controlled phase 3 study evaluates the efficacy and safety of C+N+I vs N+I in previously untreated pts with IMDC intermediate or poor risk aRCC. Eligible pts are randomized 1:1 to receive C+N+I or N+I in combination with placebo, stratified by IMDC prognostic score and geographic region. Pts receive C (40 mg oral QD) + N (3 mg/kg IV Q3W) x 4 doses + I (1 mg/kg IV Q3W) x 4 doses, followed by C (40 mg oral QD) + N (480 mg IV flat dose Q4W). Control pts receive C-matched placebo and the same treatment regimen for N+I as the experimental arm. N will be administered for a maximum of 2 years. Eligibility criteria include histologically confirmed metastatic or aRCC with a clear cell component, intermediate or poor risk RCC per IMDC criteria, measurable disease per RECIST 1.1, KPS ≥70%, adequate organ and marrow function and age ≥18 years. Exclusion criteria include prior systemic therapy for aRCC and uncontrolled significant illnesses. The primary endpoint is PFS per RECIST 1.1 by BICR; the secondary endpoint is OS. Additional endpoints include ORR, safety, correlation of biomarkers with outcomes, and pharmacokinetics of C in combination with N+I. The first patient was enrolled in June 2019 and enrollment is ongoing.
**CLINICAL TRIAL WITH RESULTS**

**CTR141. Pembrolizumab Plus Axitinib Versus Sunitinib as First-Line Therapy for Advanced Renal Cell Carcinoma (RCC): Subgroup Analysis from KEYNOTE-426 by Prior Nephrectomy.**

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**Background:** Results of the randomized, open-label, phase 3 KEYNOTE-426 study (NCT02853331) demonstrated that pembrolizumab+axitinib significantly improved OS, PFS, and ORR versus sunitinib as first-line therapy for advanced RCC. Results are presented from a subgroup analysis of patients who underwent prior nephrectomy (PN) or had not undergone prior nephrectomy (NPN).

**Methods:** Treatment-naive patients with clear cell RCC, KPS ≥70%, and measurable disease (RECIST v1.1) were randomly assigned 1:1 to receive pembrolizumab 200 mg intravenously Q3W for up to 35 doses + axitinib 5 mg orally twice daily or sunitinib 50 mg once daily (4-weeks on/2-weeks off) until progression, toxicity, or withdrawal. Primary end points: OS and PFS. Secondary end points: ORR, and safety. Subgroup analysis was unplanned; no adjustments for multiplicity were made.

**Results:** Of 861 patients, 718 (83.4%) had PN and 143 (16.6%) had NPN. OS and PFS were longer with pembrolizumab+axitinib than with sunitinib in PN and NPN subgroups (Table). ORR was higher with pembrolizumab+axitinib than with sunitinib for PN (61.8% vs 43.5%; difference [95% CI]: 18.7% [11.5-25.6]) and NPN (52.1% vs 21.4%; difference [95% CI]: 29.8% [14.2-44.4]) subgroups. Safety was similar to that of the overall population.

**Conclusions:** In this subgroup analysis, pembrolizumab+axitinib demonstrated OS, PFS, and ORR benefit relative to sunitinib in first-line advanced RCC patients with PN and NPN. These results are consistent with the primary analysis of KEYNOTE-426."

**CTR142. Phase 2 trial of lenvatinib at 2 starting doses + everolimus in renal cell carcinoma (RCC)**
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**Background:** Lenvatinib 18mg + everolimus is approved for advanced RCC following anti-angiogenic therapy. We aimed to evaluate whether a lower starting dose of lenvatinib + everolimus would provide similar efficacy with an improved safety profile.

**Methods:** Patients with measurable clear-cell RCC (1 prior VEGF-targeted therapy; prior PD-1/PD-L1 therapy permitted) were randomized 1:1 to lenvatinib 18mg or 14mg (starting dose) + everolimus 5mg daily. Titrated to lenvatinib 18mg if no intolerable grade 2 or any grade ≥3 AEs requiring dose reduction within cycle 1. Primary efficacy endpoint: noninferiority of lenvatinib 14mg versus 18mg for ORR at week 24 [ORRwk24] (Ha: odds ratio of ORRwk24@14mg versus ORRwk24@18mg ≥0.76; P-value for noninferiority test ≤0.045). Primary safety endpoint: proportion of patients with intolerable grade 2 or any ≥grade 3 TEAEs within 24 weeks.

**Results:** Primary efficacy analysis: 311 patients (lenvatinib 14mg, n=156; lenvatinib 18mg, n=155). Primary safety analysis: 309 patients (lenvatinib 14mg, n=157; lenvatinib 18mg, n=152). ORRwk24 of lenvatinib 14mg was not noninferior to ORRwk24 of lenvatinib 18mg (odds ratio: 0.88; 90% CI 0.59-1.32; P-value 0.2676). The occurrence of intolerable grade 2 or any ≥grade 3 TEAEs was similar (lenvatinib 14mg: 82.8%; lenvatinib 18mg: 79.6%; P-value 0.4763). Key efficacy and safety outcomes are in the Table.

**Conclusions:** Lenvatinib 14mg did not demonstrate noninferiority versus lenvatinib 18mg for ORRwk24 and the safety profile was similar. Lenvatinib 18mg + everolimus demonstrated similar activity in a previous phase 2 study (NCT01136733).

ClinicalTrials.gov number: NCT03173560

**CTR143. Nivolumab 6 mg/kg plus ipilimumab 1 mg/kg (N6I1) every 8 weeks (Q8W) alternating with nivolumab 480 mg Q8W for first-line (1L) advanced renal cell carcinoma (aRCC): safety and efficacy from CheckMate 920.**

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**Background:** Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (N3I1) Q3W × 4 doses then nivolumab 3mg/kg Q2W for 1L aRCC demonstrated long-term efficacy/tolerability in registrational CheckMate 214. Modified nivolumab plus ipilimumab dosing was evaluated in phase 3b/4 community-based CheckMate 920 (NCT02982954) on the premise that less frequent dosing may retain efficacy and improve safety.

**Methods:** Patients with previously untreated predominantly clear cell aRCC, any IMDC risk, KPS ≥70% received N6I1 Q8W alternating with nivolumab 480 mg Q8W for ≤2 years or until disease progression/unacceptable toxicity. Primary endpoint: all-cause grade ≥3 immune-mediated adverse events (imAEs). Key secondary endpoints: progression-free survival (PFS) and objective response rate (ORR) by RECIST v1.1 (both per investigator). Exploratory endpoints included overall survival (OS).

**Results:** Of 106 treated patients (minimum follow-up, 28.5 months), median treatment duration (range) for nivolumab was 5.1 (0.0-26.1) and for ipilimumab was 4.0 (0.0-25.7) months. No grade 5 imAEs occurred. Grade 3-4 imAEs (≥2%): diarrhea/colitis (7.5%), rash (4.7%), and hepatitis (2.8%) (Table). Median PFS: 4.8 months (95% CI, 3.0-8.3). ORR (N=96): 34.4% (95% CI, 25.0-44.8). Median time to response: 2.9 months (range, 2.5-36.9). Median OS (N=106): not reached.

**Conclusions:** Q4W nivolumab+Q8W ipilimumab dosing for 1L aRCC elicited no new safety signals and the observed antitumor activity reinforces continued use of the standard combination dosing employed in the pivotal CheckMate 214 study.
Kaelin Delivers A Keynote Lecture On The Future Of The Treatment Paradigm In VHL Disease–Associated RCC at IKCS 2020 Virtual Conference.

William G. Kaelin Jr, MD, a co-recipient of the 2019 Nobel Prize in Physiology or Medicine, Sidney Farber Professor of Medicine, Dana-Farber Cancer Institute and Harvard Medical School, and an investigator at Howard Hughes Medical Institute, delivered a keynote address for the International Kidney Cancer Symposium (IKCS 2020). Dr. Kaelin spoke of recent investigation on effective treatment of target von Hippel-Lindau (VHL) disease–associated renal cell carcinoma (RCC). “Inactivation of VHL is not sufficient for renal carcinogenesis, even if it is an initiating event. In sporadic clear cell RCC, however, VHL inactivation is the initiation event and should be targeted. HIF2 inhibition is both necessary and sufficient for VHL tumor suppression. We think HIF-2 is the driver, or oncprotein, in VHL–associated renal cell carcinoma cells and, if anything, HIF-1 seems to act as a tumor suppressor and is frequently lost in such tumors,” Kaelin said.

“You can start to dream what an eventual kidney cancer curative combination will look like. I suspect that it will contain a VEGF inhibitor, an immune checkpoint inhibitor, maybe a HIF-2α inhibitor, maybe a CDK4/6 inhibitor, and maybe even a MET inhibitor,” said Kaelin. Once, p53 was believed as an important target in these patients, however research has revealed that an intact p53 pathway is not essential for clear cell RCC HIF2-dependence, and TP53 knockout doesn’t alter PT2399 sensitivity of OSRC2 cells. “We no longer think p53 status is a biomarker for HIF2 dependence,” said Kaelin.

Though single agent TKIs such as bevacizumab (Avastin), sunitinib (Sutent), sorafenib (Nexavar), axitinib (Inlyta), pazopanib (Votrient), cabozantinib (Cabometyx), and lenvatinib (Lenvima) are indicated for RCC treatment, their use as single agents do not lead to responses in all patients, and in those who do, they eventually relapse.

Studies demonstrated that HIF-2 inhibitors alone did not generate responses in all patients. VHL-/- RCC is hypersensitive to the MET ligand hepatocyte growth factor/scatter factor in RCC, emphasizing that MET depletion preferentially kills VHL-/- cells, emphasized Kaelin. For example, the dual MET/VEGF inhibitor cabozantinib demonstrated an improvement in overall survival (OS) compared with everolimus (Afinitor), with a median OS of 21.4 months (95% CI, 18.7–not estimable) with cabozantinib and 16.5 months with everolimus (95% CI, 14.7–18.8), leading to a 34% reduction in the risk of death (HR, 0.66; 95% CI, 0.53–0.83; P = .0003).4

CRISPR-based lethal screens and utilizing CDK4/6 could be other synthetic lethality methods which appears to be HIF-independent. In an orthotopic VHL-/- kidney cancer mouse model, the CDK4/6 inhibitor palbociclib (Ibrance) was found to prolong survival, Kaelin added. Beyond its potential use in combination with HIF-2a inhibitors, CDK4/6 inhibitors could also be used as a way to enhance immunotherapy in solid tumors. “I think we might learn something from our friends in the world of breast cancer, because they already learned that combining tamoxifen with a CDK4/6 inhibitor is a good thing to do, and maybe that's because when you add an ER agonist you lower cyclin D1 transcription, and cyclin D1 is then the partner for CDK4/6, which you're now going to inhibit with a small molecule. Maybe we can do something analogous in kidney cancer by combining PT2399 with a CDK4/6 inhibitor at least for those tumors that are still HIF2 dependent.” Kaelin elaborated.

The most recent data, presented at the 2020 ASCO Virtual Scientific Program, showed that the HIF-2α inhibitor MK-6482 led to favorable efficacy and tolerability in patients with VHL disease–associated RCC.

In a phase 2 study (NCT03401788) in patients with VHL disease who have at least 1 measurable RCC tumor, did not receive prior systemic anticancer therapy, did not have metastatic disease, and had an ECOG performance status of either 0 or 1, investigators evaluated the efficacy of MK-6482, HIF-2α inhibitor. Results showed that treatment with MK-6482 led to a confirmed objective response rate (ORR) of 27.9% (95% CI, 17.1–40.8), which comprised 17 partial responses (PRs).4 43 patients (70.5%) achieved stable disease with the HIF-2α inhibitor. At 52 weeks, the progression-free survival (PFS) rate was 98.3%4. The HIF-2α inhibitor also showed promising single-agent activity in patients with heavily pretreated clear cell RCC. Based on these data, the FDA granted a breakthrough therapy designation to MK-6482 for the treatment of patients with VHL disease–associated RCC who have nonmetastatic tumors of less than 3 centimeters, unless immediate surgery is necessitated.


The FDA Granted A Priority Review To Nivolumab Plus Cabozantinib In Advanced Renal Cell Carcinoma.

The FDA has granted a Priority Review designation to supplemental application for the nivolumab (Opdivo) plus cabozantinib (Cabometyx) combination for the treatment of patients with advanced renal cell carcinoma (RCC). The designation was granted based on data from the phase 3 pivotal CheckMate-9ER clinical trial (NCT03141177). This trial demonstrated that the combination reduced the risk of disease progression or death by 49% versus sunitinib...
(Sutent) in treatment-naïve patients with advanced RCC, with a median progression-free survival of 16.6 months versus 8.3 months, respectively (HR, 0.51; P < .0001). Additional findings showed that, at a median follow-up of 18.1 months, the median overall survival was not reached in either arm, and there was a 40% reduction in the risk of death with the combination (HR, 0.60; P = .0010).

The ORR was 55.7% with the combination compared with 27.1% with sunitinib (P < .0001). In the nivolumab/cabozantinib arm, the complete response (CR) rate was 8.0%, and the partial response (PR) rate was 47.7%, while 32.2% of patients had stable disease (SD). In the sunitinib arm, CRs occurred in 4.6% of patients, PRs in 22.6%, and SD in 42.1, while 13.7% had PD and 17.1% were not evaluable/assessed.

More than 50% of patients in the combination arm required a dose reduction of cabozantinib due to adverse events (AEs). The most common any-grade and high-grade treatment-related AEs (TRAEs) appeared similar between the 2 arms. TRAEs led to treatment discontinuations in 15.3% of patients in the combination arm versus 8.8% in the control arm, and 3.1% discontinued the combination due to AEs, 5.6% discontinued nivolumab, and 6.6% discontinued only the cabozantinib. The overall rate of serious AEs was similar between the 2 arms, but liver toxicity was more common with the combination regimen compared with sunitinib. In addition, 19% of patients in the combination arm had required corticosteroids due to immune-related AEs, 4% of which required corticosteroids for at least 30 days.

The data from CheckMate-9ER study were presented during the 2020 European Society for Medical Oncology (ESMO) Virtual Congress. "With their complementary mechanisms of action and evidence that cabozantinib may promote a more immune-permissive environment, we believe there is opportunity for additive or synergistic effects with this potential combination regimen," stated Gisela Schwab, MD, president, product development and medical affairs and chief medical officer, Exelixis.

Cabozantinib was approved by the FDA in December 2017 for use in previously untreated patients with advanced RCC. The FDA approved nivolumab in November 2015 for use in patients with metastatic RCC who progressed on an angiogenesis inhibitor. Nivolumab also has an FDA-approved indication in the front-line setting for use in combination with ipilimumab (Yervoy) as a treatment for intermediate- and poor-risk patients with advanced disease.


Pembrolizumab Plus Lenvatinib Demonstrated Statistically Significant Improvement in Progression-Free Survival, OS and ORR Versus Sunitinib as First-Line Treatment for Patients with Advanced Renal Cell Carcinoma

In the pivotal Phase 3 KEYNOTE-581/CLEAR trial (Study 307) trial, combinations of KEYTRUDA®, Merck's anti-PD-1 therapy, plus LENVIMA, the orally available multiple receptor tyrosine kinase inhibitor discovered by Eisai, and LENVIMA plus everolimus were evaluated versus sunitinib for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

KEYTRUDA plus LENVIMA met the trial's primary endpoint of progression-free survival (PFS) and its key secondary endpoints of overall survival (OS) and objective response rate (ORR), demonstrating a statistically significant and clinically meaningful improvement in PFS, OS, and ORR versus sunitinib in the intention-to-treat (ITT) study population. LENVIMA plus everolimus also met the trial's primary endpoint of PFS and a key secondary endpoint of ORR, demonstrating a statistically significant and clinically meaningful improvement in PFS and ORR versus sunitinib in the ITT study population. The ITT population included patients across all Memorial Sloan Kettering Cancer Center (MSKCC) risk groups (favorable, intermediate, and poor). The safety profiles of both KEYTRUDA plus LENVIMA and LENVIMA plus everolimus were consistent with previously reported studies. Merck and Eisai will discuss these data with regulatory authorities worldwide, with the intent to submit marketing authorization applications based on these results, which will be presented at an upcoming medical meeting.

“The results for KEYTRUDA plus LENVIMA versus sunitinib, which showed a statistically significant improvement in progression-free survival, overall survival, and objective response rate, build on the growing scientific evidence that supports the investigation of KEYTRUDA-based combinations for the first-line treatment of advanced renal cell carcinoma,” said Dr. Gregory Lubiniecki, Associate Vice President, Oncology Clinical Research, Merck Research Laboratories.

“The results from KEYNOTE-581/CLEAR (Study 307) support the potential use of KEYTRUDA plus LENVIMA for the first-line treatment of advanced RCC. These data also support the potential first-line use of LENVIMA plus everolimus, which is already approved in advanced RCC following prior antiangiogenic therapy,” said Dr. Takashi Owa, Vice President, Chief Medicine Creation and Chief Discovery Officer, Oncology Business Group at Eisai.

Source: "KEYTRUDA® (Pembrolizumab) Plus LENVIMA® (Lenvatinib) Demonstrated Statistically Significant Improvement In Progression-Free Survival (PFS), Overall Survival (OS) And Objective Response Rate (ORR) Versus Sunitinib As First-Line Treatment For Patients... - Merck.Com". 2020.

Novel HIF-2α Inhibitor Achieved Durable Responses in VHL-Associated RCC

Treatment with MK-6482, an investigational HIF2α inhibitor, demonstrated durable efficacy as treatment of patients with Von Hippel-Lindau-associated renal cell carcinoma and non-renal lesions, according to phase 2 data presented during the 21st Annual Meeting of the Society of Urologic Oncology.
In the open-label phase 2 study, MK-6482 (NCT03401788), an investigational small molecule HIF-2α inhibitor, has shown demonstrated durable efficacy as treatment of patients with Von Hippel-Lindau (VHL)-associated renal cell carcinoma (RCC) and non–renal lesions, according to presented during the 21st Annual Meeting of the Society of Urologic Oncology (SUO).

Patients received 120 mg of oral MK-6482 once daily. At a median follow-up of 68.7 weeks (range, 18.3–104.7), the objective response rate (ORR) in RCC lesions among 60 evaluable patients was 36.1%, comprising 22 confirmed partial responses (PRs). There were also 7 unconfirmed PRs. Overall, 91.8% (n = 56) of patients had at least some decrease in the size of target lesions. The median duration of response had not yet been reached and the progression-free survival rate at 52 weeks was 98.3%. Thirty-eight (62.3%) patients reached stable disease, 1 patient was not evaluable for response, and 0 patients had progressive disease. Fifty patients had an ECOG performance status of 0, 10 patients had a performance status of 1, and 1 patient had a performance status of 2. Key eligibility criteria for the open-label phase 2 study (NCT03401788) included a confirmed diagnosis of VHL disease (based on germline mutation), at least 1 measurable RCC tumor, and an ECOG performance status of 0 or 1. Prior systemic anticancer therapy was not allowed and patients with metastatic disease were excluded from enrollment. At a minimum follow-up of 60 weeks, 56 (91.8%) patients remained on treatment.

“Promising clinical activity was observed with MK-6482 in treatment-naïve patients with VHL-associated RCC,” said lead study author Ramaprasad Srinivasan, MD, PhD, National Cancer Institute, Bethesda, Maryland. Clinical activity with MK-6482 was observed in non–RCC lesions. The confirmed ORR in pancreatic lesions was 63.9%, including 4 complete responses. The confirmed ORR in brain hemangioblastomas was 30.2%, with a CR rate of 11.6%. Also, 11 (68.8%) of 15 patients with retinal lesions demonstrated improvement in these lesions, with the 4 other patients reaching stable disease. Safety data showed that 60 of the 61 patients had at least 1 treatment-related adverse event (TRAE). The most common all-cause AE was grade 1/2 anemia, occurring in 51 (83.6%) patients. Eight (13.1%) patients had a grade 3 TRAE. Four (6.6%) patients had grade 3 anemia. There were no grade 4/5 TRAEs. There was 1 discontinuation due to a TRAE (grade 1 dizziness).

Currently, Nivolumab plus ipilimumab (Yervoy) has demonstrated significant efficacy in treating patients with treatment-naïve metastatic RCC compared with the prior standard-of-care sunitinib (Sutent). The investigators sought to discover if the benefit of PD-1/PD-L1 inhibitors could be extended to the neoadjuvant setting, as an earlier study of neoadjuvant treatment with the multitarget kinase inhibitor axitinib (Inlyta) had demonstrated significant shrinking of RCC tumors prior to surgery.

The study was a prospective, open-label, single arm phase 1 trial that explored the safety and tolerability of nivolumab prior to surgery in patients with resectable nonmetastatic high-risk RCC. Patients with T2a-T4 with or without positive lymph nodes were eligible for the study if they were scheduled to undergo a partial or radical nephrectomy, had an ECOG performance status of 0 or 1, and adequate organ and bone marrow function. Nivolumab was administered at 3 mg/kg on day 1 of each of a total of 3 consecutive 14-day cycles. A total of 17 patients were included in the early-phase trial consisting of 16 with ccRCC and 1 with papillary disease. Fifteen had stage cT3a disease, 2 had cT3b, and all were negative for lymph node involvement.

At 24.7 months of median follow-up, the 2-year metastasis-free survival rate was 85.1%, and the overall survival rate was 100%. The 15 patients with ccRCC were restaged prior to surgery, but an overall minimal difference was observed in both the long and short axes from baseline to after treatment with nivolumab. However, 1 patient had an immune-related pathologic response and the rest had stable disease by radiographic criteria. The 1 patient who achieved a pathologic response demonstrated a regression bed with features of wound healing as well as immune infiltration. Grade 3 adverse events (AEs) were reported in 11.8% of patients, and no grade 4 or 5 events were reported. No delays were reported in surgery, and no postoperative complications of Clavien grade 3 or higher were observed. “Early phase trial demonstrates the safety of neoadjuvant PD-1 blockade with preserved [quality of life] when administered to patients with nonmetastatic high risk ccRCC,” the study authors, led by Hiten D. Patel, MD, MPH, of the Department of Urology at Loyola University Medical Center, wrote in their poster.

Neoadjuvant nivolumab is also currently being studied in the phase 3 PROSPER RCC study in comparison with observation for patients with RCC undergoing nephrectomy (NCT03055013).


Neoadjuvant Nivolumab Safe for Nonmetastatic High-Risk RCC

In a phase 1 trial (NCT02575222), Nivolumab (Opdivo) given as a Neoadjuvant has demonstrated tolerability in patients with nonmetastatic high-risk clear cell renal cell carcinoma as reported in a poster presentation during the 21st Annual Meeting of the Society of Urologic Oncology (SUO).
Impact of COVID-19 on Clinical Trial Accrual and Delayed Diagnosis of Cancer

As we are fast approaching the holiday season this year and beginning of 2021, the status of the pandemic still looms large with no signs of slowing down. The COVID-19 pandemic has disrupted virtually every aspect of cancer care and clinical trials - from adding further risks for cancer patients, to impeding the delivery of cancer therapy, and the continuity of cancer clinical trials. For people living with cancer and even for those who have gone into remission but still require continued care/ follow-up testing, the COVID-19 pandemic has posed enormous challenges to cope with new normal.

Clinical trials across diseases including cancers are impacted by quarantines, medical resources and drug supply disruptions, shortages of staffs, site closures and travel limitations. Due to the pandemic related logistic barriers, clinical trial accrual fell about 50% immediately after the COVID-19 outbreak with some cancer centers halting enrollment on clinical trials entirely during the height of the pandemic. Major pharma companies have announced delays in enrollment for ongoing studies and initiation of future studies. Since the pandemic, a sharp decline in cancer diagnoses and routine screening were observed around the world. In the patient care setting, COVID-19 pandemic has led to elective and potentially curative surgery delays for patients with cT1b- cT2b renal cell carcinoma. However, preliminary research has indicated that up to and beyond 3 months of surgical delays did not result in an increased risk of pT3a upstaging or compromise overall survival. In the following months, a downstream ripple effect throughout the cancer care continuum could be possible from the drop-off in screenings and diagnoses, decreased patient visits, biopsies, and cancer treatments etc. Most importantly, the global efforts geared towards developing therapeutics or vaccine for COVID-19 are taking up a lot of oxygen in the oncology clinical trial space. Apparently, most of the existing cancer and non-COVID-19 research efforts are largely being set aside in favor of COVID-19 trials. Such government and industrywide push toward COVID-19 remedies shifted focus away from existing lines of clinical research, which creates uncertainty as to how to proceed with future cancer clinical trials. Even with those trials that are not terminated, the outbreak changed the way cancer clinical trials are conducted and reported, with potentially lasting implications due to pandemic-related logistical barriers.

While COVID-19 has complicated the treatment of cancer patients and continuing clinical research, it has also spurred creative solutions especially remote or decentralized clinical trials. The newly developed recommendations in light of COVID-19 impact could improve the overall trial process and also serve as a silver lining to the trials in the long term. Several measures including the leveraging of telehealth, use of e-signatures, remote monitoring of trials, and outside lab testing are effectively being exploited to make the best out of the situation. Other changes include delaying recruitment, implementing COVID-19 screening procedures, expediting changes in trial protocol and exploring alternative drug administration methods are already in place. The NCI also has released guidance specific to cancer clinical trials, including recommendations on the overnight shipping of medications to trial participants. Amid the outbreak, the widespread use of telemedicine has emerged as one of the positive changes to clinical trials. Some studies involving patients with cancers indicate that telehealth was not only associated with a higher quality of life and less depression and distress compared with usual care but also can be just as effective as in-person meetings.

In the past decade alone, breakthroughs in immunotherapy including anti-PD-1 and anti-PD-L1 based agents have revolutionized the cancer management. However, now there may be a lag before this development can take off post COVID-19 pandemic as the pandemic threatens to set back the pipeline of such oncology agents by several years. Currently, it still remains unclear whether immune checkpoint inhibitors and other immunotherapies worsen or benefit the outcomes in patients who have cancer and COVID-19 infection. Recent study conducted at the MSKCC highlighted that there was an association of immune check inhibitors with increased ICU admission rate, but did not increase the risk of mortality1. Given the limited and conflicting data on the benefit/risk of ICI therapies to patients with cancer in the pandemic setting, oncologists are left alone to carefully assess the risks and benefits managing ICI therapy on a case-by-case basis. Physicians should weigh the advantages of relapse-free survival benefit against the COVID-19 associated risks. Given the lack of robust clinical data, caution must be taken while continuing ICIs in patients with cancer who may be affected by COVID-19. It seems reasonable to suggest in patients with metastatic disease without COVID-19, ICI therapy may not be withheld. Multicenter retrospective studies will be required to provide more definitive guidance on the role of immune checkpoints in COVID-19 infection for clinicians.

Ever since the outbreak, the most inspiring aspect is that oncologists and their team members showed incredible resilience and resolve to deal with the unforeseen crisis, by exploiting timely strategies including adopting telehealth, workflow reorganization, and safety processes enhancements at their clinics. It is imperative for clinicians and researchers to learn and continuously adapt to the new standards of cancer care and risk management through implementing reforms, with the hope that we can find a silver lining in improving research efficiency and outcomes in the face of the pandemic crisis.


Robert A. Figlin, MD
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.


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.


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 CD73 negative (CS=0), CD73 low or CD73 high. 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 CD73 high tumor expression had significantly worse 5-year DFS (42%) and 10-year OS (22%) compared to those in the CD73 negative 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.


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 animals, 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 = 0.666). 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 x 10^-6 and p = 5.6 x 10^-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.

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.


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 hypo-fractionated 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.


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, OR 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.
Impact of Mycobacterial Infections on Outcomes of Patients with Metastatic Renal Cell Carcinoma

Dissecting the role of lymphadenectomy in the management of RCCs

HIF-Inhibitors in RCCs: A Review of Current Trials

Academic Mentorship: Choosing the Right Research Mentor(s)
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