Kidney Cancer

Official Journal of
Kidney Cancer Association

JOURNAL

QR - SCAN
WEBSITE

The 21st Annual Meeting of

The International Kidney Cancer Symposium

A B S T R A C T S

KidneyCancerJ
KidneyCancerJ
KidneyCancerJournal
KidneyCancerJournal

KCJ Publishes the Finest & Most Comprehensive Peer-reviewed Research in Kidney Cancer

CONTENTS

FROM CO-CHAIR'S DESK

International Kidney Cancer Symposium North America 2022: Collaborations and Connections

Eric A. Singer, MD, MA, MS, FACS, FASCO
Co-Chair

Tian Zhang, MD, MHS
Co-Chair

This year we gathered for the 21st International Kidney Cancer Symposium again in Austin, TX with more than 50 kidney cancer experts presenting over two days for 11.75 AMA PRA Category 1 CME Credits. On behalf of the Scientific Program Committee, we are again delighted to see the outstanding abstracts presented at IKCS North America 2022 published in the *Kidney Cancer Journal*. The kidney cancer community has come through the COVID19 pandemic stronger, through tireless efforts to advance treatment options, enhance our understanding of tumor biology, strengthen advocacy efforts, and support patients and their families.

The Kidney Cancer Association (KCA) 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 2022, the Kidney Cancer Association has awarded 6 Trailblazer Awards and 1 Psychosocial Focus Award to support novel and innovative research in kidney cancer.

This year we also grieve the passing of two seminal members of KCA, Drs. Christopher Wood and Nicholas Vogelzang. Dr. Wood was chair of the KCA Board of Directors at the time of his passing, a fierce advocate for his patients and renowned mentor for urology fellows and residents who trained with him at MD Anderson. Dr. Vogelzang was a founding member of the KCA, respected mentor to many medical oncologists and urologists, and true giant for the genitourinary

cancer field. In Dr. Wood's honor, the KCA has established the Christopher G. Wood Rising Star Award, the inaugural recipient of which is Dr. Daniel Shapiro. In Dr. Vogelzang's honor, the KCA has established the KCA Nicholas J. Vogelzang Humanitarian Award, the inaugural recipient of which is Dr. Vogelzang, who will be honored posthumously. Both awards will be named annually at the IKCS North America conference.

We are honored to have Dr. David McDermott, Chief of Hematology, Hematologic Malignancies, and Medical Oncology at the Beth Israel Deaconess Medical Center, give the IKCS 2022 keynote address "Kidney cancer as a model for a curable neoplasm". The IKCS is also proud to recognize Dr. McDermott for his key contributions in advancing immunotherapies for kidney cancer as the 2022 Eugene P. Schonfeld Award recipient

Merit Award recipients for outstanding abstracts included:

1st place: CD200-mediated immune evasion in clear cell renal cell carcinoma (Davies G. *et al*)

2nd place: Clinical outcomes with nivolumab/ipilimumab (nivo/ipi) with or without CBM588 in metastatic renal cell carcinoma (mRCC): Long-term follow up of a randomized phase 1b clinical trial (Dizman N., *et al*)

3rd place: Biomarkers of disease burden and treatment response in renal medullary carcinoma (Blum K., *et al*)

We hope you enjoy reading the following abstracts as much as we did seeing the science presented first-hand! Please join us next year for IKCS Europe 2023, April 21-22, in Edinburgh, Scotland, and IKCS North America 2023, November 10-11, 2023, in Nashville, TN.

Sincerely,

Eric A. Singer, MD, MA, MS, FACS, FASCO

Co-Chair

Tian Zhang, MD, MHS

Co-Chair

IKCS 2022 Scientific Planning Committee

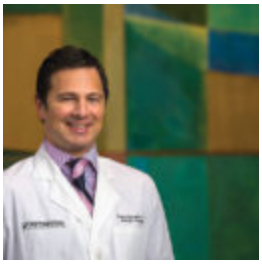
Eric A. Singer, MD, MA, FACS
Rutgers Cancer Institute of New Jersey

Tian Zhang, MD
UT Southwestern Medical Center

Maria Carlo, MD
Memorial Sloan Kettering Cancer Center

Kiran Virdee, RN, BSN, CCRN
Memorial Sloan Kettering Cancer Center

Jodi Maranchie, MD
University of Pittsburgh



Vitaly Margulis, MD
UT Southwestern Medical Center

Bradley McGregor, MD
Dana-Farber Cancer Institute

Phillip Pierorazio, MD
Penn Presbyterian Medical Center

Laura Wood, RN, MSN, OCN
Cleveland Clinic Cancer Institute

Yousef Zakharia, MD
University of Iowa Carver College of Medicine

KCA AWARDS 2022

EUGENE P. SCHONFELD AWARD

Dr. David F. McDermott, *Beth Israel Deaconess Medical Center*

CHRISTOPHER G. WOOD RISING STAR AWARD

Dr. Daniel Shapiro, *University of Wisconsin-Madison (Inaugural)*

NICHOLAS J. VOGELZANG HUMANITARIAN AWARD

Dr. Nicholas J. Vogelzang, *Comprehensive Cancer Centers of Nevada*

CLINICIANS DEBATE SESSION

REGULAR ABSTRACTS

Abstract 1: *Spatial molecular imaging to profile the epithelial to mesenchymal transition and immune crosstalk in sarcomatoid renal cell carcinoma*

Allison May, MD

BACKGROUND: Sarcomatoid renal cell carcinoma (RCC) is thought to arise from an epithelial to mesenchymal transition (EMT) of the parental tumor, most commonly clear cell RCC. These tumors are known to be highly immunogenic. Whether the EMT state impacts the immune milieu and responsiveness to immunotherapy, is unknown. This study explores the capacity of spatial molecular imaging (SMI) to dissect the tumor immune microenvironment (TiME) and EMT in sarcomatoid RCC.

METHODS: Nanostring's SMI platform, CosMx, was used to spatially capture single cell level transcriptomic data in two sarcomatoid RCC specimens, one from a responder to immunotherapy and one from a non-responder. Fields of view within sarcomatoid, clear cell, and transition areas were selected using H&E and further segmented with morphology markers SYTO11, PanCK, CD3, and CD45. We compared regions within each tumor and the two specimens.

RESULTS: Forty fields of view and over 100,000 single cells were captured. Epithelial staining was high in clear cell regions and decreased to near absent in the sarcomatoid regions. Distinct tumor cell clusters and differing immune cell types existed between clear cell and sarcomatoid areas. Clustering revealed shared tumor cell populations between the responder and non-responder as well as unique populations in each. In the sarcomatoid regions, immune infiltrate was dispersed in the non-responder, but clustered in perivascular regions in the responder. CD4+ naïve T cells and myeloid dendritic cells were higher in the responder while CD4+ memory cells, CD8+ naïve T cells, and plasmacytoid dendritic cells were more abundant in the non-responder.

CONCLUSIONS: We identified differences in the TiME between the responder and non-responder tumors that could contribute to immunotherapy responsiveness. Although no conclusions can be drawn due to the limited sample number, these data demonstrate the power of SMI to detect single cell level differences in sarcomatoid RCC in spatial relation to histology and the TiME.

Abstract 2: *Biomarkers of Disease Burden and Treatment Response in Renal Medullary Carcinoma*

Kyle A. Blum, MD, MS

BACKGROUND: Renal medullary carcinoma (RMC) afflicts young persons of African descent with sickle hemoglobinopathies. More than 90% have advanced disease and carry an objective response rate of 29% to RCC therapies with a 13-month median survival. There's a need to develop new ways to screen, diagnose, and treat RMC to raise its survival curve. We established a large RMC cohort and assessed known serum tumor markers with RMC disease severity (e.g.metastatic burden) and correlated marker levels to therapeutic response.

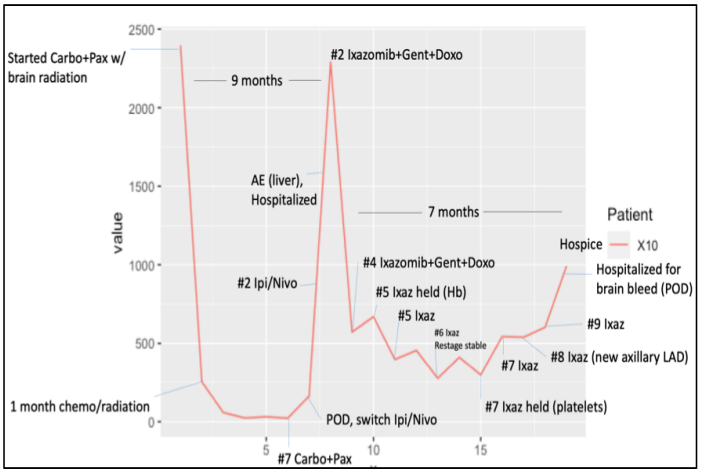
METHODS: After IRB-approval, serum markers were captured in primary RMC patients treated at MD Anderson within the past 10 years. Those without serum markers were excluded. Inclusion criteria required RMC diagnosis by either from biopsy or nephrectomy. Using serum tests, known biomarkers in other

malignancies were assessed. These markers included CA-125, CEA, AFP, CA19.9, CA15.3 and LDH and trended over time with respect to key clinical events including treatment responses, relapses, and progression of disease.

RESULTS: 18 patients met criteria. Median follow-up was 5.8 months. Median age was 30 years, with 72% male, 94% Black race, and 78% carrying hemoglobinopathy (e.g.sickle-cell trait). Approximately 89% presented metastatic. In metastatic patients, CA-125 was 20-100x above normal, and during treatment convalescence, these values recessed to lower levels. Positive treatment-response resulted in less circulating CA-125 which could be measured over time. LDH and CA-125 were consistently elevated above upper-limit normal ranges, unlike AFP, CA19.9, CA15.3, and CEA. The magnitude of LDH and CA-125 elevation was directly proportional to metastatic burden with CA-125 levels in widely metastatic patients 200+% higher than upper-limit normal.

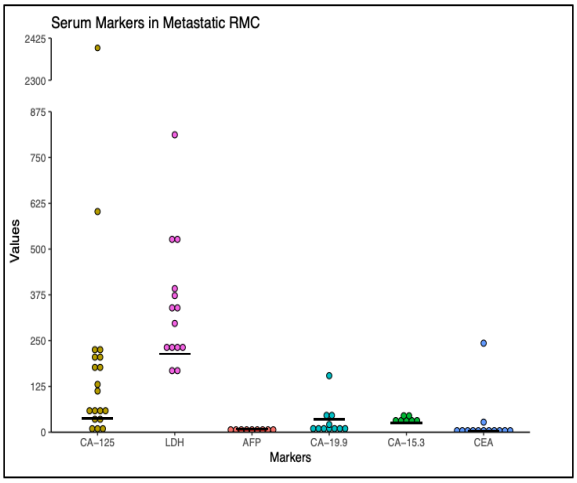
CONCLUSIONS: Trending levels of serum biomarkers such as CA-125 in RMC may assist (1) predicting development or location of metastases, (2) correlate treatment response or efficacy (3) identify a new therapeutic target. Further work to evaluate the expression of markers on the RMC cell surface is ongoing.

CA-125 Correlates With Treatment Response



A patient with untreated metastatic RMC initially with a CA-125 level of over 100x the normal range, and with different systemic treatments the serum levels would mirror residual disease burden (less disease = lower CA-125) and surrogated for treatment response, suggesting this as a potential marker for response and monitoring

CA-125 Consistently Elevated in RMC Patients



CA-125 serum levels were routinely elevated supporting the possibility that CA-125 may be expressed at high concentrations on the surface of RMC cells. Solid horizontal bars indicate upper limit of normal range per marker.

Abstract 3: ***Critical assessment of eligibility criteria in contemporary renal cell carcinoma (RCC) trials evaluating systemic therapy***

Daniela V.. Castro, MS

BACKGROUND: In a joint statement, the Friends of Cancer Research (FCR) and American Society of Clinical Oncology (ASCO) highlighted the need to broaden eligibility criteria in cancer trials to increase patient accrual and enhance the generalizability of study results (Kim et al., Clin Cancer Res 2021). In this study, we sought to characterize the frequency of exclusionary criteria in RCC trials deemed by the FCR-ASCO statement to be potentially excessive.

METHODS: Using ClinicalTrials.gov, studies with start dates from June 30, 2012 to June 30, 2022 were included. MeSH terms in our query were "(metastatic OR advanced OR stage IV OR unresectable) AND (kidney cancer OR renal cell carcinoma OR renal cell cancer)". Our query identified international studies examining patients age ≥ 18 in phase I-III trials. Pan-cancer studies and trials involving localized treatments, prognostic tools or radiation therapy were excluded from our analysis.

RESULTS: In total, 423 RCC trials were evaluated; of these, 112 (26.5%) had sufficient publicly available data for evaluation. Over one-third 44 (39.3%) of studies evaluated targeted therapy, 18 (16.1%) evaluated immunotherapy, and (48; 42.9%) evaluated combination therapy. The most frequently cited exclusionary criteria were the presence of hepatitis B/C positivity, concurrent malignancies, HIV positivity, and brain metastases, found in 100.0% (91/91), 100.0% (90/90), 98.9% (91/92) and 89.1% (90/101) of studies, respectively. Over the 10-year evaluation period, no significant trend was observed in use of these exclusionary criteria, nor were any significant differences observed in the use of these criteria among trials based on drug class.

CONCLUSIONS: A substantial proportion of contemporary RCC studies incorporate exclusionary criteria deemed by the FCR-ASCO statement to be potentially excessive. Broadening eligibility criteria will ensure that the resulting data is representative of real-world patient populations.

Abstract 4: ***Delineating Clinical and Radiologic Features of Rare Kidney Cancer Genetic Syndromes***
Pamela I. Causa Andrieu, MD

BACKGROUND: Hereditary RCC accounts for 5%-8% of all malignant renal tumors, and NCCN recognizes 7 syndromes. Clinical-radiological features of 4 are scarcely researched: Hereditary Papillary Renal Carcinoma (HPRC), Birt-Hogg-Dube syndrome (BHDS), BAP1 tumor predisposition syndrome (TPDS), and Hereditary Paraganglioma/ Pheochromocytoma syndrome (PGL/PCC).

The aim is to investigate the prevalence of those syndromes, and prevalence, clinical features, and imaging features of RCC in these syndromes.

METHODS: IRB approved protocol. 25,220 patients with cancer underwent germline analysis, >70 cancer predisposing genes, from 2015 to 2021. We identified patients with germline pathogenic/ likely pathogenic mutations in MET, FLCN, BAP1 and SDHx.

We analyzed prevalence of germline mutations, and clinical records were reviewed for clinicopathologic characteristics. For patients with RCC, CT/MRI/PET/CT at presentation was reviewed independently by two radiologists for radiologic features.

RESULTS: Imaging features of hereditary RCC were similar to that of sporadic RCC.

Mutation: Prevalence; %with RCC; mean age at diagnosis (years); histologic type; %metastasis at diagnosis; other cancers. MET: 1/25000 (0.004%); 100%, 67; Papillary (100%); 0%; none.

FLCN: 17/25000 (0.067%); 23.5%; 55; Unclassified (75%), Clear cell (25%); 25%; Colon (17.6%), Lung (11.8%), Breast, Prostate, Oral SCC, endometrial, MMMT, pancreatic, thyroid (5.9%)

BAP1: 22/25000 (0.087%); 18.2%; 58%; Clear cell (75%), Papillary (25%); 33%; Skin (40.9%), Mesothelioma (36.3%), Ovarian, cholangiocarcinoma (13.6%), Lung and HCC (9.1%), Colon, breast, oral SCC,xanthoastrocytoma (4.6%)

SDH: 39/25000 (0.155%), 23.1%; 48; SDH-deficient (67%), Clear cell (11%), Not biopsied (22%); 14%; GIST (23.1%), Breast (10.3%), Colon (7.7%), Prostate (5.1%), Skin, adrenal, cervical, glioblastoma, Testicular GCT (2.6%)

CONCLUSIONS: These mutations are very infrequent, and RCC prevalence is up to 23% in them. RCC image features are similar to non-hereditary syndromes.

Feature	**MET**	**FLCN**	**BAP1**	**SDH**
Prevalence	1/25000 (0.004%)	17/25000 (0.067%)	22/25000 (0.087%)	39/25000 (0.155%)
% With RCC	100%	23.5%	18.2%	23.1%
Mean Age at diagnosis (years)	67	55	58	48
Histologic type	Papillary (100%)	Unclassified (75%) Clear cell (25%)	Clear cell (75%) Papillary (25%)	SDH-deficient (67%) Clear cell (11%) Not biopsied (22%)
% Metastasis at diagnosis	0%	25%	33%	14%
Other cancers	None	Colon (17.6%) Lung (11.8%) Breast, Prostate, Oral SCC, endometrial, MMMT, pancreatic, thyroid (5.9%)	Skin (40.9%) Mesothelioma (36.3%) Ovarian, cholangiocarcinoma (13.6%) Lung and HCC (9.1%) Colon, breast, oral SCC, xanthoastrocytoma (4.6%)	GIST (23.1%) Breast (10.3%) Colon (7.7%) Prostate (5.1%) Skin, adrenal, cervical, glioblastoma, Testicular GCT (2.6%)

Abstract 5: ***CD200-mediated immune evasion in clear cell renal cell carcinoma***
Gemma E.. Davies, MSc, BSc

BACKGROUND: Interaction of CD200 with its receptor, CD200R, is an immunosuppressive checkpoint which contributes to cancer cell immune evasion. We have shown this interaction can protect CD200+ tumour cells by reducing CD200R+ natural killer (NK) cell cytotoxic activity and causing NK cell apoptosis in other cancer types. Bioinformatic analysis revealed a change in NK phenotype from active to resting with increased CD200 expression in clear cell renal cell carcinoma (ccRCC). We hypothesised that CD200 signalling may contribute to disease progression by promoting immune evasion.

METHODS: Normal kidney (n=30) and ccRCC tissue samples (n=300) were used to determine CD200 expression and immune response (CD4+ T Helper, CD8+ Cytotoxic T, FoxP3+ Treg and NK cells) by frequency and cell density/mm2. Immune response was compared between CD200 weak, moderate and strong expressing tumour samples. Co-culture of NK cells with ccRCC cell lines was used to determine the effect of CD200 on NK cell activation by measuring CD107a expression and tumour cell killing by NK cells. Western blot was used to study apoptotic markers.

RESULTS: Treg density and frequency increased with higher tumour CD200 expression (p=0.0001 and p=0.0034 respectively), resulting in an immunosuppressive environment. NK cell density and frequency also increased with greater CD200 expression (p=0.0013 and p=0.0004 respectively), however NK and ccRCC cell co-culture showed a decrease in CD107a expression (p=< 0.0001) and ccRCC cell killing. Western blot showed an increase in activated NK cell apoptosis.

CONCLUSIONS: ccRCC CD200 expression contributes to immune evasion by increasing Treg levels and causing activated NK cell dysfunction, apoptosis, and decreased cytotoxic response. Therefore, inhibition of the CD200:CD200R checkpoint may present a novel therapeutic target in ccRCC management.

Abstract 6: ***Clinical outcomes with nivolumab/ipilimumab (nivo/ipi) with or without CBM588 in metastatic renal cell carcinoma (mRCC): Long-term follow-up of a randomized phase Ib clinical trial***
Nazli Dizman, MD

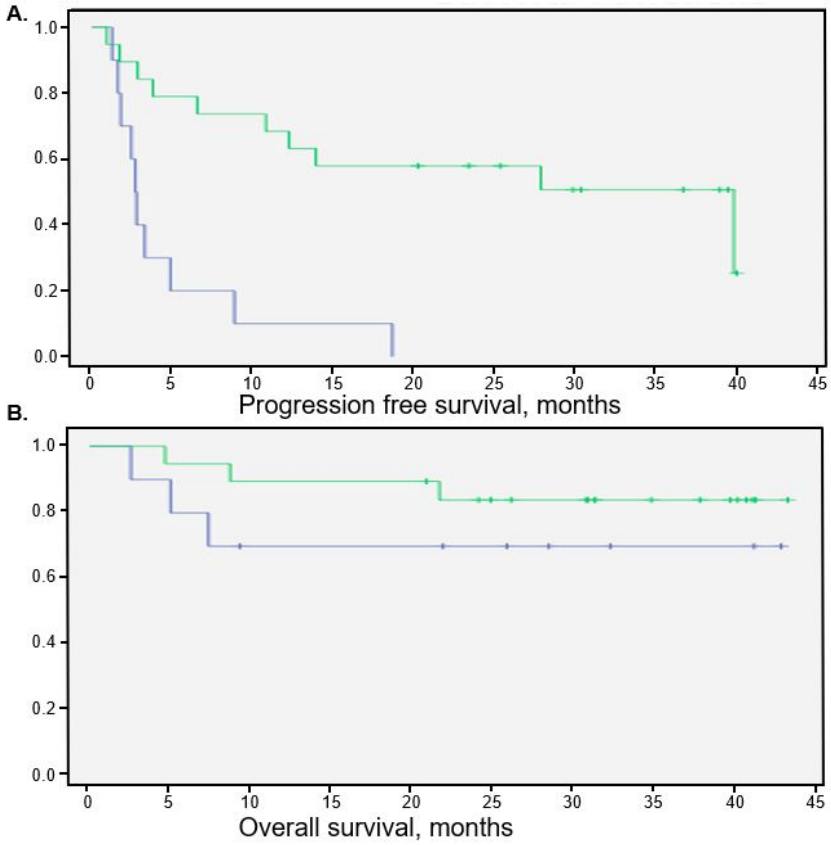
BACKGROUND: CBM588, a bifidogenic live bacterial product, demonstrated gut microbiome modulation and improvement in clinical outcomes among patients receiving nivo/ipi for first-line treatment of mRCC (Dizman et al. Nature Medicine 2022). Herein, we present the long-term follow-up data of this phase Ib clinical trial.

METHODS: Treatment naïve patients with mRCC, clear cell and/or sarcomatoid histology and IMDC intermediate/high risk were randomized to nivo/ipi or nivo/ipi/CBM588 in a 1:2 fashion. Treatment response was assessed using RECIST 1.1. Objective response rate (ORR; complete response [CR] or partial response [PR]), disease control rate (DCR; CR, PR or stable disease [SD]>6 months) and survival outcomes were compared across arms.

RESULTS: Twenty-nine (19:10 nivo/ipi/CBM588:Nivo/ipi) patients were included in the final analysis. Median age was 66.2 years, 72% were male, 83% had IMDC intermediate risk and 93% had clear cell histology. At the time of data cut-off, median follow-up was 27.7 (95% CI 25.9-29.7) months. ORR and DCR were 58% and 79% in nivo/ipi/CBM588 arm versus 20% and 20% in nivo/ipi arm, respectively (p=0.06 and p=0.004). Median progression free survival (PFS) was 36.4 (95% CI 9.4-63.5) months in nivo/ipi/CBM588 arm versus 2.5 (95% CI 2.0-2.9) months in nivo/ipi arm (HR 0.10; 95% CI 0.03-0.33, p< 0.001; Fig 1A). Median duration of response was 36.4 (95% CI 20.6-52.2) months in nivo/ipi/cbm588 arm versus 4.5 (95%

CI NA-NA). Median overall survival was not reached in either arm, with 82.8% of the cohort being alive at the time of data cut-off (Fig. 1B).

CONCLUSIONS: Although limited by sample size, nivo/ipi/CBM588 demonstrated superior clinical activity over nivo/ipi. PFS and ORR with nivo/ipi/cbm588 also exceeded those observed with nivo/ipi in historical datasets. Larger efforts investigating gut microbiome modulation via CBM588 are warranted.



Abstract 7: ***Assessment of Clavien-Dindo Classification in patients with Metastatic Clear Cell Renal Cell Carcinoma (mccRCC) who received Perioperative Cabozantinib and Nivolumab on Cyto-KIK Clinical Trial***

Karie Runcie, Assistant Professor of Medicine

BACKGROUND: The perioperative safety of cabozantinib and nivolumab in RCC and the optimal timing to hold cabozantinib prior to surgery is unknown.

METHODS: In this phase 2 trial, patients with mccRCC are given cabozantinib (40mg daily) and nivolumab (480mg q4 weeks) for 12 weeks prior to cytoreductive nephrectomy. Post-operatively, patients resume treatment with cabozantinib and nivolumab until disease progression. A 3+3 design was used to evaluate the safety of the interval (21 or 14 days) between the discontinuation of cabozantinib and nephrectomy. Evaluable patients completed at least 10 of 14 cabozantinib doses in the two-week period prior to stopping pre-operative cabozantinib and surgical resection of the primary tumor. Surgical outcomes using the Clavien-Dindo classification system is a secondary endpoint of this study.

RESULTS: 16 patients have been enrolled and 14 completed nephrectomy to date. 75% of patients are male, 25% female, ages 44-77 years old with median age at diagnosis 58.5 years old. BMIs ranged from 17.8

kg/m2 to 39.3 kg/m2 with median BMI of 28.7kg/m2. 63% of patients were classified by IMDC as intermediate-risk and 37 % as poor-risk disease. Of those patients who completed nephrectomy, dose reductions occurred in 14% and cabozantinib held in 42% of during the course of treatment. Three evaluable patients completed nephrectomy within the 21-day interval and 5 within the 14-day interval after discontinuation of cabozantinib. There were no surgical complications as assessed by Clavien-Dindo Classification in patients who completed nephrectomy, including a patient who held cabozantinib 23 days prior to surgery due to Grade 3 renal mass hemorrhage.

CONCLUSIONS: Combination cabozantinib and nivolumab can be safely administered up to 14 days prior to cytoreductive nephrectomy.

Abstract 8: ***Genetic Ancestry and Molecular Correlations in Patients with Kidney Cancers***
Ritesh Kotecha, MD

BACKGROUND: Genetic ancestry (GA) may contribute to differences seen amongst race/ethnic populations. We performed an analysis of clear cell and non-clear cell renal cell carcinoma (RCC) patients to study associations of GA with clinical presentation and molecular phenotypes.

METHODS: We performed a single-institution retrospective review of RCC patients and recorded self-reported race/ethnicity and clinicopathologic data. All patients underwent NGS profiling of normal and tumor tissues via MSK-IMPACT. We inferred GA contributions of African (AFR), East Asian (EAS), European (EUR), Native American (NAM), and South Asian (SAS) ancestry via supervised ADMIXTURE analysis. Individuals were grouped into a majority GA if a single GA fraction was >80% or were considered Admixed. We inferred HLA class I genotype and computed HLA evolutionary divergence (HED) at each locus.

RESULTS: In 953 RCC patients, the GA classifications were: EUR (78%), AFR (4.9%), EAS (2.5%), SAS (2.1%), NAM (0.2%), and Admixed (12.2%). Tumor histology distribution within GA groups varied, including clear cell (66% EUR, 43% Admixed, 26% AFR) and papillary (30% AFR, 17% Admixed, 9% EUR). Clinical presentation differences were appreciated, including metastatic disease at initial diagnosis (45% EAS, 40% AFR, 28% EUR), and IMDC intermediate-poor risk (AFR 88%, EAS 74%, SAS 73%, EUR 58%). Any germline alteration was identified in 23% AFR, 17% EUR, 7% EAS, and 0% SAS. Composite HLA class I HED was similar across GA. In clear cell RCC, somatic profiling showed similar mutational burden, yet recurrent alterations rates varied, including: VHL (78% EUR, 50% AFR, 92.9% SAS), PBRM1 (45% EUR, 28% SAS, 16.7% AFR), and BAP1 (50% AFR, 29% SAS 17% EUR).

CONCLUSIONS: Differences in disease presentation and molecular data by GA highlight population-specific variations in patients of different ancestry. Exploration of genetic and non-genetic factors will be critical to interpret disparities seen amongst populations.

CLINICAL TRIALS WITH RESULTS

Abstract 9: ***DNA methylation-based tumor microenvironment deconvolution in clear cell renal cell carcinoma reveals significant survival association with specific cell types***

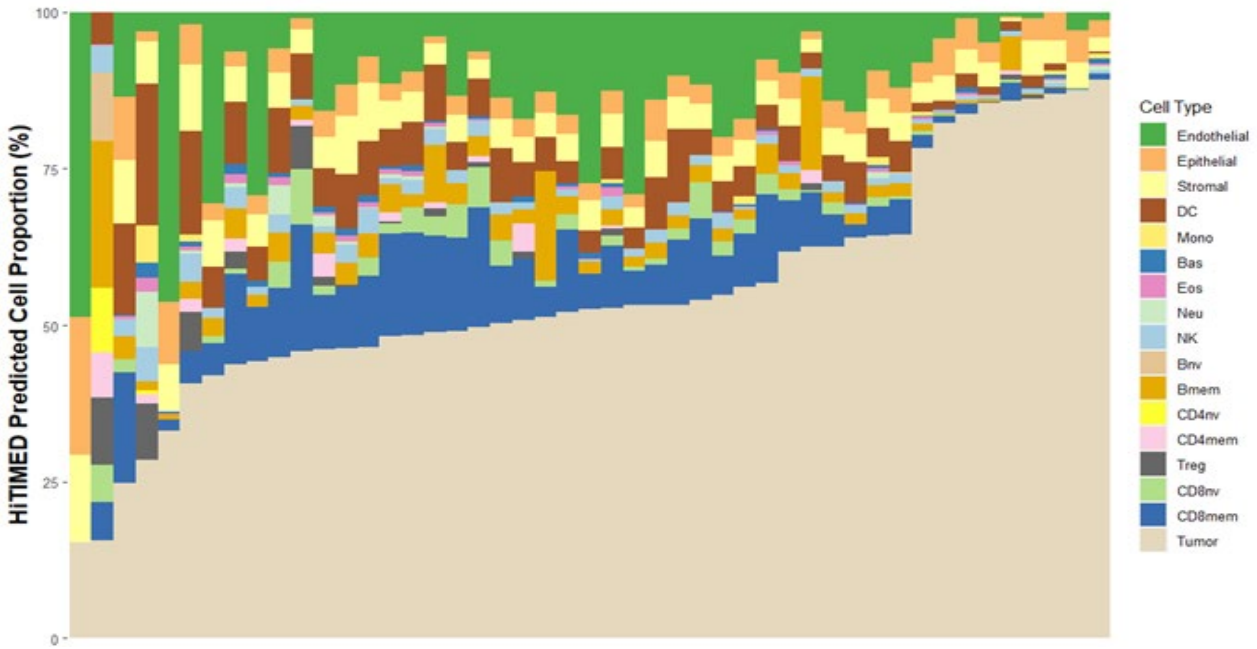
Ze Zhang

BACKGROUND: Our group recently developed a DNA methylation-based bioinformatic tool, HiTIMED, to deconvolve the tumor microenvironment (TME) with high resolution, accuracy, and specificity. Seventeen cell types from three major TME components (tumor, immune, angiogenic) can be estimated. Here, we applied HiTIMED to clear cell renal cell carcinoma (ccRCC) samples to investigate the association between TME cell composition and survival outcome.

METHODS: 47 ccRCC samples from the Dartmouth Renal Tumor Biobank were selected for a pilot study. Two hundred samples are aimed for the final study. Tandem bisulfite and oxidative-bisulfite conversion on DNA followed by hybridization to Infinium MethylationEPIC BeadChip were used to measure methylation and hydroxymethylation. HiTIMED was used to deconvolve the cell composition in ccRCC TME (Figure 1). Kaplan-Meier survival curves and Cox proportional hazard models adjusting for age, sex, and tumor stage were employed for survival analyses. Methylation dysregulation index (MDI) and hydroxymethylation dysregulation index (hMDI) were calculated.

RESULTS: A higher than the median level of stromal cell proportion (>4.38% vs. ≤ 4.38%) is significantly associated with a better survival rate (HR: 0.49, 95% CI: [0.25, 0.96]). A higher than median level of CD4 memory cell proportion (>0% vs. =0%) is significantly associated with a worse survival outcome (HR: 2.16, 95% CI: [1.14, 4.09]). A higher than the median level of T regulatory cell proportion (>0% vs. =0%) is associated with a worse survival rate (HR: 2.09, 95% CI: [1.11, 3.94]). MDI and hMDI demonstrated increasing trends with the ccRCC tumor stage.

CONCLUSIONS: DNA methylation-based estimation of cell proportions in ccRCC TME revealed stromal, CD4 memory, and T regulatory cells significantly associated with survival outcomes. The observation promises future investigations on biological implications and roles of those cells in ccRCC carcinogenesis and progression.



Abstract 10: *Epigenetic Dysregulation Activates the Oncogenic Dicarboxylic Amino Acid Transporter SLC1A1 in ccRCC*

Abhishek A. Chakraborty, PhD

BACKGROUND: The clear cell renal cell carcinomas (ccRCC), which harbor the signature inactivation of the pVHL tumor suppressor protein, represent ~75% of kidney cancers. Inactivating mutations in histone-modifying enzymes occur recurrently in ccRCC. Consistent with this, we found differences in histone modifications in pVHL-null ccRCCs [relative to the pVHL-proficient (papillary and chromophobe) RCCs], including elevated levels of acetylated lysine 27 on Histone H3 (H3K27ac), which is associated with transcriptionally active enhancer regions. We hypothesized, therefore, that elevated H3K27ac controls genes that are essential for tumorigenesis in pVHL-deficient cells.

METHODS: Our histone profiling in human tumors was done using a multiplexed Mass Spectrometry method. The genomic localization of H3K27ac was performed using ChIP-Seq and these profiles were integrated with gene expression data, measured using RNA-Seq. The SLC1A1 transporter was identified as a ccRCC oncogene using an unbiased genetic screen in vivo. These findings were validated using cell-based studies where SLC1A1 was inactivated genetically (using CRISPR/Cas9) or pharmacologically. The mechanistic basis for SLC1A1's oncogenic function was interrogated using LC-MS/MS based targeted metabolomics studies.

RESULTS: Relying on genomics studies (e.g. integrating H3K27ac marking with transcriptional output) and an in vivo "up" screen, seeking genes that were sufficient to promote tumorigenesis in pVHL-proficient cells, we identified the Asp/Glu transporter SLC1A1 as a novel oncogene in ccRCC. SLC1A1 expression is regulated by pVHL status in an HIF-independent manner. Furthermore, SLC1A1 loss promotes anti-proliferative effects in ccRCCs. Metabolomics studies indicate that Asp uptake underlies SLC1A1's oncogenic function. Finally, SLC1A1 status directly impacts Glutaminase dependence.

CONCLUSIONS: Our studies identify the Asp/Glu dicarboxylic amino acid transporter SLC1A1 as a novel actionable target in ccRCC, define the metabolic basis for this dependence, and establish SLC1A1's role as a predictor of Glutaminase dependence in ccRCC.

Abstract 11: ***Differentiation Clear Cell Renal Cell Carcinoma from Other Common Malignant and Benign Renal Masses on Multiphasic MRI: A Likert Based Multireader Analysis***

Chuthaporn Surawech, MD

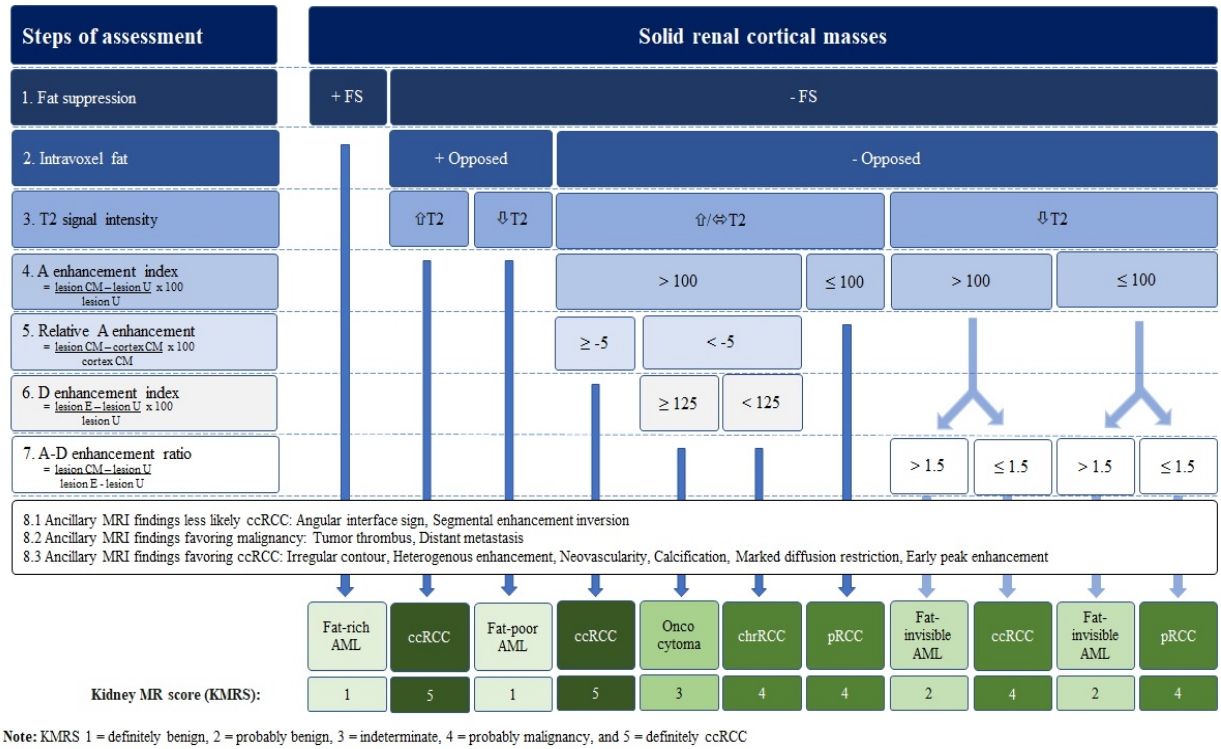
BACKGROUND: Solid renal masses can be potentially characterized using multiphasic magnetic resonance imaging (MRI). However, qualitative **METHODS** remain challenging to standardize. We assessed the diagnostic performance and the interreader agreement of the kidney MR score (KMRS), which combines quantitative and qualitative **METHODS**, in differentiating benign and malignant lesions and clear cell renal cell carcinoma (ccRCC) from other common lesions on multiphasic MRI.

METHODS: With IRB approval and HIPAA compliance, this observational study comprised non-syndromic patients with 191 pathologically proven and 11 stable, variably fatty renal masses (142 malignant, 54 benign, and 6 uncertain malignant potential). After training on 5 non-study cases, four abdominal radiologists and four abdominal radiology fellows independently interpreted the study cohort and assigned a KMRS to each lesion on a 5-point scale to indicate the probability of benignity, malignancy, and ccRCC, blinded to clinical data. The ancillary findings were used to adjust the final score.

RESULTS: A total of 178 patients (mean age, 62 years ± 17, 116 men) with 202 solid renal masses were included. In distinguishing malignant from benign lesions, a KMRS ≥ 4 had a median sensitivity, specificity,

and AUC of 87.5% (83.8-94.6%), 69.5% (64.8-77.8%), and 0.79 (0.77-0.89), respectively. The median sensitivity and specificity of the KMRS ≤ 2 in diagnosing benign lesions were 33.4% (31.5-40.7%) and 95.6% (93.9-99.3%), respectively. A KMRS of 5 had a median sensitivity, specificity, and AUC of 72.3% (65.4-78.3%), 87.0% (84.9-91.6%) and 0.82 (0.77-0.88), respectively for diagnosing ccRCC. The interreader agreement (kappa (κ) score) was 0.59-0.82.

CONCLUSIONS: The proposed KMRS had relatively high performance for diagnosing malignant from benign lesions and ccRCC from all other lesions with good to excellent interreader agreement.



Note: KMRS 1 = definitely benign, 2 = probably benign, 3 = indeterminate, 4 = probably malignancy, and 5 = definitely ccRCC

Abstract 12: ***Outcomes of active surveillance for young and healthy patients with small renal masses***
Muammer Altok, MD

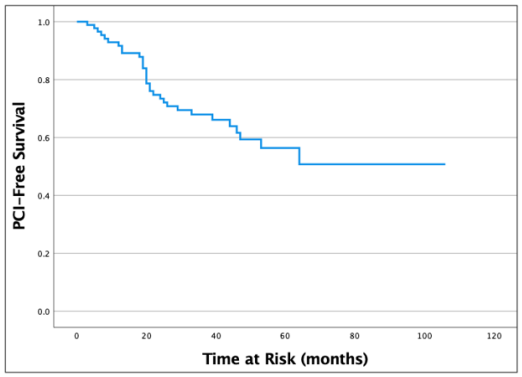
BACKGROUND: Reported outcomes for active surveillance (AS) in patients with small renal masses (SRM) are heavily biased towards older and unhealthier patients. The safety, tolerability and rates of delayed intervention (DI) for AS in younger and healthier SRM patients remains largely unexplored. Here we report outcomes at a single center for SRM patients with life expectancy (LE) >20 years managed with AS.

METHODS: From January 2013-March 2019, all patients with non-hereditary SRM presenting to a single urologic oncologist at a National Comprehensive Cancer Network institute were recommended AS if predefined PCI were absent. PCI was defined prospectively as any SRM-related symptoms, unfavorable biopsy histology, cT3a stage, or either of the following without benign neoplastic biopsy histology: longest tumor diameter (LTD) >4 cm; growth rate >5 mm/year for LTD ≤3 cm or >3 mm/year for LTD >3 cm. DI was recommended during AS only upon PCI development. Patients with LE >20 years were retrospectively identified using social security estimations adjusted by age, gender and Charlson Index. 3- and 5-year rates of PCI-freedom and DI-freedom were determined.

RESULTS: Among 90 consecutive SRM patients with LE >20 years (median age 57, IQR 47-61), 89 (99%) patients (101 SRMs) did not meet PCI at presentation and underwent AS. With median follow-up of 44

months, 31/89 (35%) AS patients developed PCI, of whom 21/31 (68%) underwent DI (all surgery). One (1%) AS patient crossed over to DI without PCI development. 3- and 5-year PCI-free rates were 68% and 56%, respectively, and 3- and 5-year DI-free rates were 75% and 67%, respectively. No patient developed metastasis.

CONCLUSIONS: AS using predefined PCI in otherwise unselected SRM patients is well tolerated and allows most SRM patients with >20 years LE to avoid treatment over 5 years. Long-term DI rates and oncologic safety require further study.



Abstract 13: ***The Role of Exercise on the Physical and Mental Health of Kidney Cancer Patients and Survivors***

Daniel Roberson, MD

BACKGROUND: Kidney cancer negatively impacts a patient's physical and mental health from diagnosis, to treatment, into survivorship. It is crucial to consider modifiable behavioral factors in order to improve quality of life of this population. We hypothesize that a lack of physical activity or exercise is associated with worse physical and mental health.

METHODS: This is a cross-sectional retrospective study of self-reported kidney cancer patients from the Behavioral Risk Factor Surveillance System database from 2016 to 2020. Descriptive characteristics were calculated. We used multivariable logistic regression modeling analyses (MVA), adjusting for gender, age, treatment status, income, marital status, smoking status, and BMI to assess the outcomes of (a) 14+ days per month when mental health was not good and (b) 14+ days per month when physical health was not good.

RESULTS: Out of 2,193,981 survey participants, we identified 576 kidney cancer patients and survivors. 217 (37.7%) reported no physical activity or exercise in the last 30 days, whereas 358 (62.3%) reported physical activity or exercise in the last 30 days. Those who were active were significantly less likely to report worse mental status compared to those who were not active (OR 0.41, 95% CI 0.20 – 0.85, p=0.02). Moreover, physical activity and exercise had similar results for the outcomes of poor physical health (OR 0.44, 95% CI 0.27 – 0.72, p< 0.01) (Table 1).

CONCLUSIONS: Those who reported physical activity and exercise were significantly less likely to report poor mental and physical health. Our results highlight the importance of exercise and physical activity as a modifiable behavioral risk factor to improve quality of life, and we postulate that physical activity may serve to mitigate or prevent common side effects of kidney cancer diagnosis, treatment, and survivorship.

	Outcome of worse mental status			Outcome of worse physical status		
	OR	95% CI	p-value	OR	95% CI	p-value
Exercise and Physical Activity						
No physical activity or exercise in last 30 days	1	Ref	-	1	Ref	-
Had physical activity or exercise	0.41	(0.20-0.85)	0.02	0.44	(0.27-0.72)	<0.01
Gender						
Female	1	Ref	-	1	Ref	-
Male	0.75	(0.38-1.48)	0.4	0.88	(0.54-1.44)	0.62
Age (continuous)	0.96	(0.93-1.00)	0.03	0.99	(0.97-1.02)	0.56
Receiving treatment for cancer?						
No, I haven't started treatment	0.39	(0.08-1.91)	0.25	1.07	(0.42-2.73)	0.89
Yes	0.75	(0.28-2.05)	0.58	2.68	(1.35-5.30)	0.01
No, I've completed treatment	Ref	-	-	Ref	-	-
No, I've refused treatment	1.16	(0.17-8.09)	0.88	2.11	(0.39-11.5)	0.39
Don't know/Not Sure	0.38	(0.04-3.81)	0.41	0.54	(0.08-3.46)	0.52
Treatment was not necessary	0.53	(0.21-1.36)	0.19	1.22	(0.67-2.23)	0.51
Income						
less-$15,000	1	Ref	-	1	Ref	-
$15,000 to <$25,000	1.02	(0.38-2.75)	0.97	0.75	(0.34-1.67)	0.49
$25,000 to <$35,000	1.48	(0.48-4.54)	0.49	0.52	(0.22-1.27)	0.15
$35,000 to <$50,000	0.67	(0.20-2.25)	0.51	0.3	(0.12-0.73)	0.01
$50,000 or more	0.49	(0.16-1.49)	0.21	0.32	(0.14-0.71)	0.01
Marital Status						
Never Married	1	Ref	-	1	Ref	-
Married/couple	0.7	(0.21-2.26)	0.55	0.89	(0.33-2.42)	0.82
Other/Divorced/Widowed/separated	1.44	(0.43-4.85)	0.55	0.85	(0.30-2.40)	0.76
Smoking status						
Never smoked	1	Ref	-	1	Ref	-
Current smoker	0.81	(0.33-1.97)	0.64	0.96	(0.49-1.88)	0.9
Former smoker	0.78	(0.37-1.68)	0.53	1.4	(0.83-2.37)	0.21
BMI						
Underweight	-	-	-	-	-	-
Normal Weight	1	Ref	-	1	Ref	-
Overweight	3.43	(1.05-11.16)	0.04	1.15	(0.58-2.27)	0.69
Obese	2.12	(0.64-6.96)	0.22	1.33	(0.69-2.56)	0.39
Physical status						
0 or less than 14 days bad physical status	1	Ref	-	-	-	-
14+ days when physical health not good	3.13	(1.58-6.19)	<0.01	-	-	-
Mental status						
0 or less than 14 days bad mental health	-	-	-	1	Ref	-
14+ days when mental health not good	-	-	-	3.15	(1.61-6.18)	<0.01

Abstract 14: ***Risk factors for end stage renal disease after treatment of renal cell carcinoma***

Track: **Post-treatment** **Surveillance**

Sven Lundstam, MD,PhD

BACKGROUND: End stage renal disease (ESRD) causes decreased quality of life for the patient and entails high treatment costs. Treatment of renal cell carcinoma (RCC) may increase the risk of ESRD.

METHODS: Patients with RCC, identified in the National Swedish Kidney Cancer Register from 2005 to 2014 and 10 matched controls for each patient were linked to the Swedish Renal Registry and the National Patient Register. ESRD was defined as chronic kidney disease stage 5 (CKD5) or treatment with dialysis or renal transplantation 0-8 years after the diagnosis of RCC.

RESULTS: 215 patients with RCC and subsequent ESRD were identified compared to 9299 patients with RCC only.

The 10 year cumulative incidence of ESRD after RCC was 2.5 %. Hazard ratio for the relative risk compared to controls was 18 for the first year and 7 for year 1 to 10.

In multivariable analyses significant ($p < 0.05$) risk factors for

ESRD were male sex (Hazard Ratio 1.5 ,95% Confidence Interval 1.1-2.1), T2-4 vs T1 (1.4, 1.01-1.92), diabetes (1.9, 1.3-2.7), hypertension (1.9, 1.4-2.6) and CKD 1-4 (15.5, 8.6-27.9). Radical nephrectomy (RN)

compared to partial nephrectomy (PN)/tumor ablation (TA) increased the risk of ESRD with a HR of 2.6 (1.3-5.2) within the first year after RCC diagnosis.

Five-year overall survival was 29 % in RCC + ESRD patients and 64 % in patients with RCC only.

CONCLUSIONS: This population-based study showed that the incidence of ESRD after diagnosis of RCC was 2.5 % which was ten times higher than in the control population. RN compared to PN/TA was a significant risk factor during the first year. During 5 years after diagnosis male sex, advanced T-stage, diabetes, hypertension and CKD 1-4 were significant risk factors for ESRD.

Abstract 15: ***Survival Outcomes Following Adoption of Risk-Adjusted AUA Surveillance Guidelines After Partial Nephrectomy***

Wesley Yip, MD

BACKGROUND: AUA guidelines for follow-up of clinically localized renal neoplasms in 2013 introduced risk-adjusted follow-up recommendations after partial nephrectomy (PN), with less frequent surveillance imaging in low-risk patients. We sought to evaluate the impact of guideline adherence at our institution on outcomes in affected patient cohorts.

METHODS: 3255 patients underwent PN between January 2000 and March 2017. We used Kaplan-Meier methods to estimate metastasis-free (MFS), cancer-specific (CSS), and overall survival (OS), and multivariable Cox proportional hazard regression for each outcome, with follow-up before or after guideline implementation as the predictor, adjusted for guideline risk [low (pT1, N0/X) vs moderate/high (pT2+)].

RESULTS: The "before" (N=2289) and "after" (N=966) groups showed similar overall tumor characteristics: median tumor size 2.9 cm in both groups; tumor stage pT1 in 79% and 80%; positive surgical margin rates of 5.8% and 5.1%, respectively. 296 patients died from any cause, 24 of whom died from kidney cancer. 47 patients had biopsy-proven metastases (Table 1), with a median follow-up time among survivors of 4.4 years (IQR 2.0, 7.6). The "after" group had significantly better MFS (HR: 0.34; 95% CI 0.13, 0.87; p =0.024) and non-significantly better CSS (HR: 0.28; 95% CI 0.06, 1.20; p = 0.086) and OS (HR: 0.75; 95% CI 0.51, 1.12; p = 0.2).

CONCLUSIONS: Detection of metastases following PN is a rare event, regardless of follow-up regimen. Adoption of the AUA guidelines may increase MFS but does not impact CSS or OS, which supports guideline adherence for risk-adapted follow-up of clinically localized renal neoplasms after PN.

Table 1: Characteristics of biopsy-proven metastases detected on follow-up

	PN Before Guidelines (N=44)	PN After Guidelines (N=3)
Location		
Lymph Nodes	7	0
Bone	5	0
Pulmonary	15	1
Non-Pulmonary Visceral	7	1
Pulmonary and Non-Pulmonary Visceral	5	1
Other Combination	5	0
Imaging Ordered for Symptoms	16	0
Imaging Ordered on Surveillance Protocol	23	3
Detection Imaging Modality		
CT	36	3
MR	3	0
XR	4	0
Nuclear Medicine	1	0
Initial Therapeutic Outcome		
Observation	8	1
Systemic Therapy	14	2
Surgical Resection	16	0
Radiation Therapy	1	0
Multimodality	5	0

Abstract 16: ***Artificial intelligence modelling to predict the risk of cardiotoxicity among renal cell carcinoma patients treated with vascular endothelial growth factor receptors tyrosine kinase inhibitors.***

Hesham Yasin, MD

BACKGROUND: Vascular endothelial growth factor receptors tyrosine kinase inhibitors (VEGFRi) are standards of care in renal cell carcinoma (RCC). Despite efficacy and safety, there is a risk for cardiotoxicity with an estimated incidence between 3-8%. Cardiotoxicity can occur months or years after treatment and can be life threatening. Historically, an oncologist refers patients to a cardiologist when cardiotoxicity is suspected/observed. However, general cardiologists may be unfamiliar with VEGFRi cardiotoxicity. Cardio-oncology, an emerging subspecialty, aims to prevent and/or treat cardiovascular complications among cancer patients/survivors. Great progress has been made in utilizing this subspecialty, but standardized referral workflow is limited. Machine learning (ML) is a discipline of artificial intelligence (AI) and computer science that utilizes algorithms to find patterns in data and help create models to predict future events. Using AI may help identify patients who face risk of cardiotoxicity to promote referral to cardio-oncology in a timely manner.

METHODS: De-identified data on RCC patients were obtained from Vanderbilt University Medical Center EMR. Random forest (RF) and artificial neural network (ANN) ML models were applied to analyze the cohort. A global team of cardio-oncologists devised cardiotoxicity risk factors used in calculating the risk groups (potential/mild/moderate/major) (see table).

RESULTS: 2,047 RCC records were analyzed. Data was randomly divided into training (80%) and validation (20%) sets. RF and ANN, applied to analyze patient records extracted to specifications outlined in the clinical risk model, performed > 95% for accuracy and at >94% precision. Limited validation showed 58% of the RCC patients treated with VEGFRi with major risk for cardiotoxicity not referred to cardio-oncology.

CONCLUSIONS: AI models accurately predict RCC patients with cardiotoxicity risk. Integration of AI models into EMR can assist oncologists with identifying these patients and referring them for proactive cardio-oncology treatment/monitoring.

CARDIOTOXICITY RISKS GROUPS	
Risk group	Risk Factors
Potential	Any patient in any of the cohorts on VEGF inhibitors
Low One or more risk factors of these risk factors	Hyperlipidemia HDL between 41 and 59 LDL between 160 and 189
Moderate Up to two risk factors of these risk factors.	Essential Hypertension HDL =< 40 Diabetes Mellitus Age over 65 LDL =>190 and/or Xanthoma BMI > 35 Smoking LVEF 51%-54% Blood Pressure >= 140/90 Pro-BNP >= 400 BNP > 100
Major One or more of these risk factors. Three or more of the moderate risk factors.	Radiation Systolic Heart Failure Ischemic Cardiomyopathy and other cardiomyopathy Coronary Artery Disease Diastolic Heart Failure Severe aortic stenosis Severe mitral regurgitation Atrial fibrillation LVEF <= 50% Severe pulmonary hypertension (RVSP > 60) Troponin > 0.02 HbA1C > 9

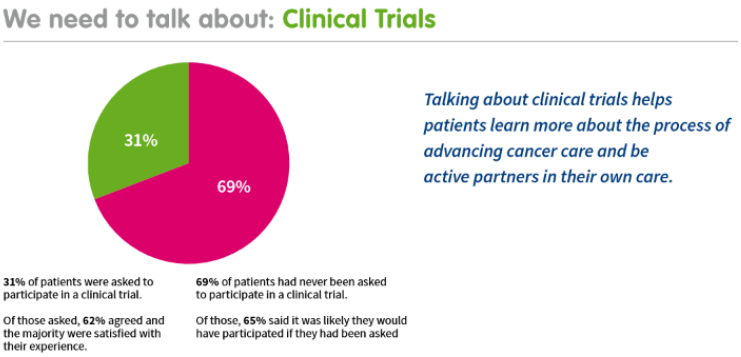
Abstract 17: ***Kidney cancer clinical trials: a decision aid for patients and clinicians***
Track: Quality of Care and Quality Improvement
Rachel H. Giles, MD PhD

BACKGROUND: The preferences and values of individuals to guide clinical decisions are central in shared decision-making. Accordingly, the International Kidney Cancer Coalition (IKCC) supports shared decision-making for kidney cancer patients and their families. Moreover, the results from the IKCC's biennial Global Patient Survey from >2000 patients and caregivers reported that 41% of respondents indicated that "No one" discussed cancer clinical trials with them. Only 31% of respondents were invited to take part in a clinical trial. However, 65% said it was likely they would have participated if they had been asked.

METHODS: The **RESULTS** of the 2020 Global Patient Survey led the IKCC to develop a clinical trial basics booklet followed by a decision aid to help kidney cancer patients and caregivers make decisions about taking part in clinical trials. These will complement the IKCC My Treatment, My Choice series of decision aids for small renal masses, locally advanced kidney cancer, and metastatic disease. These resources will be translated and used by the 48 IKCC global affiliate organisations, reaching an estimated 1.2 million kidney cancer patients, to increase awareness of the pros and cons of taking part in clinical trials. The aim is to improve recruitment and retention of patients in kidney cancer clinical trials at all points in the patient pathway, and to ensure that patient and caregiver voices are heard and acted upon in the design and management of clinical trials.

RESULTS: Results will be available soon.

CONCLUSIONS: The IKCC has developed an evidence-based decision-aid tool which fosters conversations in which the patient and their healthcare professional work in partnership to make the best possible decisions regarding clinical trials, bringing together the patient's individual preferences, personal circumstances, goals, values, and beliefs, and the clinician's expertise, treatment options, evidence, risks and benefits.



Abstract 18: **Non-index *vs Index Readmissions Following Radical Nephrectomy: Causes, Costs, and Outcomes***
Shiva Balasubramanian, B.A.

BACKGROUND: Readmission in the 90-day postoperative period represents a considerable burden on patients and hospitals. Non-index readmissions are especially burdensome as they may represent care fragmentation. Using the 2010-2014 Nationwide Readmission Databases (NRD), we aimed to describe and compare index and non-index readmissions following radical nephrectomy for treating malignant renal neoplasms.

METHODS: Patients with malignant renal neoplasms that underwent radical nephrectomy were identified and abstracted using International Classification of Diseases-9 coding. Differences in readmission-visit outcomes between index and non-index readmissions were assessed using the $\chi 2$ test. Statistical significance was defined as $p< 0.05$.

RESULTS: Of 26,794 patients that underwent a radical nephrectomy, 2,620 (9.8%) were readmitted within 90-days. Index hospital readmissions accounted for 1,826/2,620 (69.7%) readmissions and non-index hospital readmissions accounted for 794/2,620 (30.3%) readmissions. The most prevalent cause of index readmission was surgical complication accounting for 363/1,826 (19.9%) index readmissions; the most prevalent cause of non-index readmission was circulatory system pathology accounting for 151/794 (19.1%) non-index readmissions. Mean cost of a non-index readmission was $12,829±342, which was significantly lower than the mean cost of an index readmission – $13,292±319 ($p< 0.01$). In terms of readmission visit discharge disposition, a higher proportion of non-index readmission patients received a non-routine discharge (30% vs 23%, $p=0.039$). Non-index readmissions had a significantly higher mortality rate compared to index readmissions, (3.7% vs 1.1%, $p< 0.01$).

CONCLUSIONS: Non-index readmissions account for nearly one third of readmissions following radical nephrectomy to treat malignant renal neoplasms and have a higher mortality rate than index readmissions. A better understanding of non-index readmissions allows for the development of targeted interventions aimed at reducing these occurrences, thereby preventing fragmentation of care.

Table 1: Causes of Readmission Grouped by Body System

	% of Readmissions	
Cause	**Non-Index**	**Index**
Digestive	22.5	8.9
Surgical Complication	18.1	35.8
Circulatory	16.7	12.3
Other	15.8	11.0
Genitourinary	8.0	11.9
Musculoskeletal	8.0	2.1
Neoplasm	5.8	14.6
Respiratory	5.1	3.4

Table 1: Aggregated Causes of Readmission by Body System

	% of Readmissions	
Cause	**Index**	**Non-Index**
Surgical Complication	19.9	12.7
Circulatory	14.6	19.1
Digestive	14.7	13.6
Genitourinary	13.8	9.7
Neoplasm	10.9	12.2
Respiratory	6.5	6.9
Infection	4.4	4.4
Endocrine	4.5	3.1
Musculoskeletal	2.1	6.1
Other	8.6	12.2

Abstract 19: ***Non-Index vs Index Readmissions Following Partial Nephrectomy: Causes, Costs, and Outcomes***

Shiva Balasubramanian, B.A.

BACKGROUND: Partial nephrectomy is a standard treatment modality for localized renal malignancy, and post-operative readmission is an important care-quality metric. With regionalization of treatment to high-volume centers, care fragmentation in the form of non-index readmissions may occur. We sought to evaluate and compare 90-day non-index and index readmissions in terms of causes, costs, and outcomes as well as to identify risk factors for non-index readmission in the 2010-2014 Nationwide Readmissions Databases (NRD).

METHODS: International Classification of Diseases-9 coding was used to extract patients with malignant renal neoplasms treated with partial nephrectomy from the NRD. Using $\chi 2$ and independent samples t-tests, variables were evaluated for association with non-index readmission; variables significantly associated with non-index readmission were included in our multivariable logistic regression analysis. The $\chi 2$ test was used to evaluate readmission visit outcomes. We defined statistical significance as $p< 0.05$.

RESULTS: Out of 11,715 patients receiving a partial nephrectomy, 1,367 (11.7%) experienced 90-day readmission. Of these readmissions, 345/1,367 (25.2%) were to a non-index hospital and 1,022/1,367 (74.8%) were to an index hospital. Non-index readmissions had a significantly higher mean cost compared to index readmissions ($14,123±474 vs $13,863 ±371, $p< 0.01$). Readmission visit procedural utilization was significantly lower for non-index readmissions compared to index readmissions (23% vs 39%, $p< 0.01$). On multivariable analysis, longer index-visit length of stay was predictive for non-index readmission (OR 1.83, 95% CI 1.17–2.85). Congestive heart failure (OR 0.318, 95% CI 0.113–0.900) and electrolyte disorders (OR 0.41, 95% CI 0.219–0.768) were both protective against non-index readmission.

CONCLUSIONS: Non-index readmissions following partial nephrectomy, accounting for roughly 1 in 4 readmissions, are costlier than index readmissions. Increased index length of stay is a risk factor for non-index readmission. Elucidation of mechanisms driving non-index readmissions may guide preventative interventions.

Abstract 20: ***Real-world Clinical Outcomes of Patients (pts) with Metastatic Renal Cell Carcinoma (mRCC) Receiving Pembrolizumab + Axitinib (P+A) vs Ipilimumab + Nivolumab (I+N)***

Neil J. Shah, MD

BACKGROUND: IO based therapies have changed the treatment paradigm in the first-line (1L) mRCC in the last few years with robust clinical trial data. We performed comparison of real-world (rw) data for P+A with I+N for clinical outcomes among mRCC pts in community oncology setting.

METHODS: This retrospective cohort study used structured and chart review data from iKnowMed, a US community Oncology electronic health record database to identify adult clear cell mRCC pts initiating 1L P+A or I+N from 4/1/2019 to 12/31/2020 who were followed through 3/31/2021. Treatment pattern & physician-recorded response (rw-overall response rate[rwORR] & rw-disease control rate [rwDCR]) were assessed descriptively. rw-time on treatment (rwToT), rw-time to next treatment (rwTTNT), overall survival (OS) & progression-free survival (PFS) were estimated using Kaplan-Meier method.

RESULTS: Study included 331 eligible pts (P+A=44% [n=145], I+N=56% [n=186]). Median age was 65 years (Range, 59-73), 76% (n=250) were male, & 82%(P+A=76%, I+N=88%) had intermediate/poor (I/P) IMDC risk score. Median follow-up was 10.1 (Range, 5.8 - 14.7) for P+A & 10.7 (Range, 5.2 - 15.4) months for I+N. Overall, 25% (n = 83) & 11% (n = 35) pts received second-line (2L) & third-line treatments,

respectively. Cabozantinib (52%) was the most common 2L treatment. The rwORR & rwDCR were 71%, 80% & 45%, 59% for P+A & I+N, respectively. 12-month OS rate was 82.5% for P+A & 71.1% for I+N. 12-month rwTTNT, rwToT & rwPFS rate was 61.9%, 47.2%, & 55.0% for P+A & 47.0%, 26.3% & 44.9% for I+N, respectively. Clinical outcomes data for entire cohort & I/P are presented in table.

CONCLUSIONS: Our rw study of treatment exposure (rwTTNT, rwToT & PFS) of IO based mRCC treatments in the US community oncology setting provides insights into their effectiveness, tolerability, &/or compliance. Longer follow-up is needed to better characterize OS.

Clinical outcomes, months (95% CI)	Entire cohort (n=331)			I/P IMDC cohort (n=273)		
	Pemrolizumab+Axitinib (n=145)	Ipilimumab+Nivolumab (n=186)	P-value	Pemrolizumab+Axitinib (n=110)	Ipilimumab+Nivolumab (n=163)	P-value
Median rwTTNT,	21.3 (14.4,21.3)	11.9 (7.4,NR)	**0.007**	21.3 (10.5,21.3)	11.1 (6.8,14.1)	**0.028**
Median rwToT	10.5 (7.1,16.0)	4.2 (2.8,5.7)	**<0.001**	9.2 (6.2,15.9)	4.0 (2.8,5.4)	**<0.001**
Median rwPFS	13.9 (10.4,NR)	9.8 (6.0,13.8)	**0.032**	11.3 (7.6,NR)	9.5 (5.8,13.3)	0.121
rwORR-n(%)	103 (71%)	84 (45%)	**<0.001**	75 (68%)	73 (45%)	**<0.001**
rwDCR-n(%)	116 (80%)	109 (59%)	**<0.001**	85 (77%)	93 (57%)	**0.001**

*NR: Not Reached

Abstract 21: ***Short-Term Outcomes of Active Surveillance for Small Renal Masses in Patients With End-Stage Renal Disease and Immunosuppression***

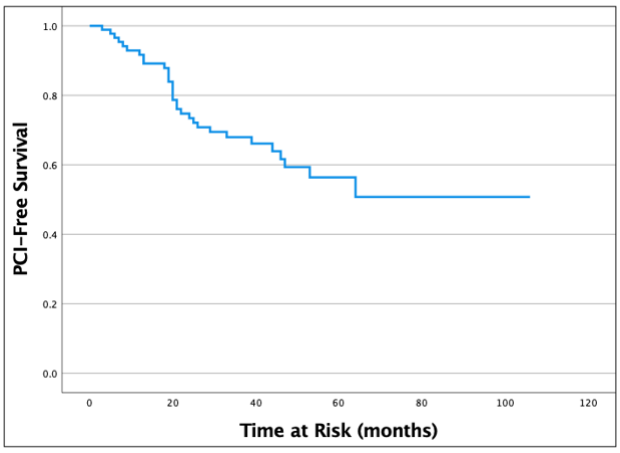
Zoe S. Gan, MD

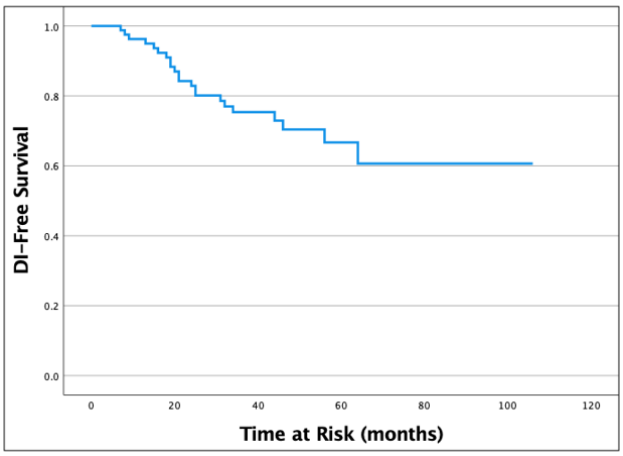
BACKGROUND: Renal transplant candidates are often referred to urology for treatment of a small renal mass (SRM) suspicious for a cT1a renal cell carcinoma. Active surveillance (AS) for SRMs may minimize morbidity of treatment, but outcomes of AS in renal transplant candidates and immunocompromised patients have not been established.

METHODS: The multi-institutional Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) prospective registry, including patients with SRMs ≤ 4 cm from 2009 onwards, was reviewed up to December 2021. Patients with end-stage renal disease (ESRD) or immunocompromised status (prior organ transplant, immunosuppressive medications, leukemia or lymphoma, HIV or AIDS) were included. For included patients, the following variables were extracted: follow up period, mass size at diagnosis, mass growth rate, timing and type of intervention if applicable, and development of metastases.

RESULTS: Of 15 patients with ESRD (including 8 transplant candidates), the mean size of the SRM at diagnosis was 2.3 cm, and over a mean follow up period of 2.4 years, the mean SRM growth rate was 0.1 cm/year. Six patients (40%) underwent either intermediate (4 patients) or delayed intervention (2 patients). Of 11 patients (60%) remaining on surveillance, none developed metastases. Of 44 immunosuppressed patients, the mean size of the SRM at initial diagnosis was 1.9 cm, and over a mean follow up period of 3.5 years, the mean SRM growth rate was 0.2 cm/year. Fourteen patients (32%) underwent either immediate (9 patients) or delayed intervention. Of 30 patients (68%) remaining on surveillance, none developed metastases.

CONCLUSIONS: Limited prospective data suggests that ESRD and immunosuppressed patients on AS for SRMs have similar short-term outcomes to those of immunocompetent controls with SRMs of the same size, suggesting promise for the safety of AS in renal transplant recipient candidates.





Abstract 22: ***Healthcare resource utilization (HCRU) and costs in metastatic renal cell carcinoma (mRCC) patients (pts) receiving first-line (LOT1) pembrolizumab + axitinib (P+A) or ipilimumab + nivolumab (I+N)***

Neil J. Shah, MD

BACKGROUND: Approval of immuno-oncology (IO) agents have changed treatment paradigm for mRCC pts. While IO-based therapies have demonstrated improved survival, these can be associated with considerable HCRU and costs necessitating their examination in real-world practice

METHODS: This retrospective claims analyses utilizing Optum Research Database included adult pts with mRCC diagnosis with receipt of P+A or I+N as LOT1 from January-2018 to May-2020 (first claim=index date). Patients were followed through August 2020. All eligible pts required continuous enrollment for minimum 6-months prior and 3-months post index date unless death occurred. Per-pt-per-month (PPPM) all-cause HCRU counts, and associated costs were examined during first 90 days (LOT1-90) and entire LOT1 duration.

RESULTS: Study identified 507 pts (P+A=126, I+N=381). Average age was 67 years, 71% were male, mean NCI Charlson score was 2.4, and lung (55%) was the most common metastatic sites. P+A and I+N pts had similar baseline characteristics. Total % of pts with ambulatory visits was similar for P+A and I+N for LOT1-90 and entire LOT1 (99.2vs.100.0%, p=0.082 for both). During LOT1-90, we observed a lower % of P+A pts with ER visits and inpatient (IP) stay compared to I+N (34vs.48, p=0.008; 19vs.38, p< 0.001, respectively), and a shorter mean (SD) IP stay for P+A vs. I+N during LOT1-90 (1.9 (6.5)vs.5.6(13.24) days, p< 0.001). Similarly, P+A had lower mean PPPM ambulatory visits, IP stay, and ICU stay during LOT1-90 and entire LOT1 (Table). Mean PPPM total (medical + pharmacy) and medical costs were lower for P+A compared to I+N, but pharmacy costs were higher for P+A for both LOT1-90 and entire LOT-1 (Table).

CONCLUSIONS: This study noted significantly higher HCRU with I+N including higher mean PPPM ambulatory visits, IP stays, and ICU stays compared to P+A. Although, P+A had higher mean PPPM

pharmacy costs, the total cost (medical plus pharmacy) were significantly lower compared to I+N.

	LOT1-90 P+A	LOT1-90 I+N	*p*-value	Entire LOT1 P+A	Entire LOT1 I+N	*p*-value
Resource use, PPPM mean (SD)						
Ambulatory	6.68 (3.37)	7.52 (4.52)	**0.029**	6.28 (2.80)	7 (4.20)	**0.031**
ER visit	0.32 (0.74)	0.4 (0.65)	0.246	0.32 (0.76)	0.38 (0.58)	0.361
IP stay	0.09 (0.22)	0.23 (0.38)	**<0.001**	0.11(0.20)	0.23 (0.36)	**<0.001**
ICU stay	0.05 (0.16)	0.1 (0.29)	**0.015**	0.06 (0.15)	0.1 (0.28)	**0.02**
Cost, PPPM mean (SD)						
Total (Medical + pharmacy)	36,963 (15,240)	48,939 (37,040)	**<0.001**	31,868 (14,739)	37,115 (31,993)	**0.013**
Medical	21,123 (14,737)	48,436 (37,154)	**<0.001**	19,328 (13,573)	36,645 (32,048)	**<0.001**
Pharmacy	15,840 (6,150)	502 (2,697)	**<0.001**	12,540 (5,473)	469 (2,630)	**<0.001**

Abstract 23: ***Real-world Assessment of Changing Treatment Patterns and sequence for patients with Metastatic Renal Cell Carcinoma (mRCC) in the first-line (1L) setting***

Neil J. Shah, MD

BACKGROUND: Several immune-oncology (IO) agents and tyrosine kinase inhibitors (TKIs) have revolutionized 1L treatment landscape of mRCC. Limited data exists on evolving real-world treatment patterns and sequence of these agents at the community oncology setting.

METHODS: We used data from The US Oncology Network of over 1,300 providers from over 480 sites across United States from 01/01/2018 to 12/31/2020 (study period). Eligible study population included mRCC patients who received ipilimumab+nivolumab (Ipi+nivo) (IO+IO); pembrolizumab+axitinib (Pembro+axi) (IO+TKI); and axitinib (Axi) or cabozantinib (Cabo) or pazopanib (Pazo) or sunitinib (Suni) (TKIs monotherapy) in 1L setting until 09/30/2020. Descriptive statistics were used for cohort characterization

RESULTS: We identified 3,756 mRCC patients, of which 1,538 were eligible including 42% (n=641) IO+IO, 18% (n=279) IO+TKI, and 40% (n=618) TKI monotherapy. Median age for the entire cohort was 67.1 years (range 25.0, 93.3), 70% (n=1,076) were male, 70% (n=1,081) were white, 38% (n=587) had BMI ≥ 30 and 79% (n=1,208) had clear cell histology. Among entire cohort, 87% (n=1,338) had intermediate/poor risk score as per International mRCC Database Consortium risk model. We noted a trend towards increased utilization of IO+IO and IO+TKI following their respective FDA approvals (IO+IO: April 2018, IO+TKI: April 2019) (Table). During the study period, overall, 35% (n=535), 12% (n=184), and 4% (n=62) mRCC patients received second-line (2L), third-line (3L) and fourth-line (4L) treatments, respectively. Cabo (49%) and pazo (12%); cabo (51%) and ipi+nivo (23%); and nivo (45%) and ipi+nivo (20%) were the most common 2L treatments in IO+IO, IO+TKI, and TKI monotherapy cohorts, respectively.

CONCLUSIONS: This large real-world study examined use of new FDA approved mRCC treatments and their impact on treatment paradigm. The results show a rapid adaptation of these newer treatments in the community oncology settings. A longer follow-up is needed to assess their clinical impact and optimal treatment strategy in subsequent setting.

	Overall (n=1,538)	IO+IO (n=641)	IO+TKI (n=279)	TKIs mono (n=618)
Index date year, (row%)	2018 (N=474)	171 (36%)	-	303 (66%)
	2019 (N=577)	270 (47%)	119 (21%)	188 (33%)
	2020 (N=587) *	200 (41%)	160 (33%)	127 (22%)
Received 2nd Line treatments, (column %)	535 (35%)	247 (39%)	53 (19%)	235 (38%)
Top 5 treatment sequence, (column %)		Cabo (n=120, 49%)	Cabo (n=27, 51%)	Nivo (n=105, 45%)
		Pazo (n=30, 12%)	Ipi+nivo (n=12, 23%)	Ipi+nivo (n=46, 20%)
		Pembro+axi (n=25, 10%)	Everolimus+ Lenvatinib (NR)	Cabo (n=15, 6%)
		Axi (n=19, 8%)	Nivo (NR)	Pembro+axi (n=14, 6%)
		Suni (n=17, 7%)	Suni (NR)	Pazo (n=12, 5%)

Abstract 24: ***Depth of response associated with first-line immunotherapy-based combinations in metastatic clear cell renal cell carcinoma.***

Kelly N. Fitzgerald, MD

BACKGROUND: First-line treatment options for clear cell renal cell carcinoma (ccRCC) include ipilimumab with nivolumab (IO/IO) or several VEGFR-targeted therapies in combination with a PD-1 inhibitor (TKI/IO). Depth of response (DpR) has been proposed as a predicter of sustained benefit from IO-based therapies. Here, we examine the relationship between DpR and OS in patients receiving 1st line IO/IO vs TKI/IO for metastatic ccRCC.

METHODS: A retrospective analysis was performed on patients treated for ccRCC with 1st line IO/IO or TKI/IO at MSKCC between 1/1/2014 and 12/30/2020. DpR is defined as the nadir of tumor shrinkage by RECIST 1.1 criteria. Partial response groups were defined as PR1 (80-99%), PR2 (60-79%), and PR3 (30-59%). Overall survival (OS) from start of 1st line therapy to death or last follow-up is estimated with the Kaplan-Meier method and reported for each DpR group.

RESULTS: One hundred seventy-three patients received 1st line IO/IO (N=90) or TKI/IO (N=83). Differences in the IO/IO group versus TKI/IO include more patients with brain metastases (9% vs 0, p=0.007) and intermediate-poor IMDC risk (88% vs 68%, p=0.007), and fewer with prior nephrectomy (67% vs 86%, p=0.005). Objective response rates for IO/IO and TKI/IO groups were respectively 38% (95% CI: 28, 49) and 65% (95% CI: 54, 75; P< 0.001). Patient distribution across response groups is shown in Table 1; the difference in distribution was significantly different between IO/IO and TKI/IO treatment groups; P=0.002. Twenty four-month survival estimates for response groups are shown in Table 1.

CONCLUSIONS: Patients receiving first-line IO/IO or TKI/IO therapies had a significant difference in the distribution of radiographic DpR groups, with more CR and PR seen in the TKI/IO group and more SD and PD seen with IO/IO. Patients whose best response was CR, PR1, or PR2 had higher 24-month OS than patients with PR3, SD, or PD.

	FREQUENCY			OVERALL SURVIVAL*	
Depth of response	Overall (N=173)	First-line IO/IO (n=90)	First-line TKI/IO (n=83)	No. of events	24-month survival estimate (95% CI)
CR	20 (12%)	9 (10%)	11 (13%)	1	94% (65, 99)
PR1	21 (12%)	9 (10%)	12 (14%)	1	100%
PR2	18 (10%)	7 (8%)	11 (13%)	5	94% (63, 99)
PR3	29 (17%)	9 (10%)	20 (24%)	8	79% (57, 91)
SD	62 (36%)	36 (40%)	26 (31%)	30	57% (42, 69)
PD	22 (13%)	19 (21%)	3 (4%)	12	52% (29, 71)
Median follow-up times for survivors is 32 months.					

Abstract 25: ***Clinical manifestations of -Hogg-Dube Syndrome in a large clinical cohort***
Track: Real-World Evidence

Raju Chelluri, M.D., M.S

BACKGROUND: Birt-Hogg-Dube (BHD) syndrome is an underdiagnosed autosomal dominant condition caused by folliculin (FLCN) gene mutations and is characterized by fibrofolliculomas, pulmonary cysts, and renal masses. Our study characterizes our center's cohort of BHD patients to describe the range of presentations.

METHODS: A single center, retrospective cohort study of patients with BHD syndrome was performed. The medical record was queried for clinical data corresponding to renal mass, pulmonary, and dermatologic findings. Results were reported as median and inter-quartile range (IQR). Germline mutation status is reported.

RESULTS: Eighty-one BHD patients were identified. Median age of BHD diagnosis was 38 (28-57) years old. Ten (12.3%) patients had a total of 15 renal masses. Age at first tumor diagnosis was 58 [50.8-60.2] years with median lesion size being 1.5 [1-2.1] cm. Six (60%]) tumor patients were managed non-operatively and 4 (40%) underwent resection. Surveilled tumor growth rate was 0 [-0.02 – 0] cm/yr during a median 2.3 [2.3-5.6] year follow-up. Twenty-six (32.1%) patients had characteristic skin findings at diagnosis with fibrofolliculomas being documented in 47 (58%) total patients at a median age of 46.5 (33-58) years. Twenty-eight (34.6%) patients had a history of pneumothorax at diagnosis with pneumothorax affecting 34 (42%) total patients. Notably, 9/47 (19.1%) patients with fibrofolliculomas and 4/34 (11.8%) patients with pneumothorax history had a renal mass. Four (40%) renal tumor patients had pneumothorax history.

CONCLUSIONS: Renal tumors were found to affect 12.3% of BHD patients in this clinical cohort. BHD-associated renal masses were noted to mostly small, indolent with a static growth rate. Only 19% patients with fibrofolliculomas and 12% of patients with pneumothorax developed a renal mass. Of patients with a renal mass, 40% experienced a pneumothorax in their lifetime. Limitations of this study include its retrospective nature, small sample size of BHD patients with renal lesions, and low follow-up time.

Abstract 26: ***Role of Histology in Influencing Outcomes after Cytoreductive Nephrectomy for Metastatic Renal Cell Carcinoma***

Pranjal Agrawal, BA

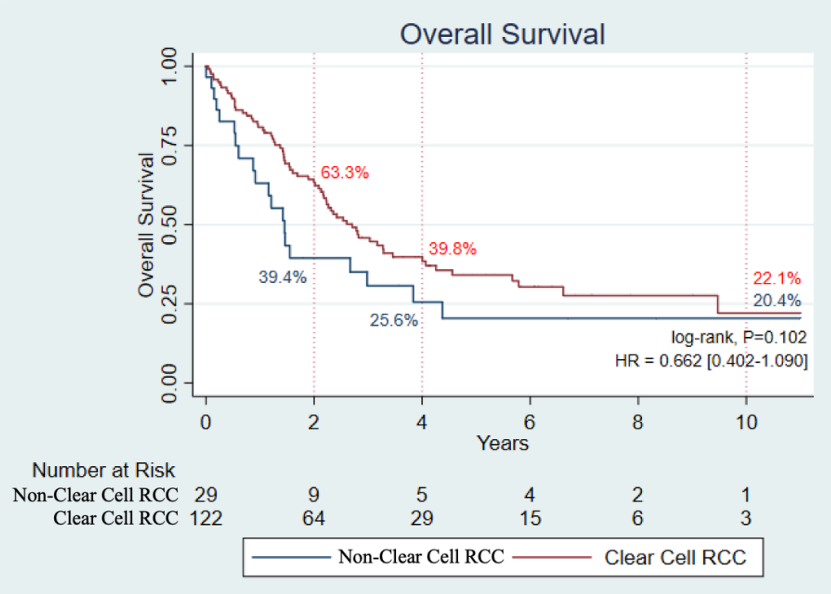
BACKGROUND: Studies evaluating the role of cytoreductive nephrectomy (CN) have been conducted primarily in patients with clear-cell RCC (ccRCC), while evidence for non-clear-cell RCC (nccRCC) remains scarce. We sought to characterize survival outcomes among patients who underwent CN for metastatic RCC (mRCC) based on histologic subtype.

METHODS: We identified patients with mRCC who received CN at our institution between 1996-2021 and stratified by histology (ccRCC or nccRCC). Baseline clinicopathologic characteristics were compared and overall survival (OS) was assessed using the Kaplan-Meier method. Independent predictors of OS were identified using Cox regression analyses.

RESULTS: Of 155 patients identified, 126 (81.3%) had ccRCC, and 29 (18.7%) had nccRCC. Patients with nccRCC were more likely to be Black (27.6 vs 3.2%, p< 0.001), present with preoperative symptoms (51.7% vs 21.4%, p=0.020), and have lower primary tumor stage (p = 0.046). There were no differences in baseline comorbidities (p=0.68), cN stage (p=0.06), or number of metastatic sites (p=0.55) between cohorts. Patients with nccRCC were less likely to receive systemic therapy (48.3% vs 73.8%; p=0.006), though the timing of therapy with respect to CN did not differ (p=0.16) between groups. Perioperative and postoperative outcomes were similar between groups, with no differences in blood loss (p=0.20), complications (p=0.51), hospital length-of-stay (p=0.59), or 90-day readmission rates (0=0.30). After a median follow-up of 20.9 months, similar OS was observed between groups (p=0.102; Figure 1). On Cox-regression, histology wasn't associated with OS; sarcomatoid features and higher metastatic burden were strong predictors for worse OS on multivariable analysis.

CONCLUSIONS: nccRCC histology doesn't negatively impact survival outcomes after CN for mRCC compared to ccRCC. While patient selection remains paramount to determining eligibility for CN, our results suggest that histologic subtype shouldn't be an exclusionary factor to offer CN at high-volume, experienced centers.

Figure 1: Overall survival of patients after cytoreductive nephrectomy stratified by histology subtype.



Abstract 27: ***Cytoreductive Nephrectomy with Concomitant Tumor Thrombectomy in Metastatic Renal Cell Carcinoma***

Pranjal Agrawal, BA

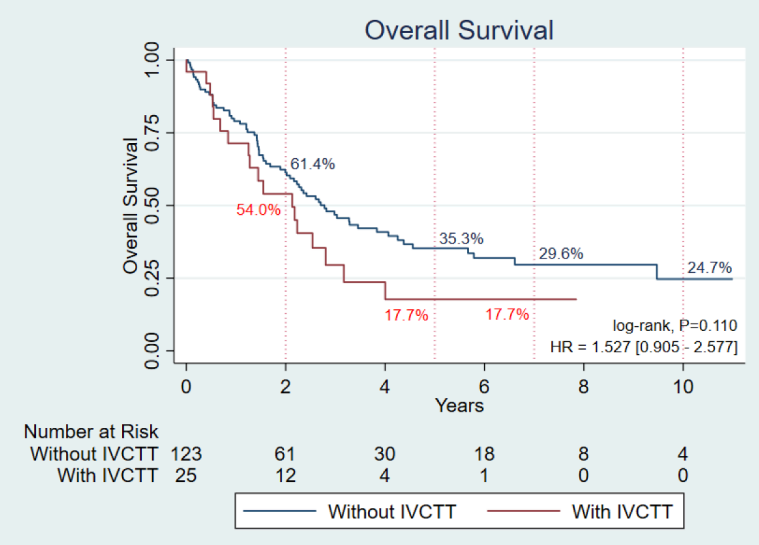
BACKGROUND: While surgery is the mainstay treatment for IVC tumor thrombus (IVCTT) arising from RCC, the timing of cytoreductive nephrectomy (CN) in the metastatic setting (mRCC) remains less well-elucidated, given the role of systemic therapy. Patients with IVCTT and mRCC pose an even greater challenge, as effectively treating the IVCTT while avoiding metastases progression must be counterbalanced.

METHODS: We identified patients with mRCC who underwent CN at our institution. Patients undergoing CN were stratified by IVCTT presence. Baseline characteristics were compared between groups and differences in overall survival (OS) were assessed using the Kaplan-Meier method. Predictors of OS were identified using Cox regression analyses.

RESULTS: Of 152 patients, 26 exhibited IVCTT. Compared to patients without IVCTT, those with were more likely to have more baseline comorbidities (CCI score of 9 vs 8, p< 0.001), larger primary tumor (11.5 vs 8.5 cm; p< 0.001), and sarcomatoid features (30.8% vs 8.7%, p< 0.001), while rhabdoid features were less prevalent (0% vs 10.3%, p=0.035). Rates of systemic therapy administration, timing of systematic therapy with respect to CN, and the number of metastatic sites did not differ between the two cohorts. Patients with IVCTT had increased estimated blood loss (1000 vs 250 mL, p< 0.001) and length of hospital stay (5.5 vs 3 days, p=0.022) compared to patients without IVCTT, while rates of intraoperative complications (p=0.085) and 90-day readmission (p=0.97) were similar. No difference in OS was observed (Figure 1). On Cox-regression, IVCTT presence was not significantly associated with OS.

CONCLUSIONS: Although IVC tumor thrombectomy with CN is associated with surgical morbidity, we didn't observe worse OS in patients undergoing CN in the presence of IVCTT compared to those without IVCTT. Patient selection and CN timing with respect to systemic therapy must be carefully weighed at high-volume, experienced centers to effectively treat the IVCTT while avoiding metastases progression.

Figure 1: Overall survival of patients after cytoreductive nephrectomy stratified by IVCTT presence.



Abstract 28: ***Treatment decisions among patients newly diagnosed with clinical T1 masses***
Track: Therapeutics- Local (Primary and Metastases)

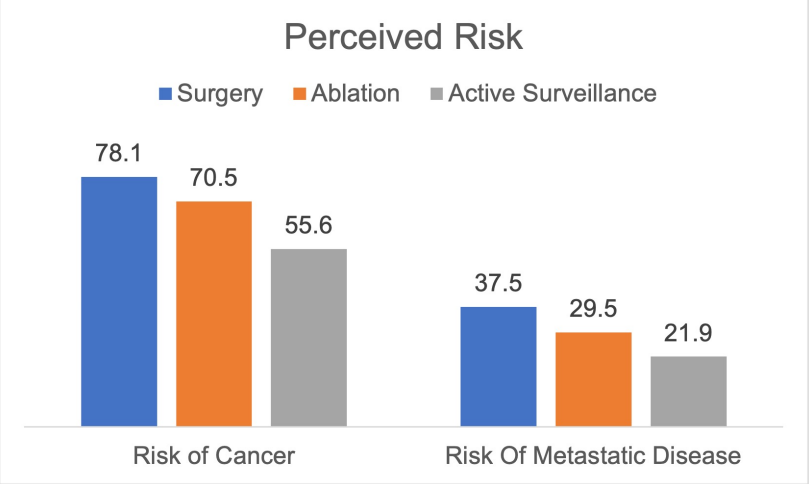
Kathryn H. Gessner, MD, PhD

BACKGROUND: Patients with clinical T1 renal masses face an increasingly complex decision given the multitude of available management options. In this study, we evaluate clinical, tumor, and decision-making factors driving treatment selection among patients with clinical T1 renal masses.

METHODS: From October 2018–June 2022, we enrolled patients with new clinical T1 renal masses onto GRADE-SRM (Genomic Risk Assessment and Decisional Evaluation for Small Renal Masses), a comparative, non-randomized hybrid trial investigating the decision-making experience and cancer genomics. At study entry, participants completed a baseline survey to characterize decision-making, communication, demographic characteristics, health status, tumor burden, and perceived risk of cancer presence and metastatic potential. Treatment decision served as the primary outcome defined as surgery, ablation, and active surveillance. We compared treatment decision by patient and tumor characteristics using bivariable analyses.

RESULTS: For 245 subjects, 59% selected surgery, 34% opted for active surveillance, and 5% chose ablation. Treatment decisions varied by age ($p< 0.001$), gender ($p=0.015$), performance status ($p< 0.001$), comorbidity ($p< 0.001$), cardiac history ($p=0.008$), eGFR ($p=0.007$), mass size ($p< 0.001$), nephrometry score ($p=0.001$), and solid vs. cystic mass ($p< 0.001$). Treatment decisions further related to information-seeking behavior ($p=0.020$), decisional conflict ($p=0.040$), and cancer worry ($p=0.004$). Subjects selecting active surveillance perceived cancer and metastasis risks to be lower than subjects choosing surgery/ablation (Figure). Renal mass biopsy was also associated with decisions for surgery or ablation ($p=0.020$).

CONCLUSIONS: In patients with clinical T1 renal masses, treatment decisions differed based on patient health and tumor characteristics, likely in response to potential risks and benefits for management options. Beyond these less modifiable factors, treatment decisions also differed based on patient risk perception, information processing, and decision-making behavior. These relationships highlight the opportunity for communication frameworks and prognostic biomarkers to further improve the patient decision-making experience.



Abstract 29: ***Cytoreductive nephrectomy (CN) for patients with metastatic sarcomatoid and/or rhabdoid (S/R) renal cell carcinoma (RCC) treated with immune checkpoint therapy (ICT)***

Andrew W. Hahn, MD

BACKGROUND: RCC with S/R dedifferentiation are highly aggressive tumors associated with a poor prognosis but often respond to ICT. There remains uncertainly regarding the role of CN for mRCC patients with S/R who received ICT. Here, we report outcomes with ICT for patients with mRCC and S/R dedifferentiation by CN status.

METHODS: We performed a retrospective review of mRCC patients with sarcomatoid, rhabdoid, or sarcomatoid plus rhabdoid dedifferentiation who received an ICT-based regimen at two tertiary cancer centers. ICT treatment duration (TD) and overall survival (OS) from ICT initiation were recorded. To address immortal time bias, we generated a time-dependent Cox regression model that included a time-dependent nephrectomy variable and five confounders identified by a directed acyclic graph.

RESULTS: 157 patients with mRCC and S/R dedifferentiation received ICT. 85 patients had intermediate-risk and 57 had poor-risk IMDC. 118 patients underwent CN, and of those, 89 underwent upfront CN and 29 underwent a delayed CN. Nivolumab plus ipilimumab (41%) was the most common treatment followed by ICT monotherapy (28%). CN was not associated with ICT TD (HR 1.01, 95% CI 0.67-1.53), nor was CN associated with OS from ICT initiation (HR 0.79, 95% CI 0.47-1.33, p=0.37). In patients who underwent upfront CN compared to those who did not undergo CN, there was no association with ICT duration nor OS (HR 0.61, 95% CI 0.35-1.06, p=0.08).

CONCLUSIONS: In this multi-institutional cohort of mRCC with S/R dedifferentiation treated with ICT, CN was not associated with improved ICT treatment duration or superior OS when accounting for immortal time bias. Further studies which explore the impact of CN in this patient population are needed, including improved tools for patient selection in this setting.

Abstract 30: ***Treatment-free survival (TFS) in patients with advanced renal cell carcinoma (aRCC) treated with nivolumab and ipilimumab (NIVO/IPI) versus sunitinib (SUN): 60-month update of Checkmate 214***

Charlene M. Mantia, MD

BACKGROUND: Treatment with immunotherapy can be associated with prolonged disease control after discontinuation without the need for further anticancer therapy. Treatment-related adverse events (TRAEs) can also persist after therapy cessation. TFS with and without toxicity can characterize survival time.

METHODS: Data from 1096 patients with aRCC treated with first-line NIVO/IPI (n=550) vs. SUN (n=546) in the CheckMate 214 trial were analyzed. TFS was defined as the area between Kaplan-Meier curves for time from randomization to protocol therapy cessation and time from randomization to subsequent therapy initiation or death.

RESULTS: At 60 months from randomization, 63% and 55% of favorable-risk patients and 43% and 31% of intermediate/poor-risk patients treated with NIVO/IPI and SUN were alive. For favorable-risk patients, the 60-month mean TFS was 14.4 vs. 5.5 months after NIVO/IPI vs. SUN, of which TFS with grade 2+ TRAEs was 5.0 vs. 2.1 months and grade 3+ TRAEs was 1.2 vs. 0.3 months with NIVO/IPI vs. SUN. For intermediate/poor-risk patients, the 60-month mean TFS was 10.1 vs. 4.1 months for NIVO/IPI vs. SUN, of which TFS with grade 2+ TRAEs was 4.0 vs. 2.0 months and grade 3+ TRAEs was 0.6 vs. 0.3 months with NIVO/IPI vs. SUN. At 60 months, 16% and 7% of favorable-risk patients and 18% and 4% of

intermediate/poor-risk patients were surviving treatment-free after NIVO/IPI vs. SUN. Subgroup analyses are ongoing.

CONCLUSIONS: While overall survival was similar for favorable-risk patients in both treatment groups, patients treated with NIVO/IPI spent more time surviving treatment-free without toxicity compared to SUN after 60 months of follow up. Intermediate/poor-risk patients treated with NIVO/IPI had longer survival and longer TFS without toxicity compared to SUN.

Survival State	60-month mean time, months					
	Favorable-risk IMDC			Intermediate/Poor-risk IMDC		
	NIVO/IPI (n=125)	SUN (n=124)	Difference (95% CI)	NIVO/IPI (n=425)	SUN (n=422)	Difference (95% CI)
Overall Survival	47.9	49.2		38.6	32.2	
Time on protocol therapy	15.1	21.6	-6.5 (-10.5, -2.4)	16.2	11.2	5.0 (2.8, 7.1)
TFS	14.4	5.5	8.9 (4.9, 12.8)	10.1	4.1	6.1 (4.2, 7.9)
TFS with grade 2+ TRAEs	5.0	2.1	2.9 (0.5, 5.4)	4.0	2.0	2.0 (0.9, 3.2)
TFS with grade 3+ TRAEs	1.2	0.3	1.0 (-0.2, 2.1)	0.6	0.3	0.3 (0.0, 0.7)

Abstract 31: ***Updated efficacy of lenvatinib + pembrolizumab versus sunitinib in patients with advanced renal cell carcinoma (aRCC) in the CLEAR study***

Camillo G Porta, MD

BACKGROUND: The phase 3 CLEAR study showed statistically significant PFS and OS benefits, and improved ORR with lenvatinib + pembrolizumab versus sunitinib in patients with aRCC in the 1L setting. We report updated efficacy and describe patients who completed 2 years of pembrolizumab and continued lenvatinib monotherapy.

METHODS: Patients with aRCC and no prior systemic therapy were randomized (1:1:1) to receive lenvatinib 20 mg PO QD + pembrolizumab 200 mg IV Q3W; lenvatinib 18 mg + everolimus 5 mg PO QD; or sunitinib 50 mg PO QD (4 weeks on/2 weeks off). Randomization was stratified by geographic region and MSKCC prognostic group. In this descriptive follow-up analysis (data cutoff March 31, 2021), we report updated PFS, ORR, and DOR, by independent imaging review per RECIST v1.1 for lenvatinib + pembrolizumab and sunitinib, and an exploratory analysis of patients who completed 2 years of pembrolizumab and continued lenvatinib.

RESULTS: The Table shows updated efficacy results. Median survival follow-up was 33.7 and 33.4 months for patients randomized to lenvatinib + pembrolizumab (N=355) and sunitinib (N=357), respectively. Of patients who completed 2 years of pembrolizumab (n=101), most (n=65) had IMDC intermediate/poor risk and fewer (n=36) had favorable risk disease, consistent with the intention-to-treat population. Pembrolizumab completers had a 36-month OS rate of 94.5%; 69 (68.3%) of these patients had treatment-related treatment-emergent adverse events.

CONCLUSIONS: Lenvatinib + pembrolizumab continued to show a clinically meaningful benefit versus sunitinib, consistent with prior results of the CLEAR study. A large proportion of patients treated with lenvatinib + pembrolizumab completed 2 years of pembrolizumab and continued with lenvatinib monotherapy with ongoing clinical benefit. The results further support lenvatinib + pembrolizumab as a standard of care in 1L aRCC.

	LEN + PEMBRO (N=355)	SUN (N=357)
Median PFS[a], mos (95% CI)	23.3 (20.8, 27.7)	9.2 (6.0, 11.0)
PFS HR (95% CI)	0.42 (0.34, 0.52)	
Median OS, mos (95% CI)[b]	NE (41.5–NE)	NE (38.4–NE)
OS HR (95% CI)[b]	0.72 (0.55–0.93)	
ORR, % (95% CI)	71.0 (66.3, 75.7)	36.1 (31.2, 41.1)
Relative risk, % (95% CI)	1.97 (1.69, 2.29)	
CR, %	17.2	4.2
Median DOR, mos (95% CI)	26.0 (22.2, 41.4)	14.7 (9.4, 16.8)

Data cutoff: March 31, 2021 (7 months of additional follow-up from the primary analysis).
[a]PFS was the primary endpoint in the primary analysis; [b]OS was previously reported at Kidney Cancer Research Summit, 2021.
CI, confidence interval; CR, complete response; DOR, duration of response; HR, hazard ratio; LEN, lenvatinib; mos, months; NE, not estimable; OS, overall survival; ORR, overall response rate; PEMBRO, pembrolizumab; PFS, progression-free survival; SUN, sunitinib.

Abstract 32: ***Efficacy and safety of nivolumab plus ipilimumab versus sunitinib for first-line treatment of patients with advanced sarcomatoid renal cell carcinoma (sRCC) in the phase 3 CheckMate 214 trial with extended 5-year minimum follow-up***

Nizar M.. Tannir, MD

BACKGROUND: First-line nivolumab plus ipilimumab (NIVO+IPI) provided efficacy benefits over sunitinib (SUN) in patients with intermediate/poor (I/P)-risk sRCC at 42 months follow-up. We report an exploratory post hoc analysis of NIVO+IPI versus SUN in patients with I/P-risk and sRCC with long-term follow-up of 5 years.

METHODS: Patients with clear cell advanced RCC were randomized 1:1 to NIVO 3 mg/kg plus IPI 1 mg/kg Q3W×4, then NIVO 3 mg/kg Q2W versus SUN 50 mg QD (4 weeks; 6-week cycles). Patients with sRCC were identified via independent central pathology review of archival tumor tissue or histological classification per local pathology. Endpoints included overall survival (OS), progression-free survival (PFS) per independent radiology review, and objective response rate (ORR) per RECIST v1.1 in all I/P-risk patients with sRCC and by baseline PD-L1 expression. Safety outcomes used descriptive statistics.

RESULTS: Of 1096 randomized patients in CheckMate 214, 139 I/P-risk patients with sRCC were identified. More patients remained on treatment at 5 years with NIVO+IPI versus SUN (12% vs 0). The primary reason for discontinuation was disease progression (NIVO+IPI, 37%; SUN, 71%). Efficacy benefits continued to favor NIVO+IPI versus SUN, including OS, PFS, and ORR (Table). Median duration of response was longer (NR vs 25 months) and more patients had complete responses (23% vs 6%) with NIVO+IPI versus SUN, respectively. Efficacy was better with NIVO+IPI versus SUN regardless of PD-L1 expression (Table). No new safety signals emerged.

CONCLUSIONS: The long-term survival benefits and durable and deep responses with NIVO+IPI versus SUN in I/P-risk patients with sRCC support NIVO+IPI as a preferred first-line therapy in this population.

	All			Tumor PD-L1 ≥ 1%			Tumor PD-L1 < 1%		
	NIVO+IPI (N = 74)	SUN (N = 65)	*P* value	NIVO+IPI (N = 36)	SUN (N = 33)	*P* value	NIVO+IPI (N = 35)	SUN (N = 29)	*P* value
mOS (95% CI), months	49 (25–NE)	14 (9–23)	–	NR (30–NE)	21 (9–41)	–	40 (19–NE)	14 (6–20)	–
OS HR (95% CI)	0.46 (0.29–0.71)		0.0004	0.40 (0.19–0.84)		0.0143	0.42 (0.22–0.78)		0.0049
OS probability ≥ 5 years (95% CI), %	47 (35–58)	21 (12–32)	–	55 (37–70)	29 (15–45)	–	44 (27–60)	14 (4–29)	–
mPFS (95% CI), months	26 (7–NE)	5 (4–7)	–	NR (9–NE)	6 (3–7)	–	9 (3–47)	5 (4–17)	–
PFS HR (95% CI)	0.50 (0.32–0.80)		0.0036	0.29 (0.14–0.57)		0.0002	0.65 (0.34–1.24)		0.1894
PFS probability ≥ 5 years (95% CI), %	46 (33–58)	12 (3–27)	–	60 (41–75)	14 (4–31)	–	33 (17–49)	NR[a]	–
ORR (95% CI), %	61 (49–72)	23 (14–35)	<0.0001	69 (52–84)	24 (11–42)	–	54 (37–71)	21 (8–40)	–
Complete response, %	23	6	–	25	9	–	23	3	–
Partial response, %	38	17	–	44	15	–	31	17	–

[a]Minimum follow-up NR; 0 patients at risk at 5 years.
CI, confidence interval; HR, hazard ratio; m, median; NE, not estimable; NR, not reached; PD-L1, programmed death ligand 1.

Abstract 33: ***Long-term PFS from TIVO-3: Tivozanib (TIVO) vs sorafenib (SOR) in relapsed/refractory (R/R) advanced RCC***

Michael Atkins, MD

BACKGROUND: The TIVO-3 trial supported FDA-approval of TIVO in R/R advanced RCC, demonstrating significantly improved PFS over SOR in the primary independent review committee [IRC] analysis (HR: 0.672, 95% CI: 0.52-0.87). Long-term survival without disease progression (LT-PFS) is a clinically meaningful outcome among patients with R/R mRCC and ≥2 lines of prior therapy. We assessed the proportion of TIVO-3 patients living progression-free with R/R mRCC at 6-month intervals up to 4 years post-initiation of TIVO or SOR.

METHODS: Exploratory analysis of LT-PFS was calculated using investigator-assessment [INV] with a data cut-off of May 24, 2021. PFS hazard ratio and landmark values of LT-PFS at 6, 12, 18, 24, 30, 36, 42 and 48 months are reported. Results include the ITT population, with censoring for missing assessments and discontinuation without PD. Cox proportional hazards and log-rank statistics were used to estimate the HR and 95% CI for INV-PFS; odds ratios (ORs) are reported for landmark timepoints up to 36-months. LT-PFS across prespecified subgroups were analyzed descriptively.

RESULTS: 350 patients were randomized to TIVO (n=175) or SOR (n=175). INV PFS was superior with TIVO vs SOR (HR: 0.624, 95% CI: 0.49-0.79). Landmark LT-PFS rates up to 48-months are consistently higher with TIVO vs SOR, with 12% vs 2% and 7.6% vs 0% at 3- and 4-years, respectively (Table 1). Despite low numbers of patients at risk with extended follow-up, subgroups with ≥15% LT-PFS at 3-years include IMDC favorable risk, female gender, ECOG PS0, age ≥65 years, and region NA – all confined to the TIVO arm.

CONCLUSIONS: INV PFS with long-term follow-up is consistent with primary IRC PFS. Patients treated with TIVO were up to 5X more likely to experience LT-PFS compared to SOR. A clinically relevant minority of patients are alive and progression-free on TIVO at 3- and 4-years.

Table 1. Landmark LT-PFS in TIVO-3

LT-PFS at:	At Risk (n)	TIVO n=175 % (95%CI)	SOR n=175 % (95%CI)	Absolute Difference	Odds Ratio (TIVO/SOR) 95% CI
6-mos	124	49.6 (42-57)	35.1 (27-43)	14.5%	1.81 (0.85-3.87)
12-mos	68	31.2 (24-39)	18.4 (12-25)	12.8%	2.02 (0.59-6.9)
18-mos	45	24.2 (18-31)	8.8 (5-14))	15.4%	3.32 (0.38-18.9)
24-mos	31	18.3 (13-25)	4.8 (2-10)	13.5%	4.46 (0.09-216)
30-mos	22	13.9 (9-20)	3.2 (1-7)	10.7%	4.88 (0.02-1504)
36-mos	19	12.3 (8-18)	2.4 (1-6)	9.9%	5.73 (0.1-10873)
42-mos	14	9.2 (5-15)	1.6 (0-5)	7.6%	*
48-mos	10	7.6 (4-13)	0	7.6%	*

* not calculated for limited sample size

Abstract 34: ***Characterization of Patients Undergoing Consolidative Nephrectomy after Immunotherapy***

Stephen Reese, MD

BACKGROUND: There remains uncertainty around how to manage patients who experience complete or partial responses after systemic therapy and then undergo consolidative nephrectomy.

METHODS: We conducted a single-institution (Memorial Sloan Kettering Cancer Center) retrospective analysis of patients treated with immunotherapy with metastatic cancer at the time of treatment (n=23). Patients were stratified based on final surgical pathology given presence of residual disease or pT0. Overall survival (OS) was calculated by the Kaplan-Meier method

RESULTS: All patients had metastatic disease at presentation and almost all had clear cell histology (n=22). All patients who had pT0 at time of surgery were treated with combination ipi + nivo, were on systemic therapy for almost a year prior to surgery and had a significant change in size of primary tumor (-3.75cm). 14 patients (60.87%) had stable mets or were NED after surgery. Median follow-up after surgery was 33 months. Median OS was not reached at time of follow-up, however survival was 52% for patients with residual tumor and 100% for pT0 patients.

CONCLUSIONS: Patients with metastatic disease who demonstrated partial or complete response after immunotherapy and subsequently underwent consolidative nephrectomy had durable overall survival at follow-up, including a sub-set of pT0 patients who were all alive at follow-up.

Table 1. Cohort of patients undergoing consolidative nephrectomy

	Residual Disease (n=17)	pT0 (n=6)	
Patient Characteristics			
Age	61.963 (12.63)	63.783 (9.91)	P=0.21
Gender			P=0.54
Male	17 (94.12%)	6 (100%)	
ASA	3 (0)	3 (0)	P=0.10
Survival Status			
Months Follow-up	33.13 (23.50)	31.30 (57.27)	P=0.57
% OS Survival	9 (52.94%)	6 (100%)	P=0.05
Post-op Clinical Course			P <0.01
Progression	9 (52.94%)	0 (0%)	
Stable Mets	6 (35.29%)	1 (16.67%)	
NED	2 (11.76%)	5 (83.33%)	
Tumor Characteristics			
Stage at Diagnosis			P=1.00
Metastatic (M1)	17 (100%)	6 (100%)	
Size of Primary Tumor at Diagnosis	7.30 (4.4)	7.55 (1.6)	p=0.72
Change In Primary Mass Size from Diagnosis to Surgery	0 (1.80)	-3.75 (1.6)	<0.01
Histology			P=0.54
Clear Cell	16 (94.12%)	6 (100%)	
Unclassified	1 (5.88%)	0 (0%)	
Sarcomatoid Features			P=0.19
Yes	4 (23.53%)	0 (0%)	
Upfront Immunotherapy			P=0.16
IO	2 (11.76%)	0 (0%)	
IO/IO*	11 (64.71%)	5 (83.33%)	
IO/VEGF	4 (23.53%)	0 (0%)	
Interferon	0 (0%)	1 (16.67%)	
Time on Immunotherapy prior to Surgery (years)	0.75 (0.84)	0.88 (1.00)	P=0.79

* All patients received Nivolumab + Ipilimumab as combination IO therapy.

Abstract 35: ***Activity of tivozanib in non-clear cell renal cell carcinoma (nccRCC): Subgroup analysis from a phase 2 randomized discontinuation trial***

Pedro Barata, MD

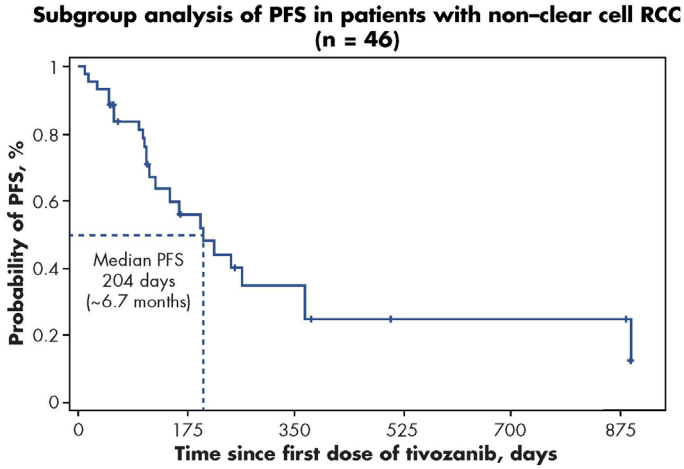
BACKGROUND: Non-clear cell renal cell carcinoma (nccRCC) is a blanket term for a collection of heterogenous and biologically diverse RCC histologies including (but not limited to) papillary, chromophobe and unclassified subtypes. Tivozanib is a selective VEGFR tyrosine kinase inhibitor with demonstrated activity in RCC with clear cell component. Here we report efficacy of tivozanib in a histologically diverse nccRCC subset included in a phase 2 study.

METHODS: We conducted a subgroup analysis of patients with nccRCC enrolled in the study 201 (NCT00502307), a phase 2 randomized discontinuation trial of tivozanib in patients with RCC who had no prior VEGF targeted treatment. Clinical outcomes including investigator (INV)-assessed overall response rate (ORR), disease control rate (DCR, defined by CR+PR+SD), and progression free survival (PFS) were examined. Safety outcomes for all patients are reported in the original publication (Nosov, JCO 2012).

RESULTS: Of the 272 patients enrolled, 46 (16.9%) patients had nccRCC. [11 (4%) papillary, 2 (0.7%) chromophobe, 2 (0.7%) collecting duct, and 31 (11.4%) unclassified/mixed]. Of the 46 nccRCC patients, 38 were continuously treated with tivozanib and the best ORR was 21.1% (confirmed) and 31.6% (confirmed and unconfirmed). The DCR was 73.7%. The median PFS was 6.7 months (204 days) (95%CI: 125-366 days) (Figure 1). Of note, 8 patients with SD after 16 weeks on tivozanib were randomized to 12 weeks of placebo and may have progressed during that timeframe before unblinding and resuming tivozanib. Safety was not

analyzed by histology but there were no new safety signals and was consistent with tivozanib labelling in the ITT population.

CONCLUSIONS: Tivozanib demonstrated activity and a favorable safety profile in patients with nccRCC. This data adds to the body of evidence supporting VEGFR TKI use in advanced RCC including in non-clear cell histologies.



Patients who experienced events, n (%)	24 (52.2%)
Patients who were censored, n (%)	22 (47.8%)
KM estimates (days):	
25% PFS (95% CI)	111 (60, 164)
50% PFS (95% CI)	204 (120, 366)
75% PFS (95% CI)	892 (249, NE)

Abstract 36: ***Impact of subsequent therapies in patients with advanced renal cell carcinoma (aRCC) receiving lenvatinib plus pembrolizumab or sunitinib in the CLEAR study***

Martin H. Voss, MD

BACKGROUND: In the open-label phase 3 CLEAR study, lenvatinib + pembrolizumab had significant PFS and OS benefits over sunitinib among patients with aRCC in the 1L setting. We evaluated PFS on next-line therapy ("PFS2") and explored the effect of subsequent anticancer therapy on OS in the lenvatinib + pembrolizumab and sunitinib arms of CLEAR.

METHODS: PFS2 was defined as time from randomization to disease progression (assessed by investigator) on next-line treatment or death from any cause (whichever occurred first). PFS2 was evaluated in all patients randomly assigned to lenvatinib 20mg orally QD + pembrolizumab 200mg IV Q3W (N=355) or sunitinib 50mg orally QD (4 weeks on/2 weeks off) (N=357) using Kaplan-Meier estimates and compared between treatment arms via a log-rank test stratified by geographic region and MSKCC prognostic groups. The HR and CI were estimated using Cox regression with Efron's method for ties, using the same stratification factors. A post hoc analysis accounting for the effect of subsequent anticancer therapy on OS (time from randomization to death from any cause) using 2-stage estimation was conducted.

RESULTS: Subsequent anticancer therapy is summarized in the Table. Among all patients, PFS2 was longer with lenvatinib + pembrolizumab than with sunitinib (Table). The unadjusted OS HR for lenvatinib + pembrolizumab versus sunitinib (from the primary analysis) was 0.66 (95% CI 0.49–0.88); the HR for OS adjusted for subsequent therapy was 0.54 (bootstrap 95% CI 0.39–0.72).

CONCLUSIONS: Lenvatinib + pembrolizumab had statistically significant and clinically meaningful benefits over sunitinib in CLEAR. Findings remained consistent after accounting for subsequent therapies, as evidenced by prolonged PFS2 and adjusted OS. Results further support lenvatinib + pembrolizumab as a standard of care in 1L aRCC.

Parameter	LEN + PEMBRO (N=355)	SUN (N=357)
Patients receiving any subsequent systemic anticancer therapy[a], n (%)	117 (33.0)	206 (57.7)
Anti-VEGF	108 (30.4)	120 (33.6)
PD-1/PD-L1 checkpoint inhibitor	29 (8.2)	154 (43.1)
MTOR inhibitor	6 (1.7)	17 (4.8)
CTLA-4 inhibitor	6 (1.7)	18 (5.0)
Other	12 (3.4)	20 (5.6)
Median (range) time to next line therapy[b], mos	12.68 (1.45–37.36)	6.62 (0.39–28.52)
Median (range) duration of first subsequent anticancer therapy[c], mos	5.16 (0.10–30.23)	6.82 (0.03–30.72)
PFS2, median (95% CI)	Not reached (NE–NE)	28.7 mos (23.0–NE)
PFS2 HR (95% CI)	0.50 (0.39–0.65)	
Nominal *P* value	<0.0001	
PFS2 rate at 24/36 mos, % (95% CI)	72.7 (67.3, 77.4) / 61.9 (53.7, 69.0)	54.2 (48.4, 59.6) / 42.9 (32.8, 52.5)

[a]Monotherapy or in combination; [b]includes patients with available start date of first subsequent systemic anticancer medication; [c]includes patients with available start and end dates of first subsequent systemic anticancer medication. CI, confidence interval; HR, hazard ratio; LEN, lenvatinib; mos, months; NE, not estimable; PEMBRO, pembrolizumab; PFS2, progression-free survival on next-line therapy; SUN, sunitinib.

Abstract 37: ***A randomized phase 2 study with a cell-based immune primer plus sunitinib versus sunitinib aone in metastatic Renal Cell Carcinoma.***

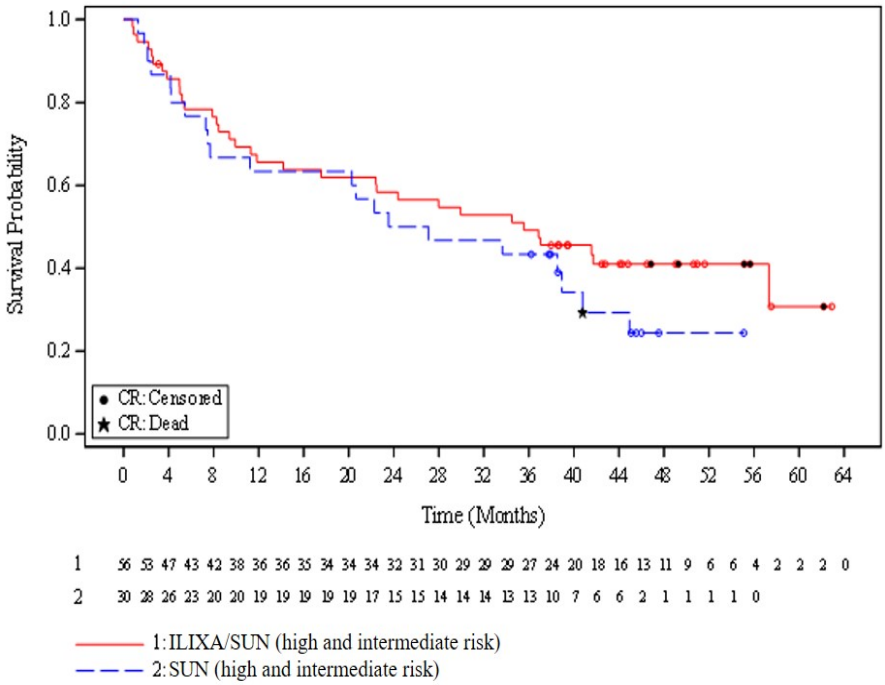
Börje Ljungberg

BACKGROUND: The prognosis in patients with synchronous metastatic renal cell carcinoma (mRCC) remains poor. Despite prosperous improvements with single agent tyrosine kinase inhibition (TKI) and additionally effects by immune checkpoint inhibitor (ICI) combinations (ICI/ICI or ICI/TKI), the treatments are insufficient. Innovative treatment options can be beneficial.

METHODS: A randomized (2:1) phase 2 multicenter trial enrolled 88 patients with synchronous mRCC to treatment with the combination of two doses of allogeneic monocyte-derived dendritic cells (ilixadencel) and sunitinib (ILIXA/SUN) (58 patients) or sunitinib monotherapy (SUN) (30 patients). The ilixadencel was administrated intratumorally two weeks apart, followed by nephrectomy and sunitinib. The experimental arm was compared with nephrectomy and sunitinib monotherapy. Primary endpoints were 18-month survival rate and overall survival (OS). A secondary endpoint was objective response rate (ORR) assessed up to 18 months post enrollment. Statistic evaluations included Kaplan-Meier, log-rank tests, Cox regression and stratified Cochran–Mantel–Haenszel tests.

RESULTS: Median OS was 35.6 months in the ILXA/SUN arm versus 25.3 months in the SUN arm (HR 0.73, 95%CI:0.42-1.27), while the 18-month OS rate was 63% and 66% in the ILIXA/SUN and SUN arms, respectively. Confirmed ORR in ILIXA/SUN arm was 42.2% (19/45), including 3 patients with complete response (CR), versus 24.0% (6/25) in the SUN arm (p=0.13) without any CR. At the last scheduled imaging follow-up at 18 months two additional patients in the ILIXA/SUN arm (total 5 of 45 = 11%) had developed CR and one SUN patient (1/25). The five ILIXA/SUN patients who achieved CR, were all alive at the latest survival follow up, while the SUN CR patient had died.

CONCLUSIONS: The study failed to meet its primary endpoints. However, ilixadencel in combination with sunitinib was associated with a numerically higher response rate, including longstanding CRs, compared with sunitinib monotherapy, suggesting an immunologic effect of the experimental treatment.



Abstract 38: ***Association between depth of response (DepOR) and clinical outcomes: exploratory analysis in patients with previously untreated advanced renal cell carcinoma (aRCC) in CheckMate 9ER***

Andrea B. Apolo, MD

BACKGROUND: Among patients with untreated aRCC in CheckMate 9ER, superior progression-free survival (PFS; HR, 0.56) and overall survival (OS; HR, 0.70) were maintained, and objective response and complete response (CR) rates were doubled for nivolumab plus cabozantinib (NIVO+CABO) versus sunitinib (SUN) with extended 25.4-month minimum (32.9-month median) follow-up. This exploratory analysis evaluated DepOR and clinical outcomes in CheckMate 9ER.

METHODS: Patients received NIVO (240mg) every 2 weeks plus CABO (40mg) once daily or SUN (50mg once daily; 4 weeks; 6-week cycles). DepOR subgroups were based on best overall response (blinded independent central review [BICR], RECIST v1.1) and best tumor reduction thresholds (CR; partial response subdivided by tumor reduction of ≥80% [PR1]; ≥60%-< 80% [PR2]; or < 60% [PR3]; stable disease; and progressive disease). PFS (per BICR) and OS by DepOR subgroups were analyzed after a 6-month post-randomization landmark. Treatment-related adverse events (TRAEs) were also assessed.

RESULTS: Of patients randomized to NIVO+CABO or SUN, at the 6-month landmark 236/323 and 157/328 were progression-free and alive and 293/323 and 253/328 were alive and categorized by DepOR subgroup. Greater proportions of patients receiving NIVO+CABO had deeper responses versus SUN (CR, PR1, PR2; Table). Deeper responses with NIVO+CABO were associated with improved 12-month PFS rates versus SUN for CR (94.9% vs 82.4%), PR1 (81.3% vs 37.5%), and PR2 (72.1% vs 53.2%). Increasingly deeper responses led to better OS outcomes overall; yet OS rates and medians were comparable between arms for CR and PR1-3 (Table). No meaningful patterns for overall TRAEs by subgroup were identified.

CONCLUSIONS: More patients achieved deeper responses with NIVO+CABO versus SUN and deeper responses were generally associated with improved PFS and OS.

Table

	NIVO+CABO						SUN					
	PFS[a] (N = 236)			OS[a] (N = 293)			PFS[a] (N = 157)			OS[a] (N = 253)		
DepOR	n	12-mo rate, %[b,c]	Median (95% CI), mo	n	18-mo rate, %[c]	Median (95% CI), mo	n	12-mo rate, %[b,c]	Median (95% CI), mo	n	18-mo rate, %[c]	Median (95% CI), mo
CR	40	94.9	NR (26.0–NE)	40	97.5	NR (NE–NE)	17	82.4	NR (15.9–NE)	17	100	NR (30.2–NE)
PR1	32	81.3	24.3 (17.0–NE)	33	97.0	NR (28.9–NE)	8	37.5	6.5 (0.9–NE)	9	100	NR (19.7–NE)
PR2	37	72.1	24.8 (13.4–NE)	38	83.5	NR (31.7–NE)	18	53.2	12.0 (7.9–NE)	18	88.2	NR (NE–NE)
PR3	62	46.7	10.4 (5.5–14.0)	69	78.3	NR (30.5–NE)	45	57.0	15.9 (6.8–21.6)	49	75.3	NR (25.1–NE)
SD	65	33.5	6.3 (4.0–10.6)	99	59.6	28.7 (17.8–NE)	69	22.6	5.2 (3.7–6.7)	123	68.0	NR (24.6–NE)
PD	0	–	–	14	35.7	10.1 (4.8–25.1)	0	–	–	37	39.1	13.7 (6.5–18.6)

[a]At the 6-mo landmark. [b]12-mo PFS rate is presented due to low patient numbers at later time points. [c]12-mo and 18-mo rates are from the 6-mo landmark.
CI, confidence interval; NE, not estimable; NR, not reached; PD, progressive disease; SD, stable disease.

Abstract 39: *Maturation of overall survival (OS) in TIVO-3 with long-term follow-up*

Brian Rini, MD

BACKGROUND: Maturity of survival data is a consideration in the value assessment and confident clinical application of oncology drugs based on trial evidence. TIVO-3 supported FDA-approval of tivozanib (TIVO) in relapsed/refractory (R/R) advanced RCC, meeting the primary endpoint of significantly improved PFS over sorafenib (SOR) (HR: 0.73, 95% CI, 0.56-0.95). Long-term follow-up analyses demonstrate that the PFS rate at 3-years with TIVO is >5x higher than with SOR (12% vs 2%, respectively), yet a significant OS benefit for TIVO has not been observed to date. Here we report the contribution of event accumulation and data maturation on the stability of KM survival estimates.

METHODS: Intent-to-treat analyses of Cox proportional hazards and log-rank statistics were used to estimate the HR and 95% CI for OS in the TIVO-3 trial at prespecified (2-years after last-patient-in [LPI]; ≥251 events) and exploratory extended follow-up timepoints (≥270 events; database closure). Patients were followed for survival until death, consent withdrawal, or loss to follow-up.

RESULTS: 350 patients were randomized 1:1 to TIVO (n=175) or SOR (n=175). 2-years post LPI and a mean follow-up of 17.9 months (data cut-off August 2019), 65% of patients experienced an event (HR: 0.99, 95% CI, 0.76-1.29). Subsequent analyses are reported at 20.3 (May 2020), 21.9 (January 2021), and 22.8 (May 2021) months follow-up. Accumulation of events and HR over time is shown in the Table. After almost 23 months of follow-up and realization of 80% of events, OS HR has decreased to below 0.90, in favor of TIVO.

CONCLUSIONS: Serial OS analyses using KM estimates are subject to increased curve reliability with decreased censoring and limited residual patients at risk for death. Long-term follow-up of TIVO-3 suggests early and consistent PFS benefit with TIVO over SOR is associated with an OS HR decline over-time with more events.

Table 1. TIVO-3 OS HR with extended follow-up

Data cut-off date	Follow-up, months mean (95% CI)	Events, n	HR (95% CI)
August 2019	17.9 (16.7–19.1)	227	0.99 (0.76–1.29)
May 2020	20.3 (18.8–21.8)	251	0.97 (0.75–1.24)
January 2021	21.9 (20.2–23.6)	270	0.91 (0.72–1.17)
May 2021	22.8 (20.9–24.6)	280	0.89 (0.70–1.14)

Abstract 40: ***Phase I trial of combination therapy with avelumab and cabozantinib in patients with newly diagnosed metastatic clear cell renal cell carcinoma***

Haoran Li, MD, PhD

BACKGROUND: Immune therapy combinations are now standard first-line therapy for pts with mccRCC. We hypothesize that Ave + Cabo will be safe and show clinical activity in mccRCC.

METHODS: Phase I 3+3, clinical trial with three dose levels: Cabo 20mg, 40mg and 60mg + Ave (10mg/kg q2weeks) in each arm. Primary endpoints are safety and identification of the recommended phase II dose (RP2D). Key secondary endpoints include objective response rate (ORR) and radiographic progression free survival (PFS). There is a pre-planned dose expansion cohort of 3 patients of the maximum tolerated dose as confirmation of the RP2D.

RESULTS: Twelve patients with newly diagnosed mccRCC were enrolled: Three patients in the 20 and 40 mg cohorts each, and six patients in the 60 mg cohort. IMDC risk were: four (favorable), six (intermediate), and two patients (poor). No dose-limiting toxicities (DLTs) were observed in any cohort (Table 1). Dose reductions were required in 5 of 6 pts in the Cabo 60 mg cohort after the DLT period. . ORR was 50% with one CR and, five PR. The overall clinical benefit (CR+PR+SD) was noted in 92% of the patients. Progress-free survival rate (PFS) was noted in 67.7%, and 33.5% of patients respectively at 6 and 12 months. Additional details will be presented at the meeting.

CONCLUSIONS: Cabo/Ave in mccRCC is safe and preliminarily efficacious. The recommended RP2D dose for the combination is Cabo 40mg/day and Ave 10mg/kg q2 weeks due to a high incidence of intolerable grade 2 toxicity for Cabo 60mg/day. To our knowledge, this is the first study to provide the safety data for this novel combination and warrants further validation in larger studies.

Abstract 41: ***Efficacy of nivolumab plus ipilimumab in T1aN0M0 renal cell carcinoma patients ineligible for surgery and ablation***

Ilya Tsimafeyeu, M.D.

BACKGROUND: We hypothesized that immunotherapy could eliminate the primary tumor in T1aN0M0 RCC patients ineligible for surgery and nephron-sparing interventions.

METHODS: In phase 2 pilot study patients with biopsy-proven clear-cell RCC of ≤4 cm (cT1a), no evidence of metastases, and unable to have surgery or ablation received ipilimumab (1 mg/kg) every 3 weeks for four doses, and nivolumab (240 mg) every 2 weeks during 16 weeks. The primary endpoint was complete response rate. Simon's two-stage design was used. The H0 that the true complete response rate was 11%. This design yields a type I error rate of 0.05 and power of 0.9 when the true complete response rate is 60% (Ha). The null hypothesis should be rejected if 3 or more responses are observed in 8 patients.

RESULTS: Between February 2020 and June 2021, 8 patients were included. Median age was 77.9 years (range 73-89). Patients were predominantly male (75%), 62.5% had centrally located RCC, 25% had ECOG PS 1, and 75% had comorbidities. All patients completed immunotherapy without grade ≥2 adverse events. With a median follow-up of 15 months (95% CI 7.0–20.5), 1-year progression-free survival was 100%. No complete responses were observed. Partial responses were found in 3 patients (37.5%). Primary tumor continued to shrink after completion of therapy. Median size of the primary at RCC diagnosis and after immunotherapy was 3.11 cm (range 2.2–3.9) and 2.05 cm (1.2–4.0), respectively. Any shrinkage of the primary tumor was reported in 5 (62.5%) patients (change in median sum of diameters -21%). Only one patient had tumor enlargement (+0.5 cm (+13%) after 9 months.

CONCLUSIONS: The complete regression of the primary tumor in T1aN0M0 RCC patients who received immunotherapy was not observed. However, we found a reduction in tumor size in half of the patients. Treatment with nivolumab and ipilimumab was safe in patients with comorbidities.

Abstract 43: ***Risk of Thromboembolism in Patients Receiving Immunotherapy-Based Combinations for Metastatic Renal Cell Carcinoma***

James Schuster, MD

BACKGROUND: Most patients with treatment-naïve metastatic renal cell carcinoma (mRCC) receive combination-based therapy with either two immune-oncology checkpoint inhibitors (IO/IO) or an IO agent in combination with a vascular endothelial growth factor receptor (VEGF-R) tyrosine kinase inhibitor (IO/TKI). The rates of thromboembolism (TE) in these cohorts are not clearly described and can potentially impact decision-making between IO/IO and IO/TKI.

METHODS: We conducted an IRB-approved cohort study of patients with mRCC treated with IO-based combinations between January 2015 and April 2021 at the Cleveland Clinic. TE events, including venous and arterial, were identified in each group. Competing risk regression was done to identify factors associated with the development of TE following therapy. All-cause mortality treated as a competing event.

RESULTS: Of 220 patients identified, 92 (42%) received IO/TKI and 128 (58%) received IO/IO. Median age was 65 years, 78% male, 80% clear cell histology. Baseline characteristics were similar between the two groups. At a median follow-up of 23.0 months, 10.9% of all patients had a TE. The one-year incidence of TE was 8.0% (95% CI: 3.5-14.9%) with IO/TKI and 8.6% (95% CI: 4.6-14.3%) with IO/IO with similar incidence between the two groups (HR 0.742, 95% CI 0.318-1.732). Presence of TE was associated with decreased overall survival (HR 2.357, 95% CI 1.362-4.079). There was no difference in incidence of TE based on patient age, gender, race, prior history of TE, International Metastatic Renal Cell Carcinoma (IMDC) risk group, or Khorana score.

CONCLUSIONS: Incidence of TE is relatively high but appears to be similar between IO/IO and IO/TKI regimens in treatment-naïve mRCC. TE is also associated with decreased overall survival. Further investigations comparing these TE rates vs those in patients receiving IO and TKI monotherapies is ongoing.

Abstract 44: ***-Mutant Renal Cell Carcinoma: A Comprehensive Characterization of a Lethal Unclassified Renal Cell Carcinoma***

Stephen Reese, MD

BACKGROUND: The use of genomic and molecular classification of renal cell carcinoma has led to an increasing

appreciation of tumor biology and as well as characterization of previously unclassified subset of tumors. We present

a series of previously unclassified renal cell carcinoma patients that are primarily driven by a mutation in the NF2 gene.

METHODS: We queried the MSK Clinical Sequencing Cohort, a database containing 90,744 patients who were sequenced using MSK-IMPACT, a DNA sequencing platform that captures 468 whole exome cancer genes. We found 48 patients with an NF2 mutation who had tumors designated as "unclassified" based on their pathology report. We also identified patients in our prospectively maintained surgical registry if they had undergone extirpative kidney surgery.

RESULTS: Our cohort was notable a small mass size (4.70cm,) however 32 out of 48 patients (66.67%) of patients had metastatic disease at presentation. Most patients who underwent resection had evidence of non-localized disease on surgical pathology. The median overall survival for our cohort of patients was 18.35 months compared to 45.83 months in a cohort of high-risk sequenced renal cell carcinoma patients. Genomic analysis of sequenced tumors demonstrated that the NF2 mutation was noted to be a primary driver of tumorigenesis (87.50%), with a high frequency noted to be a clonal event (72.92%) and a high proportion of biallelic mutations (81.25%), all suggestive that NF2 is the primary driver of tumorgenesis.

Table 1. Patient Demographics and Genomic Characterization

	NF2 Cohort (n=48)
Male (%)	31 (64.58%)
Age (median [IQR])	63.5 (16)
Race (%)	
- Asian	3 (6.25%)
- Black	4 (8.33%)
- White	35 (72.92%)
- Unknown	6 (13.95%)
BMI (median [IQR])	25.2 (8)
Tumor features	
Size in cm (median [IQR])	4.70 (4.7)
Clinical Stage	
T1	33 (68.75%)
T2	8 (16.67%)
>=T3	7 (14.58%)
Metastases at Presentation	
Yes	32 (66.67%)
Surgery Performed?	
Yes	13 (27.08%)
Node Positive	
pN+	10/13 (76.92%)
Cytoreductive Nephrectomy	
Yes	5/13 (38.46%)
Overall Survival (mo.)	
NF2 Mutation	18.35 (32.19)
Kidney Cohort[1]	45.83 (54.58)
Survival	
Deceased	23 (47.92%)
Genomic Data	
Driver	42 (87.50%)
Biallelic	39 (81.25%)
Conality	
Clonal	35 (72.92%)
Sub-Clonal	8 (16.67%)
Indeterminate	5 (10.42%)
Cancer cell fraction	0.97 (0.23)
Mutational Type	
Frameshift Deletion	20 (41.67%)
Frameshift Insertion	5 (10.42%)
Missense	4 (8.33%)
Nonsense	12 (25%)
TMB Percentile	60.25 (37.90)
Fraction Genome Altered	0.13 (0.24)
MSI Score	0.27 (0.56)
Mutation Count	4 (3)

CONCLUSIONS: We provide clinical and genomic characterization of a group of patients who were previously found to be unclassified renal cell carcinoma, however now found to have NF2 mutation as the putative driver of tumorigenesis. NF2 mutated renal cell carcinoma is an aggressive histology that undergoes early metastatic spread at small tumor size and is lethal.

Abstract 45: ***Metagenomic analysis of the gut microbiome in metastatic renal cell carcinoma patients with sarcopenia***

Neal S. Chawla, MD

BACKGROUND: Sarcopenia, defined as loss of skeletal muscle mass, is associated with inferior outcomes in metastatic renal cell carcinoma (mRCC). Herein, we investigate the role of gut microbial metabolic pathways on the development of sarcopenia in mRCC.

METHODS: Patients with mRCC that had an investigational stool collection and a prior computed tomography scan were included. Axial images of the L3 vertebral segment were identified from three consecutive scans. SliceOMatic software was used to estimate the muscle mass area on each image. The

mean skeletal muscle area was normalized for squared height (cm2/m2), with patients being classified as sarcopenic or non-sarcopenic, based on validated reference values for males and females. Stool microbial profiles were analyzed using MetaPhlAn 3.0. Functional pathways associated with particularly abundant microbiota in relation to sarcopenia (measured by LDA effect size analysis) were identified using the HUMAnN 3.0 platform.

RESULTS: In total, 62 patients met criteria for inclusion (45:17 M:F). The median age was 69 (range 33-93) and predominantly of White race (64.6%). The majority histology was clear cell (88.7%). A total of 27 patients were sarcopenic, while 35 were non-sarcopenic. Parabacteroides distasonis, and Dialister species were associated with sarcopenia to the greatest degree, with LDA scores >3. In contrast, Bacteroides vulgatis, Collinsella aerofaciens, Streptococcaceae species, and Monoglobius species were associated with the absence of sarcopenia. Distinct metabolic pathways, in particular gluconeogenesis I (P=0.009), methanogenesis from acetate (P=0.041), and pathway 7254 of TCA cycle VII (P=0.041) were significantly associated with sarcopenia. In contrast, the colanic acid/M antigen pathway was negatively associated with sarcopenia (P=0.033).

CONCLUSIONS: Distinct bacterial populations appear to express metabolic pathways associated with a catabolic state in mRCC patients with sarcopenia.

Abstract 46: ***Prospective evaluation of mutation concordance between standard-of-care renal mass biopsy and nephrectomy specimens in small renal masses***

Kathryn H. Gessner, MD, PhD

BACKGROUND: For patients with clinical T1 renal masses, renal mass biopsy (RMB) yields pathologic information but has limited ability to identify patients with high-risk disease. We hypothesize that genomic characterization of biopsy specimens may improve RMB prognostic performance. This study seeks to evaluate how accurately prospectively collected RMB tissue can identify DNA mutations present in nephrectomy specimens.

METHODS: From October 2018–June 2022, patients with new clinical T1 kidney tumors were enrolled onto GRADE-SRM (Genomic Risk Assessment and Decisional Evaluation for Small Renal Masses), a comparative, non-randomized hybrid trial assessing decision-making experience and cancer genomics. Patients underwent standard clinical counseling and, tissue from surgery, RMB, and germline DNA was obtained for genomic analysis. Targeted exon sequencing was performed using UNCseq v10.2 platform and variants were filtered using standard criteria. Mutation concordance was defined as percent of mutations in nephrectomy specimen also identified in the biopsy.

RESULTS: Of 43 patients who underwent both RMB and surgery, 14 patients with ccRCC had tissue from both procedures collected and used for analysis. The median number of mutations in nephrectomy specimens was 11 compared to 10 in RMB specimens. Mutation concordance between paired nephrectomy and RMB specimens ranged from 0%-83% (mean 34%, SD 28%). Multifocal samples from nephrectomy specimens generally demonstrated a higher concordance to nephrectomy specimens (16%-100%; mean 67%, SD 26%).

CONCLUSIONS: In this study, mutational concordance between nephrectomy and RMB specimens ranges from 0-83%. These results highlight that additional sampling may be necessary to use prognostic information from RMB to guide clinical decision-making. Future research will focus on evaluating the concordance of known RCC driver mutations and investigating transcriptomic similarities between RMB and nephrectomy specimens.

Abstract 47: ***Epigenetic, transcriptional, and compositional shifts in clear cell renal cell carcinomas***

Lucas A.. Salas, MD PhD MPH

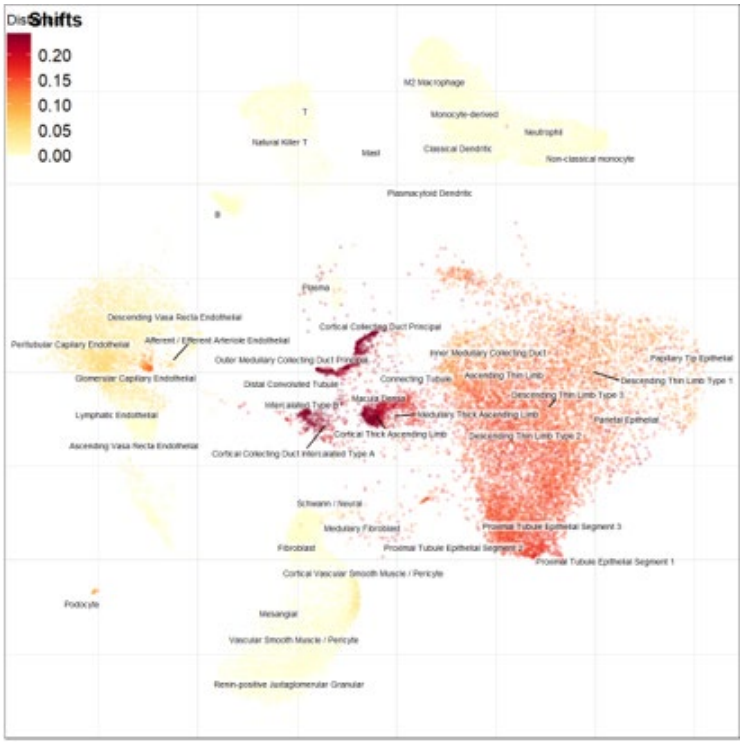
BACKGROUND: Clear cell renal cell carcinoma (ccRCC) is a group of tumors characterized by alterations in chromosome 3p, 90% of them showing alterations in the VHL gene. Here we aim to evaluate biobanked samples to characterize single-cell epigenetic, transcriptional, and compositional shifts in tumor vs normal-adjacent samples.

METHODS: We analyzed 57 tumor samples and six normal-adjacent kidney samples from patients in the Dartmouth Renal Tumors Biobank collected between 1994 and 2009. Samples were mechanically and enzymatically disassociated and preserved at -80 Celsius until processing. Cells were processed using the 10X multiome protocol. RNA counts and Chromatin accessibility peaks were extracted using Seurat.

RESULTS: The mean age was 61.7 yrs (SD: 12.5), with 67% being stages I and II. 85,771 cell samples were analyzed. Relative compositional shifts were observed with an increased proportion in the tumors vs. normal adjacent in immune cells (22 vs. 15%), descending and ascending thin limbs (36 vs. 23%, and 2 vs. ~0%), fibroblasts (22 vs. 15%) pericytes (13 vs. 5%) and T cells (7 vs. 1.8%).

37% of all the cells captured in the tumor were aneuploid, predominantly from descending thin limb (24% of all cells). We observed a shift in the tumor's proportions of ascending thin limb cells and an increase in the cortical thick ascending limb cells in the normal-adjacent samples. After adjusting for sample cell compositions, we calculated gene programs. The top program showed 125 genes related to chromatin binding and organization, 2-oxoglutarate, and dioxygenase activity.

CONCLUSIONS: Distributional shifts with alterations in cell composition, gene expression, and chromatin accessibility of the ccRCC samples were observed. Predominant tumor cells were the descending thin limb, and aneuploid descending thin limb cells were captured in both the tumor and normal-adjacent samples. Altered programs were observed related to aneuploid cells.



Abstract 48: ***A Case of Metastatic Renal Cell Carcinoma to The Maxillary Sinus Initially Presenting as Recurrent Epistaxis***

Justin Mehr, B.S.

BACKGROUND: Metastatic neoplasms to the sinonasal tract are rare. However, in the presence of suspected metastasis to this region, renal cell carcinoma is the most commonly implicated primary tumor.

METHODS: Here we present an unusual case of a 74-year-old female who was diagnosed with renal cell carcinoma after the discovery of oligometastatic disease to the maxillary sinus first presenting as recurrent epistaxis.

RESULTS: A 74-year-old female presented with a 3-week history of intermittent epistaxis. Medical history included diabetes, hypertension, and atrial fibrillation currently on coumadin. Following spontaneous resolution of epistaxis and an unremarkable workup, patient was discharged with instructions to follow-up with Otolaryngology outpatient. A cranial CT scan obtained by Otolaryngology showed complete opacification of the right frontal, ethmoid, and maxillary sinuses. MRI showed an enhancing right maxillary sinus mass with extension into the nasoethmoidal cavity. Right nasal endoscopy, maxillary antrostomy, and removal of maxillary sinus mass was performed and histological exam revealed cells consistent with metastatic clear cell renal cell carcinoma (ccRCC). CT scan revealed a 4.9-cm left renal mass with bilateral enhancing adrenal nodules and a solitary right lung nodule. Patient was begun on immunotherapy, first Nivolumab/Ipilimumab then switched to Nivolumab/Cabozantinib to minimize continued epistaxis for which concurrent radiation therapy was also used. Ten months into treatment, repeat scans revealed regression of metastatic lesions and primary site renal mass. Decision was made to proceed with cytoreductive nephrectomy one year from discovery of maxillary sinus mass. A 3.5-cm left renal mass was removed. Imaging two months after nephrectomy showed recurrence of maxillary sinus mass. Repeat endoscopic mass resection and debridement with histological exam revealed metastatic ccRCC.

CONCLUSIONS: Albeit uncommon, metastatic renal cell carcinoma should be a differential diagnosis in patients presenting with nasal and paranasal sinus masses.

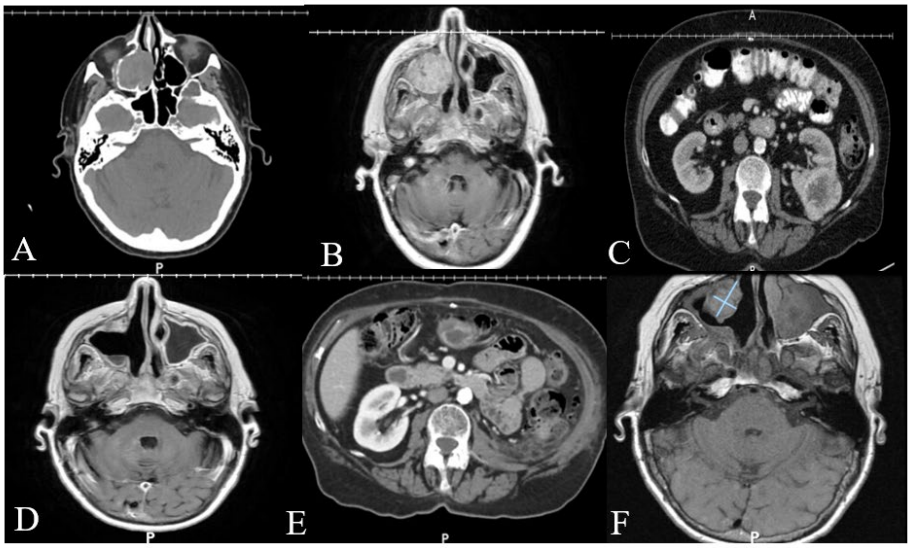


Figure 1: Patient Imaging (A) Initial CT sinus without contrast showing right sided sinonasal tract mass. (B) Follow-up MRI brain imaging confirming R-sided mass. (C) CT abdomen and pelvis showing left sided 4.9 cm renal mass (D) MRI brain imaging at 10-months status-post mass resection and immunotherapy showing resolution of mass (E) MRI abdomen and pelvis imaging 2-months post-cytoreductive nephrectomy (F) MRI brain imaging 2-months post-cytoreductive nephrectomy showing recurrence of right sided mass, noted with blue "X".

CT = Computerized Tomography; MRI = Magnetic Resonance Imaging

TRIALS IN PROGRESS

Abstract 51: ***A phase II study of lenvatinib plus everolimus versus cabozantinib in patients with metastatic renal cell carcinoma (mRCC) that progressed on a PD-1/PD-L1 checkpoint inhibitor (LenCabo)***

Andrew W. Hahn, MD

BACKGROUND: Combinations of immune checkpoint therapies (ICT) and angiogenesis targeted therapy (TT) are standard first-line treatment for patients with mRCC. Many patients receive cabozantinib or lenvatinib plus everolimus after progression on ICT combinations. These therapies were approved for treatment after progression on angiogenesis TT and have overlapping mechanisms of action with some first-line ICT combinations. Further, lenvatinib and cabozantinib have similar, but distinct, mechanisms of action, and the two agents have not been compared in a randomized clinical trial. We hypothesize that lenvatinib plus everolimus will produce a longer progression-free survival (PFS) compared to cabozantinib in patients with mRCC that progressed on a prior PD-1/PD-L1 checkpoint inhibitor.

METHODS: This multicenter, phase II, randomized study is evaluating lenvatinib plus everolimus versus cabozantinib in patients with metastatic clear cell RCC (ccRCC) who received 1-2 prior lines of treatment in the advanced setting. The most recent treatment must include a PD-1 or PD-L1 checkpoint inhibitor. The study will enroll 90 patients and randomize in a 1:1 fashion to lenvatinib plus everolimus or cabozantinib. Patients are stratified by IMDC risk group and prior receipt of angiogenesis TT. Crossover after progression is permitted. The primary endpoint is PFS. Secondary endpoints include objective response rate, disease control rate, overall survival, health-related quality of life, and incidence of grade 3/4 adverse events. PFS will be monitored using Bayesian optimal phase 2 design, and an interim analysis will be performed at 50 patients. The study has enrolled 8 patients to date at 1 US site and will open at 2 additional US sites by February 2023. NCT05012371

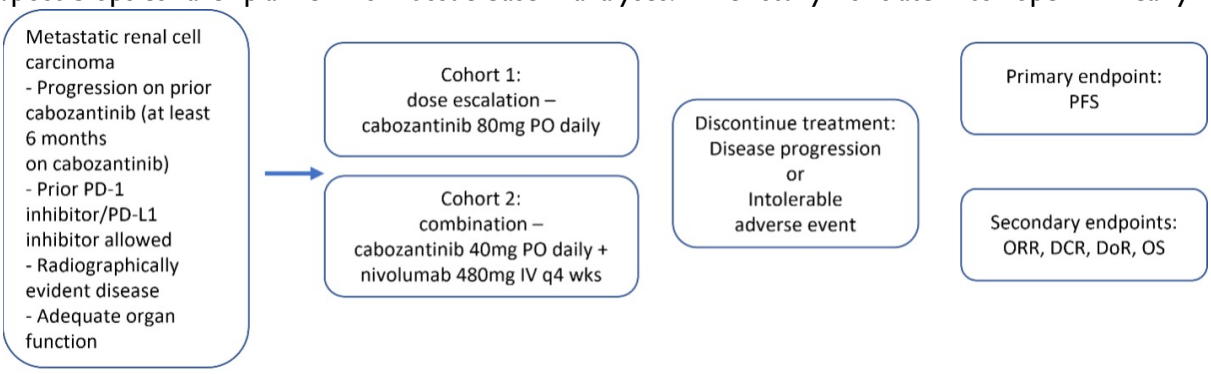
Abstract 53: ***Phase 2 trial for sequential treatment after cabozantinib progression in metastatic renal cell carcinoma (Seq-Cabo)***

Qian Qin, MD

BACKGROUND: Cabozantinib has become an established treatment for mRCC in both front-line and refractory settings with favorable response rates. However, the majority of patients develop treatment resistance to cabozantinib.

METHODS: We designed a two-cohort phase 2 trial to salvage cabozantinib response, either by escalating the dose of cabozantinib to 80mg PO daily (cohort 1) or by combining cabozantinib 40mg PO daily with nivolumab 480mg IV every 4 weeks (cohort 2) based on investigator choice (Figure 1). Main inclusion criteria include: progressive mRCC after prior cabozantinib monotherapy, radiographically measurable disease, ECOG < 2, adequate end-organ function, minimum of 4 weeks from any other anti-cancer therapies, and age >18 years. Main exclusion criteria include: prior treatment with concurrent cabozantinib/nivolumab, uncontrolled cardiovascular disorders or diabetes mellitus, uncontrolled HIV, concurrent malignancy (excepting completely excised skin cancers and organ-confined Gleason 6 prostate cancer), and pregnancy. Primary endpoint is progression free survival. With the null hypothesis that the median PFS (mPFS) is 3 months tested against an alternative hypothesis that the mPFS is 6 months, and assuming a 2-sided significance level of 10%, 80% power, and 10% drop out, along with 2-year accrual and 1 year follow up, 18

patients per cohort (36 patients total) will be enrolled. Pharmacokinetics, circulating biomarkers, and pre-/post-biopsies are planned for tissue-based analyses. The study is slated to open in early 2023.



Abstract 50: ***TiNivo-2: A Phase 3 Study to Compare Tivozanib+Nivolumab to Tivozanib Monotherapy in Patients with Renal Cell Carcinoma (RCC) Who Have Progressed Following ≤2 Lines of Therapy including an Immune Checkpoint Inhibitor (ICI)***

Toni Choueiri, MD

BACKGROUND: Tivozanib, a highly selective and potent VEGFR TKI, has demonstrated efficacy in advanced RCC with minimal off-target toxicities and favorable AE profile. Tivozanib was approved by the FDA for the treatment of patients with RCC who had progressed on ≥2 prior systemic therapies. Tivozanib was combined with nivolumab in a phase 1b/2 trial showing an ORR=56%, DCR=96%, median PFS=18.9 months and tolerable safety profile.

METHODS: TiNivo-2 (NCT04987203) is a phase 3, randomized, open-label study to compare tivozanib+nivolumab to tivozanib monotherapy in patients with RCC who have progressed following ≤2 lines of therapy including ICI. Eligibility criteria: ≥18 years, clear cell RCC, ECOG PS 0-1, and disease progression during or following ≥6 weeks of treatment with ICI. Patients will be stratified by IMDC risk category and whether ICI was received in most recent line of treatment. Patients will receive tivozanib 1.34mg orally once daily for 21 days followed by 7 days off as monotherapy, and tivozanib 0.89mg at the same schedule plus nivolumab 480mg intravenously every 4 weeks as combination. Study assessments include CT/MRI of the chest, abdomen, and pelvis every 8 weeks for 2 years and every 12 weeks thereafter until progression. Primary objective is to compare PFS of tivozanib+nivolumab to tivozanib. A sample size of 326 patients, with 191 events will provide ≥80% power to detect a 50% improvement in PFS, 12 months vs. 8 months. Secondary endpoints include OS, ORR, DoR, and safety/tolerability. Exploratory endpoints include QoL (FKSI-DRS and EORTC QLQ C-30) and the pharmacokinetics of tivozanib. TiNivo-2 is actively enrolling and planning to open at 190 sites in the US and EU.

Abstract 55: ***A pilot study of the immunomodulatory agent acarbose in combination with standard therapy in metastatic renal cell carcinoma (RCC)***

Arnab Basu, MD, MPH

BACKGROUND: Acarbose is a pseudo-tetra saccharide of bacterial origin and an orally active alpha glucosidase inhibitor that delays the digestion and absorption of ingested complex carbohydrates. Consumption of Acarbose leads to a higher fraction of complex carbohydrates passing through the lower

gut. Studies have previously demonstrated increases in species such as Bifidobacterium in gut flora linked with acarbose consumption. Emerging evidence suggests that the gut microbiome may be linked to improved response or acquired resistance to immune checkpoint blockade, and may also have an independent effect on tumor proliferation. We hypothesize that Acarbose may thus improve the outcomes in patients treated with immune checkpoint inhibitors or immunogenic tumor subtypes while being tolerable for patients. We thus designed a pilot study to evaluate the safety of feasibility of combining acarbose with standard of care (SOC) therapy in renal cell carcinoma patients.

METHODS: In this open label, single arm, single-center pilot study, adult patients with advanced/metastatic clear cell or non-clear cell renal cell carcinoma are eligible. An estimated 24 patients will be enrolled. Patients treated with all immunotherapy based standard of care regimens will be included. Acarbose will be dosed as 25 mg PO three times a day continuously with escalation based on clinical tolerance to 100 mg PO three times a day. Study treatment continues until RECIST 1.1 disease progression or other discontinuation criteria are met. The co primary endpoints are safety as assessed per NCI Common Terminology Criteria for Adverse Events (CTCAE v.6.0) and changes in specific bacterial species in the gut flora. Secondary endpoints include estimated median progression free survival and overall survival of patients treated with SOC+Acarbose

Abstract 49: ***A randomized trial of radium-223 (Ra-223) dichloride and cabozantinib in patients (pts) with advanced renal cell carcinoma (RCC) with bone metastases (RADICAL / Alliance A031801)***

Rana McKay, MD

BACKGROUND: Bone metastases are prevalent in approximately 30% of pts with advanced RCC. Pts with bone metastases have a worse prognosis and are at risk of symptomatic skeletal events (SSEs). Cabozantinib, a vascular endothelial growth factor (VEGF) receptor and MET kinase inhibitor, has improved survival in pts with RCC and has enhanced activity in bone. Ra-223, an alpha-emitting radioisotope with natural bone-seeking proclivity, has prolonged survival in men with advanced prostate cancer. We previously conducted a pilot study of Ra-223 with VEGF inhibition in pts with RCC and bone metastases and demonstrated safety and declines in markers of bone formation and resorption. Given that decreasing rates of SSEs and improving outcomes are unmet needs in pts with RCC and bone metastases, we designed a randomized phase 2 study through the National Clinical Trials Network (NCTN) investigating cabozantinib with or without Ra-223 in pts with RCC with bone metastases.

METHODS: This is an open-label multicenter study. Eligible pts have metastatic RCC of any histology with ≥1 metastatic bone lesions untreated with prior radiation therapy and any number of lines of prior therapy. Pts with non-clear cell RCC are eligible (capped at 20% of accrual). Pts must have a Karnofsky performance status of ≥60% and be on osteoclast-targeted therapy unless otherwise contraindicated. Pts are randomized 1:1 to cabozantinib with (Arm A) or without (Arm B) Ra-223. Starting dose of cabozantinib for Arm A is 40 mg to be escalated to 60 mg daily after cycle 1 (1 cycle=28 days) if there is no persistent grade 2/≥3 toxicity. Ra-223 is administered at a fixed dose of 55 kB/kg IV every 28 days x 6 doses. The primary endpoint is SSE-free survival. Secondary endpoints include safety, progression-free survival, overall survival, quality of life measures, and correlative analyses including liquid biopsy studies and tumor tissue analysis.

Abstract 54: ***APART – A Phase 2 trial of Axitinib, Palbociclib and Avelumab as advanced Clear Cell Renal Cell Carcinoma (ccRCC) Therapy***

Stephanie Berg, DO

BACKGROUND: There is a need to develop new therapeutic combinations and targets for the treatment of advanced ccRCC. The cell cycle pathway is dysregulated in a significant proportion of ccRCC and pre-clinical studies have suggested that CDK4/6 inhibitors (i) have single-agent activity in ccRCC as well as synergism with IO. We hypothesize that this triplet will have efficacy and demonstrate additive activity compared to the approved doublet.

METHODS: NCT05176288 is a multi-center single-arm phase 2 trial. The primary objective is to evaluate the ORR per RECIST 1.1 of axi+avelumab+palbociclib in untreated advanced ccRCC. Secondary objectives: evaluate safety, the rate of CR and deep PR (≥80% reduction in target lesions) and determine PFS and OS. Exploratory objectives: immunologic and biologic correlates of response, resistance and survival with the triplet. Optional research biopsies will be performed as well as bulk whole-exome sequencing (seq) and single-cell RNA-seq to evaluate changes in gene signatures and immune cell populations during therapy. Alterations in candidate genes (cyclin D, CKD4 and CDK6) will be correlated with response to therapy. Blood will be collected to evaluate serum thymidine kinase 1 (sTK1) levels, a functional biomarker of cell cycle activity. Key eligibility criteria: untreated advanced ccRCC (sarcomatoid histology allowed), measurable disease per RECIST 1.1, adequate organ/marrow function, ECOG ≤2. Exclusions: prior systemic therapy, untreated brain metastases, active autoimmune disease or a history of interstitial lung disease. Patients who have received adjuvant or neoadjuvant immunotherapy are eligible provided >12 months have elapsed. All IMDC risk groups are permitted. The planned sample size of 25 patients will provide 85% power to detect an improvement in ORR from 50% (seen with axitinib/avelumab) to 75% with the triplet under the exact binomial test at a one-sided alpha of 0.05. This would provide a clinically meaningful signal to merit further study of this triplet.

Abstract 52: ***LITESPARK-011: a randomized, phase 3 study of belzutifan plus lenvatinib versus cabozantinib after anti–PD-1/PD-L1 therapy in patients with advanced renal cell carcinoma***

Daniel YC Heng, MD

BACKGROUND: First-line anti–PD-1/PD-L1 immunotherapy is standard of care for renal cell carcinoma (RCC), but treatment options are limited once progression occurs. Hypoxia-inducible factor (HIF)-2α has been identified as a key oncogenic driver in clear cell RCC (ccRCC). The first-in-class HIF-2α inhibitor belzutifan showed antitumor activity in ccRCC both as monotherapy and with cabozantinib. The randomized phase 3 LITESPARK-011 trial (NCT04586231) will evaluate the efficacy and safety of belzutifan + lenvatinib versus cabozantinib in heavily pretreated patients with advanced ccRCC who experienced progression after anti–PD-1/PD-L1 therapy.

METHODS: Approximately 708 patients will be enrolled. Adults aged ≥18 years with locally advanced/metastatic ccRCC, no more than 2 prior systemic therapies (only 1 prior anti–PD-1/PD-L1 agent), measurable disease per RECIST v1.1, progression on or after a first- or second-line anti–PD-1/PD-L1 agent (most recent therapy or adjuvant treatment with progression on or within 6 months of last dose), and KPS score of ≥70% will be eligible. Patients will be randomly assigned 1:1 to receive oral belzutifan 120 mg once daily (QD) + lenvatinib 20 mg QD or oral cabozantinib 60 mg QD, stratified by geographic region (Western Europe, North America, or rest of the world), IMDC score (1, 2, or 3-6), and number of prior therapies (1 or 2). CT/MRI assessments will occur every 8 weeks (Q8W) through week 80, then Q12W thereafter. AEs will be reported through 30 days after treatment cessation (90 days for serious AEs).

Primary end points are PFS per RECIST v1.1 by blinded independent central review (BICR) and OS; secondary end points include ORR and DOR per RECIST v1.1 by BICR and safety and tolerability. LITESPARK-011 is recruiting patients in Asia, Australia, Europe, North America, and South America.

LATE-BREAKING ABSTRACTS

Abstract 42: ***Peripheral blood biomarkers to predict serious immune related adverse events in patients with metastatic renal cell carcinoma undergoing treatment with immune checkpoint blockade***

John Leppert, MD MS

BACKGROUND: Reactivation of the immune system by ICB results in reduced tolerance to self, manifested as a spectrum of symptoms referred to as immune related adverse effects (irAEs). We hypothesized that induced phosphorylation with cytokines and growth factors of intracellular signaling proteins in peripheral blood immune cells could uncover populations associated with the development of clinically significant irAEs.

METHODS: We designed a blood test based on profiling phosphorylated intracellular signaling proteins in immune cell phenotypes using single cell CyTOF. Peripheral blood collected before the start of ICB treatment was treated ex vivo with immune receptor ligands. The resulting CyTOF datasets were comprised of i) frequencies of distinct immune cell phenotypes, ii) basal levels of phosphorylated signaling proteins and iii) changes in levels of phosphorylated signaling proteins after exposure to ligands. Patients were closely monitored for irAEs. Data were analyzed using Stacked Generalization (SG) predictive modeling, optimized for CyTOF data, to identify proteomic features that could stratify patients who went on to develop clinically significant irAEs.

RESULTS: We assessed >2800 single-cell immune features (immune cell phenotype, endogenous signaling activity, and signaling responses) in whole blood from 20 patients. A multi-omic analysis identified a predictive model that accurately differentiated patients with and without severe adverse events (AUC = 0.91, p-value< 0.05, stacked generalization model with cross-validation). The most informative features included the relative frequencies of distinct immune cell phenotypes and responses to ex vivo stimulation with immune ligands (Cytomix 1 and 2: IL-2, IL-4, IL-6, M-CSF, IFNb, and TNFa). Critical model features included Induced pSTA5 signaling in CD4CD57 cells, induced pSTAT3 signaling in CD4T effector memory expressing CD45RA (Temra) cells, and frequencies of CD4CD57, CD8CD57, CD4TemCD57, and CD8TemCD57 cells.

CONCLUSIONS: Immune features in peripheral blood may predict development of clinically significant irAEs in patients with mRCC initiating immune checkpoint blockade.

KCA TRAILBLAZER AWARDS 2022

SIGNIFICANCE STATEMENT

DISSECTING THE IMMUNOBIOLOGY OF CHROMOPHOBE RENAL CELL CARCINOMA USING SINGLE-CELL TRANSCRIPTOMICS

David A. Braun

Yale School of Medicine

While immune checkpoint inhibitors (ICIs) have been transformative for the management of advanced clear cell renal cell carcinoma (ccRCC), unfortunately patients with chromophobe renal cell carcinoma (chRCC) have not substantially benefitted from these therapies. While most scientific and clinical studies focus on clear cell histology, the tumor and immune biology of chRCC is radically different, and immunotherapies for advanced chRCC remain an area of unmet clinical need. In our proposal, we plan to dissect the tumor and immune microenvironment of chRCC using single-cell sequencing approaches, with the goal of providing insights into why ICIs are generally ineffective in this disease and how we could design novel immune-based strategies to overcome immunoresistance. Using cutting-edge single-cell transcriptomics, we will first determine the specific transcriptional programs that are associated with malignant behavior. Second, we will systematically and comprehensively dissect the specific immune populations that infiltrate chRCC to determine the immune composition and transcriptional phenotypes. Finally, we will infer the specificity of T cells in chRCC to better understand whether they are more likely to be tumor-specific or be "bystander" T cells, incapable of tumor recognition. Overall, the goal of this proposal is to develop an improved understanding of chRCC at the bench that can then be rapidly translated into new therapies at the bedside for chRCC patients, and ultimately improve the outcomes of patients with advanced chRCC disease.

IMPACT OF CBM588 ON METABOLOMIC PROFILE IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA (mRCC)

Nazli Dizman, MD

Yale School of Medicine

Previous work has suggested an association between the gut microbiome and clinical outcomes with immune checkpoint inhibitors (ICI) in metastatic renal cell carcinoma (mRCC). 1 Our group recently reported a randomized phase I study examining the impact of CBM588, a live bacterial product, in patients with mRCC receiving nivolumab/ipilimumab. 2 CBM588 contains Clostridium butyricum, a species that has been shown to increase the production of short-chain fatty acids (SCFA) in the gut lumen and enhance the abundance of Bifidobacterium species in mice - both of which have been associated with a higher likelihood of response to ICIs in clinical studies. 3 In our state-of-art phase I study, the addition of CBM588 to nivolumab/ipilimumab led to a significant improvement in progression free survival and objective response rate over nivolumab/ipilimumab. 2 Although these findings should be viewed with caution due to the small sample size, modulation of the gut microbiome function and enhancement of chemokines observed in CBM588 arm supported the signals observed in clinical outcomes. However, a plausible and direct mechanism to explain the clinical benefit associated with CBM588 requires further study utilizing metabolomic methodology.

We are grateful to the Kidney Cancer Association for supporting our further translational efforts examining SCFA levels in blood samples of patients enrolled in our phase I study, as well as preclinical studies to replicate our clinical investigation in syngeneic and xenograft mouse models. These efforts will allow us to inspect the impact of CBM588 on the evolution of gut and blood metabolomics, the systemic immune response over time, and their relationship with response kinetics.

COMPARISON OF IMMUNE MICROENVIRONMENT BETWEEN PATIENTS OF AFRICAN AND EUROPEAN ANCESTRY WITH RENAL CELL CARCINOMA

Pooja Ghatalia, MD

Fox Chase Cancer Center

Multiple factors such as cultural, socioeconomic, psychosocial, and healthcare access lead to a higher cancer burden and poor disease outcomes in patients of African Ancestry (AA) with renal cell carcinoma (RCC). In addition to these factors, worse outcomes in patients of AA may at least partly result from a distinct tumor biology in these patients. Whether differences in the genomic and immune profile exist across kidney cancers of AA and European ancestry (EA) is unknown. Our understanding of the immune biology in patients of AA is further limited by their under-representation (<1%) in the pivotal phase III clinical trials studying immune checkpoint inhibitor (ICI)-based combinations in metastatic RCC. Since ICIs form the backbone of treatment of metastatic RCC, there is a pressing and unmet need to study the immune microenvironment of RCC tumors across patients of AA and EA. This will guide treatment selection and ultimately address disparities in clinical outcomes. The overall goal of this project is to determine differences in the tumor immune microenvironment across patients of AA and EA.

EXPLORATION OF THE CAUSES AND EFFECTS OF INCREASED PIM1 KINASE ACTIVITY IN RENAL CELL CARCINOMA

Sheldon Holder, MD, PhD

The Legorreta Cancer Center at Brown University

In 2016, there were an estimated 62,700 new diagnoses of kidney and renal pelvis cancers. In 2022 the incidence is estimated to be 79,000. These data show almost a 26% increase in diagnoses over only a 6-year period. The etiology of this increase in diagnoses is unknown, however, this trend highlights a growing need to develop new therapies for renal cell carcinoma (RCC). Although multiple new therapeutic regimens for RCC have recently been approved (pembrolizumab/lenvatinib, cabozantinib/nivolumab, axitinib/pembrolizumab, axitinib/avelumab, and nivolumab/ipilimumab) only one of the newly approved regimens exploits a new target – the hypoxia inducible factor 2 alpha (HIF2a) inhibitor belzutifan. This therapeutic reality underscores the critical need for effective therapies that exploit new clinically relevant treatment targets in RCC. PIM1 kinase is a serine/threonine kinase that acts to inhibit apoptosis, promote cell cycle progression, increase proliferation, and confer chemoresistance. PIM1 protein levels are increased in human RCC tissue and cell lines, and knockdown of PIM1 expression attenuates proliferation, migration, invasion, and angiogenesis in RCC cells. Furthermore, PIM kinase inhibitors induce tumor regression in RCC mouse models and data show a statistically significant poorer survival among RCC patients whose tumors express increased PIM1 mRNA. These data demonstrate that PIM1 is an important and promising therapeutic target in RCC. In this project we seek to identify oncogenic signals upstream and downstream of PIM1 to identify new therapeutic targets for RCC. Our preliminary data suggest an active IL6/JAK/STAT/PIM1 pathway in RCC. Because an IL-6 antibody and a JAK inhibitor are already being used safely in the clinic for non-RCC indications, RCC clinical trials using these agents can be developed immediately, potentially increasing treatment options for RCC patients. We anticipate this project will reveal additional potential targets that we will evaluate for therapeutic efficacy in the lab and in the clinic.

ADVANCING A CELL SURFACE THERAPEUTIC TARGET IN TRANSLOCATION RENAL CELL CARCINOMA

Srinivas Viswanathan, MD, PhD

Dana-Farber Cancer Institute

Translocation renal cell carcinoma (tRCC) is a rare and highly aggressive subtype of non-clear cell renal cell cancer driven by in-frame fusions involving a transcription factor in the *MiT/TFE* family, most commonly *TFE3*. No molecularly-targeted treatment for tRCC currently exists, and prognosis for this RCC subtype is poor. tRCC also responds less well to therapies that are effective in clear cell RCC, such as VEGF pathway targeted therapies and immunotherapies. As such, the nomination of therapeutic targets in tRCC represents a major unmet need in kidney cancer research. This proposal focuses on targeting of cell-surface proteins that are specific to tRCC. In preliminary studies, we have identified several such candidates and have generated antibodies against one. In this project, we will test and compare antibodies against cell-surface targets in tRCC and ultimately develop the best ones into therapies that can be delivered to patients with tRCC. The long-term goal of this target is to advance specific molecular ("targeted") therapies for tRCC, which could change the way patients with this subtype of kidney cancer are currently treated.

DESIGN OF CAIX TARGETED FINE-TUNED IMMUNE RESTORING SAFE (FIS) CAR-T CELL THERAPY FOR METASTATIC CLEAR CELL RENAL CELL CARCINOMA (mccRCC)

Yufei Wang, PhD

Dana-Farber Cancer Institute

Clear cell renal cell carcinoma (ccRCC) has a poor prognosis as 30% of patients develop metastasis and the 5-year overall survival rate of metastatic RCC is only 10%. There's an urgent need to design a clinically translatable therapy for metastatic ccRCC (mccRCC) patients who do not have a curative treatment now. Chimeric antigen receptor (CAR) T cell therapy has gained great success in treating hematological malignancies; however, it has not yet been translated to solid tumors primarily due to the immunosuppressive tumor microenvironment (TME) and on-target off-tumor toxicities.

Here, I propose to engineer carbonic anhydrase IX (CAIX) targeted affinity Fine-tuned Immune restoring Safe (FIS) CAR-T cells which utilize an affinity / avidity optimized single-chain variable fragment (scFv) G9 as the CAR moiety plus a T cell activation-induced gene circuit. The affinity / avidity fine-tuned CAR is able to only recognize high antigen expressing tumor cells but not low antigen expressing normal tissues to mitigate on-target off-tumor side effects. In addition, the gene circuit, serving as a switch, enables FIS CAR-T cells to secrete immune checkpoint inhibitors (ICIs) at the tumor site in a controlled release manner to combat immunosuppression as well as address the toxicities associated with systemic checkpoint blockade administration.

In summary, this novel CAR-T cell therapy will greatly impact human health because FIS CAR-T may restore active local antitumor immunity by releasing the immune brakes, effectively inhibit tumor growth by targeting CAIX+ tumor cells, as well as limit toxicities associated with systemic administration of ICIs and CAR-T off-tumor killing of CAIX low expressing normal tissues, thus prolonging the survival of patients with mccRCC.

IMPROVING PATIENT-REPORTED OUTCOMES FOR RENAL CANCER PATIENTS ON ACTIVE SURVEILLANCE

Erin Tagai, PhD, MPH

Fox Chase Cancer Center

Although small renal masses (SRM; masses < 4cm) are typically slow growing and do not become symptomatic or lead to death, their incidence has been rising since the 1990s. A significant number of SRM are either benign (30-40%) or indolent malignancies (85%; i.e., will not become symptomatic or contribute to mortality), making them an excellent candidate for treatment de-escalation such as active surveillance (AS). Most guidelines recommend that AS be used in patients presenting with smaller renal mass size, medical comorbidities, increasing age, and decreased life expectancy. Moreover, AS is the optimal strategy for renal function preservation in patients with reduced renal function, since it reduces the risk of long-term chronic kidney disease. Overall safety estimates are comparable for patients who are managed with AS compared to active treatment (i.e., radical or partial nephrectomy, ablation). Therefore, AS appears to be an optimal management regimen for this population to improve patient safety and clinical outcomes. However, approximately 50% of patients with SRM who stop AS for definitive treatment do so because of AS-related distress [i.e., a patient's negative response (cognitive, physical, social, spiritual) resulting from AS that interferes with coping ability], placing patients at unnecessary risk of treatment complications. Additionally, patients on AS may be at risk of reduced functional, physical, or social quality of life (QoL). Using a mixed method approach, this study will identify modifiable psychosocial factors (e.g., self-efficacy for patient-provider communication or using coping skills) associated with AS-related distress and QoL among patients on AS for a SRM. Study findings have the potential to improve patient-reported outcomes through the identification of modifiable psychosocial factors that can be integrated into a patient-centered intervention (e.g., through patient-targeted skills building for improving communication with their medical team) to help patients manage AS-related distress and QoL and ultimately avoid unnecessary treatment.

Continuing Medical Education (CME)

Jointly provided by

KidneyCancerAssociation

The France Foundation

Target Audience: This educational activity is intended for medical oncologists and urologists who treat patients with kidney cancer. Fellows, trainees, nurses, nurse practitioners, physician assistants, and other healthcare professionals involved in the management of kidney cancer are invited to participate.

Statement of Need: Education and interaction surrounding the space of renal cell carcinoma are paramount to improving patient care. This program is targeted to physicians, advocates, researchers, and care team members to help promote learning and collaboration for advancement in the renal cancer space.

Educational Learning Activity Objectives: Upon completion of this course, the participants should be able to:

- Characterize the various therapies currently available for locally advanced and metastatic renal cell carcinoma
- Identify the novel approaches to non-clear RCC patient management
- Understand the role of the tumor microenvironment in kidney cancer
- Discuss how to design biomarker driven clinical trials in kidney cancer

Accreditation Statement:

JOINT ACCREDITATION
INTERPROFESSIONAL CONTINUING EDUCATION

In support of improving patient care, this activity has been planned and implemented by The France Foundation and the Kidney Cancer Association. The France Foundation is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Credit Designation:

Physicians: The France Foundation designates this live activity for a maximum of 11.75 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.