THE KIDNEY CANCER ASSOCIATION PRESENTS

IKCS

NORTH AMERICA

## 2026 INTERNATIONAL KIDNEY CANCER SYMPOSIUM: NORTH AMERICA

# Abstract Book

November 19–21, 2026

Dallas, Texas



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# Introduction

We are thrilled to introduce the abstracts selected for the 2026 IKCS: North America meeting! These studies represent the finest work our scientific community has to offer. Together, they summarize what is currently known about kidney cancer and point toward where the field is going next. That progress matters to researchers and clinicians, and above all to the patients and families who turn to us for hope when facing a hard diagnosis. We are deeply grateful to the Scientific Planning Committee for the care they put into evaluating submissions and choosing the work with the strongest impact, originality, and relevance. Please take the time to connect with the science you encounter and with the people presenting it.

Together, we hold both the responsibility and the honor of shaping what comes next for kidney cancer.



**Salvatore La Rosa, PhD**
Chief Scientific Officer, KCA

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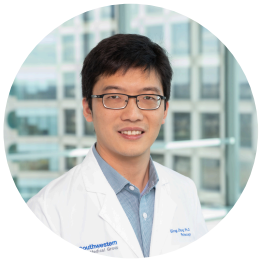
We extend a warm welcome to all the attendees at the Kidney Cancer Association's 2026 IKCS: North America here in Dallas, Texas! Over the course of this meeting, we will examine science that challenges assumptions, introduces new ways of thinking about kidney cancer, and moves us toward better care for our patients. Congratulations to every researcher chosen to present their findings as well as all the speakers who will offer perspective on where kidney cancer care stands today. United by a common commitment to this field, we hope you find the program inspiring and look forward to the spirited conversations that this innovative work will bring.



**Dr. Laura Bukavina**



**Dr. Dan Geynisman**



**Dr. Qing Zhang**

Co-Chairs, 2026 IKCS: North America Scientific Planning Committee

# Thank You 2026 IKCS: North America Scientific Planning Committee

We extend our heartfelt gratitude to our dedicated planning committee for their exceptional contributions to this year's symposium. Your commitment and expertise have been invaluable in making this event a success.

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# Abstracts

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A1 – Artificial Intelligence, Digital Health & Computational Oncology

REGULAR ABSTRACT

# A Highly Sensitive Blood-Based Transcriptomic Platform for Detecting Early-Stage Renal Cell Carcinoma


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Background: There is no validated blood test or recommended screening approach for early-stage renal cell carcinoma (RCC). RCC sheds limited tumor-derived material into circulation, which limits DNA-based liquid biopsies for early detection. We developed a blood-based transcriptomic platform that sequences RNA from a circulating cellular fraction of whole blood and reads the systemic host response to the tumor rather than tumor-shed material.

Methods: The discovery cohort comprised 159 participants: 77 patients with RCC (94% localized) and 82 controls. RNA from 5 mL EDTA whole blood was stabilized, extracted, and profiled by Illumina whole-transcriptome sequencing. A version-controlled, locked analysis pipeline generated normalized gene counts, and a machine-learning classifier built on the EM-RCC-2 gene panel produced a continuous cancer-associated score (0 to 1). A blinded holdout of 32 participants (15 RCC, 17 controls) was withheld from all training and optimization; the full pipeline, including differential expression, gene selection, tuning, and calibration, was re-derived on the remaining 127 participants, and the holdout was scored once.

Results: In the blinded holdout, the classifier detected 12 of 15 RCC cases (80% sensitivity) at 94% specificity (16 of 17 controls); sensitivity across five independent holdout draws was 76 +/- 6%. In the full discovery cohort, in-sample performance reached approximately 95% sensitivity at 99% specificity. In exploratory analyses, cancer-associated scores increased with tumor grade and size, supporting future study for risk stratification.

Conclusions: This blood-based RNA platform detected localized RCC with high sensitivity in blinded held-out samples, supporting a noninvasive approach to detecting RCC early, when curative surgery is possible. A prospective validation study in an independent, recruitment- and batch-matched cohort, including a dedicated benign renal mass arm, a locked classifier, and a prespecified analysis plan, is planned.

A2 – Artificial Intelligence, Digital Health & Computational Oncology

REGULAR ABSTRACT

# Single cell trajectory mapping identifies divergent mesenchymal and antigen-presenting tumor cell states in sarcomatoid renal cell carcinoma

Sarcomatoid differentiation in renal cell carcinoma is traditionally viewed as an epithelial-to-mesenchymal transition (EMT), but the cellular trajectories and heterogeneity underlying this process remain poorly defined. We performed 1,000-plex single-cell spatial transcriptomic profiling (CosMx) of pathologist-annotated clear cell and sarcomatoid regions from four patient tumors to define tumor cell states and their relationships across sarcomatoid transformation, with preliminary findings replicated in a separated dataset of three patient ccRCC/sRCCx tumors profiled using a 6,000 gene set. Multiple malignant populations were identified within both clear cell and sarcomatoid compartments. Pseudotime analysis ordered these states along a trajectory originating in clear cell RCC, progressing through a transitional state enriched for stem-like and inflammatory programs, and branching into distinct sarcomatoid populations. Notably, these endpoints were molecularly divergent. Gene set enrichment analysis showed that one was defined by higher EMT and collagen-associated programs consistent with canonical sarcomatoid differentiation. In contrast, an alternative sarcomatoid population exhibited lower EMT activity but prominent antigen-presentation (HLA-DR/DP/DQ, CD74, B2M and TAP1/TAP2), immune checkpoints, and interferon-gamma signaling. These preliminary findings suggest that sarcomatoid differentiation may not represent a uniform terminal EMT program, but rather a branched process capable of generating biologically distinct sarcomatoid states. Because one endpoint acquires tumor-intrinsic antigen presentation and immune checkpoints while the other builds a matrix-remodeling mesenchymal phenotype, the two may differ substantially in immunotherapy responsiveness. Together, these data reveal underrecognized molecular diversity within sarcomatoid RCC, with potential therapeutic implications.

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A3 – Artificial Intelligence, Digital Health & Computational Oncology

REGULAR ABSTRACT

# A dual-axis transcriptomic model of clear cell renal cell carcinoma evolution linking driver mutations and the tumor microenvironment to prognosis and treatment benefit


Background: In clear cell renal cell carcinoma (ccRCC), biallelic VHL loss precedes divergence into PBRM1- or BAP1-mutant lineages, yet genotype explains phenotypic heterogeneity inconsistently. Existing classifiers conflate tumor and microenvironmental signal, so we asked whether a compartment-aware framework could link driver mutation to transcriptomic phenotype and outcome.

Methods: We developed multi-dimensional cross-dataset non-negative matrix factorization (mcNMF), which retains only programs whose inter-gene relationships persist across datasets, isolating biology from noise. Across 2,163 tumors from three cohorts (TCGA, IMmotion151 [IM151], JAVELIN Renal 101 [JR101]), mcNMF defined 17 consensus transcriptomic programs (CTPs). Cellular origin was resolved with single-cell data and 131 patient-derived tumorgrafts. Restricting input to tumor-cell-intrinsic CTPs enabled trajectory inference on bulk cohorts, validated intratumorally by Visium and multiregional DNA/RNA sequencing.

Results: Tumor-cell-intrinsic CTPs were associated with RCC drivers across all three datasets ($p<0.001$), including VHL, PBRM1, BAP1, PTEN/TSC1, NF2, TP53, TFE3/TFEB fusions, and CDKN2A loss. Trajectory inference resolved two orthogonal axes, trajectory (PBRM1-like versus BAP1-like) and transcriptomic stage (TS, Early to Late). TS advanced with nuclear grade, genomic alterations, and increased from conventional to sarcomatoid regions. Trajectories differed in microenvironment (vascular versus T-cell enriched) but converged on a myeloid- and stromal-rich late state, reconciling reports linking PBRM1 to both angiogenic and inflamed tumors, which differ in TS (Figure 1). In TCGA, Late TS was independently prognostic for overall survival (HR 3.47, 95% CI 1.87-6.43), while grade and BAP1/PBRM1 status were not. TS was associated with PFS in IM151 and JR101, where two tumor-intrinsic programs, R1 and MP-Prolif, interacted (i.e., predicted response) with treatment arm in both ($p<0.05$).

Conclusions: The dual-axis transcriptomic model of ccRCC evolution links genotype, microenvironment, and outcome, outperforming grade and mutation status. An open-source R package assigns stage and trajectory in any expression dataset, enabling testing in adjuvant and frontline settings.

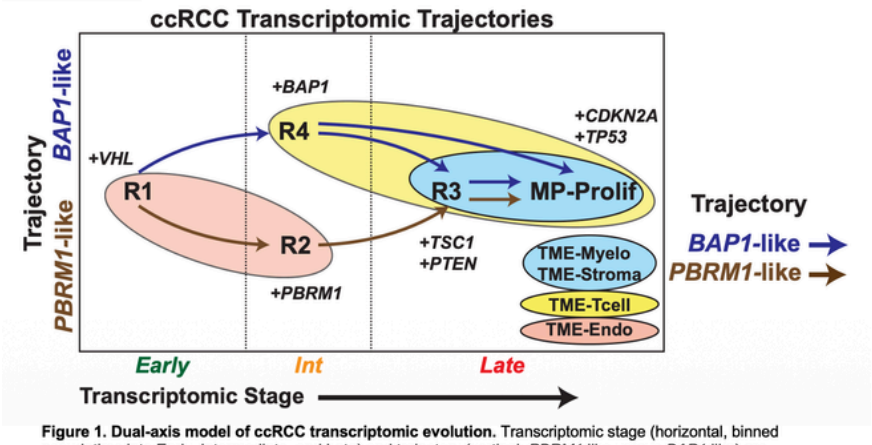




**Figure 1. Dual-axis model of ccRCC transcriptomic evolution.** Transcriptomic stage (horizontal, binned pseudotime into Early, Intermediate, and Late) and trajectory (vertical, *PBRM1*-like versus *BAP1*-like) are orthogonal. Tumors diverge from an early *VHL*-altered R1 transcriptional state into R2 or R4, then converge on R3 and MP-Prolif. Ovals show dominant microenvironmental CTPs.


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A4 – Artificial Intelligence, Digital Health & Computational Oncology

REGULAR ABSTRACT

# Digital twins as ethical enablers of next-generation ccRCC bone metastasis research


Bone metastasis is a lethal consequence of advanced renal cancer, contributing to substantial morbidity, increased mortality, and healthcare burden. In vivo experiments provide critical insight into cellular mechanisms underlying cancer progression and therapy response but are limited in their ability to address the complexity of bone metastasis efficiently and raise ethical concerns regarding animal harm and distress. In silico models can explore numerous experimental conditions while reducing time, resources, and animal use. We hypothesize that integrating in vivo experiments with computational modeling will overcome these limitations and optimize the research pipeline. Accordingly, this work develops digital twins to monitor bone metastasis progression, predict therapy response, and evaluate effects on bone mechanical properties.

By combining three-dimensional multiphoton microscopy with a stochastic agent-based model, we developed the in vivo-inspired, spatially explicit multicellular Agent-Based Model of Bone Metastasis ($A(BM)^2$), which replicates tumor growth, angiogenesis, and interactions with the bone microenvironment, including bone resorption. Model parameters were derived from in vivo renal tumor data and calibrated using a random forest regressor to reproduce observed growth rates. We validated the model by simulating the anti-angiogenic effects of cabozantinib and anti-resorptive effects of zoledronic acid, demonstrating its potential to predict therapeutic outcomes and clarify bone metastasis dynamics.

In parallel, we developed a digital twin for mechanical testing of long bones and vertebrae by integrating finite element analysis with micro-CT-derived bone geometry and material properties. Compression testing revealed increased trabecular bone fragility following Radium-223 treatment, while three-point bending showed no cortical fragility post-treatment but significant fragility following osteolysis.

Overall, this digital twin framework enables integrated investigation of tumor progression, therapy response, and bone mechanics while reducing reliance on animal models and supporting the 3Rs principle.



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B1 – Basic Science/Tumor Biology/Microenvironment

REGULAR ABSTRACT

# Spatial Xenium Profiling of ccRCC and Sarcomatoid RCC Regions Reveals Distinct Immune, Stromal, and Matrix-Remodeling Programs

Sarcomatoid differentiation in renal cell carcinoma is associated with aggressive clinical behavior, but its spatial relationship to clear cell RCC (ccRCC) tumor regions and the surrounding microenvironment remains incompletely defined. We analyzed 10x Xenium spatial transcriptomic data from seven patient samples that have matched ccRCC and sRCC tissue sections. Across the samples, 681,181 cells were assigned to ccRCC-candidate tiles and 327,203 cells to sRCC-candidate tiles. sRCC regions showed increased fractions of tumor/epithelial-like cells, cycling tumor/epithelial-like cells, pericyte/mural cells, endothelial/perivascular cells, IFN-stimulated tumor-like cells, and inflammatory myeloid/macrophage populations. In contrast, ccRCC- regions were relatively enriched for CD8/cytotoxic T cells, fibroblast/CAF populations, and cycling pericyte/mural cells. Differential expression analysis using paired sample-region pseudobulk comparisons identified sRCC-high genes associated with extracellular matrix remodeling, invasion, and inflammatory signaling. These results suggest that sRCC regions are spatially associated with mesenchymal, matrix-remodeling, proliferative, and myeloid-enriched programs, whereas ccRCC regions retain stronger lymphoid associated signatures.

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B2 – Basic Science/Tumor Biology/Microenvironment

REGULAR ABSTRACT

# Sleeping Beauty transposon screens to identify mechanisms of resistance to HIF-2α antagonists in ccRCC


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Clear cell renal cell carcinoma (ccRCC) is driven by the constitutive stabilization of HIF-2α through loss of the VHL tumor suppressor. Belzutifan, an allosteric inhibitor that disrupts the HIF-2α/ARNT1 complex, is an effective and well-tolerated therapy for advanced ccRCC, but prolonged treatment often leads to acquired resistance, the mechanisms of which remain poorly understood. To define how ccRCC tumors evade HIF-2α antagonism, we are performing unbiased forward genetic screens using the Sleeping Beauty (SB) transposon system in patient-derived ccRCC tumor grafts. The system pairs the SB transposase with a modified version of the T2/Onc3 transposon, which carries only a CAG promoter and splice donor. We deliver the transposase as mRNA and the transposon as minicircle DNA. Inside the cell, the transposase integrates the transposon at random TA dinucleotides, and cassettes landing upstream of a gene in the same orientation drive its ectopic overexpression. Mutagenized cells are cultured on top of a three-dimensional collagen matrix to mimic in vivo ECM stiffness, and treatment with belzutifan selects for cells harboring activating insertions that confer resistance. Transposon-directed sequencing recovers recurrent integration events, and genes targeted above expectation across independent replicates are nominated as candidate drivers. SB is particularly well suited to identifying drivers of drug resistance for three reasons: it produces gain-of-function events at single alleles, directly modeling the oncogene-activation events likely to bypass HIF-2α inhibition; unlike CRISPR activation screens, it requires no Cas9 pre-engineering, minimizing manipulation of the grafts; and insertion sites are identified by targeted sequencing without a predefined guide library, at far lower sequencing depth than those required for CRISPR screens. Overall, our strategy enables efficient and rapid discovery of drivers of cancer drug resistance.

B3 – Basic Science/Tumor Biology/Microenvironment

REGULAR ABSTRACT

# Modulating EGFR signaling pathways by glycosylation for cancer treatment

Protein glycosylation and phosphorylation play critical roles in regulating diverse cellular processes, yet their interplay remains underexplored. This study employed dose-dependent glycosylation inhibition to investigate the role of glycosylation, particularly phosphorylation, in epidermal growth factor (EGF) signaling. Using quantitative proteomics, we analyzed global protein expression, glycopeptides, and phosphopeptides in EGF-stimulated and unstimulated conditions. Results revealed that glycosylation inhibition disrupted phosphorylation patterns in EGF-regulated pathways. Notably, 215 EGF-regulated phosphopeptides exhibited dose-dependent changes, with pathways such as ERBB, MAPK, and mTOR signaling being significantly affected. Protein–protein interaction analysis highlighted glycosylation-dependent modulation of phosphorylation in cytoskeletal remodeling and growth factor signaling. Correlation analysis identified site-specific glycopeptides, such as Asn568 of EGFR, that influenced phosphorylation of downstream signaling proteins. Additionally, individual proteins such as RCN1 and SLC4A7 exhibited glycosylation- and phosphorylation-regulated patterns. These findings underscored the role of glycosylation in maintaining phosphorylation-dependent signaling fidelity, providing insights into the function of glycosylation in cell signaling pathways.

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B4 – Basic Science/Tumor Biology/Microenvironment

REGULAR ABSTRACT

# BAP1/PBRM1 Double-Mutant ccRCC Shows Increased DNA Damage Repair Dysregulation


BAP1 and PBRM1 are two commonly altered chromatin regulators in clear cell renal cell carcinoma (ccRCC) and are generally considered to be mutually exclusive. However, BAP1/PBRM1 double-mutant tumors (DM) still occur in approximately 1% of patients with more aggressive disease. In this study, we focused on the DNA damage repair features of DM ccRCC using patient RNA-seq and whole-exome sequencing data.

We first selected BAP1-deficient tumors from the UTSW database and performed PBRM1 staining to identify regions with single or combined gene loss. Sequencing then performed on 25 selected samples from 14 patients, including 1 wild-type sample, 8 PBRM1-mutant samples, 3 BAP1-mutant samples, and 13 DM samples. These data were combined with the published UTSW TTH RNA-seq cohort and grouped by mutation status, tumor grade, and SETD2 staining. UMAP analysis showed clear separation between normal and tumor samples. DM tumors partially overlapped with both high-grade PBRM1-mutant tumors and BAP1-mutant tumors.

Comparing each tumor group with normal samples identified 282 DEGs shared by all tumor groups and 164 DEGs shared by high-grade tumors. DM tumors also showed 239 group-specific DEGs, which were enriched in double-strand break repair and DNA recombination pathways. STEM analysis further identified genes with gradually increased expression from normal, low-grade PBRM1-mutant, high-grade PBRM1-mutant, high-grade BAP1-mutant, to DM tumors. These genes were enriched in chromosome segregation, cell cycle, DNA replication, and genome maintenance pathways.
Detailed analysis of HR, NHEJ, and MMEJ showed broad dysregulation of DNA repair genes in DM tumors. WES analysis also showed an increased ID83 fraction in DM tumors, and BAP1-mutant tumors showed a higher frequency of BRCA2-type HRD-like features, although these trends did not reach statistical significance. Together, these results suggest that DM ccRCC represents a high-grade tumor state with enhanced DNA damage repair dysregulation.



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B5 – Basic Science/Tumor Biology/Microenvironment

REGULAR ABSTRACT

# Genome-wide CRISPR screen identifies a cytokine-enhancer circuit driving HIF-2α activation in renal cancer

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Resistance to HIF-2α inhibitors such as belzutifan underscores the need to better understand how HIF-2α is transcriptionally regulated in clear cell renal cell carcinoma (ccRCC). Here, we uncover a cytokine-driven enhancer mechanism that sustains HIF-2α expression through the JAK1/STAT3 signaling pathway. Using a genome-wide CRISPR screen in von Hippel–Lindau–deficient (VHL-deficient) ccRCC cells, we identified SOCS3 as a key negative regulator of HIF-2α. Mechanistically, loss of SOCS3 activates JAK1/STAT3 signaling, leading to the recruitment of STAT3 to distal enhancers upstream of endothelial PAS domain-containing protein (EPAS1) that physically loop to its promoter to drive HIF-2α transcription. This cytokine-enhancer circuit was recapitulated in samples from patients with ccRCC and functionally validated using CRISPR interference (CRISPRi), which disrupted enhancer-promoter looping and reduced tumor growth in HIF-2α–dependent models. SOCS3 overexpression or pharmacologic inhibition of JAK1/STAT3 markedly suppressed HIF-2α expression and tumor progression both in vitro and in vivo. Unlike prior studies focusing on VHL/HIF occupancy–driven enhancer activation, this work defines a trans-acting cytokine–JAK1/STAT3 pathway that transcriptionally controls EPAS1. Together, these findings reveal a targetable enhancer mechanism that sustains HIF-2α expression and suggest that combined inhibition of JAK1/STAT3 and HIF-2α may overcome therapeutic resistance in kidney cancer.

B6 – Basic Science/Tumor Biology/Microenvironment

REGULAR ABSTRACT

# Direct in vivo activation of tumor-infiltrating lymphocytes by a multivalent nanoengager drives systemic antitumor immunity


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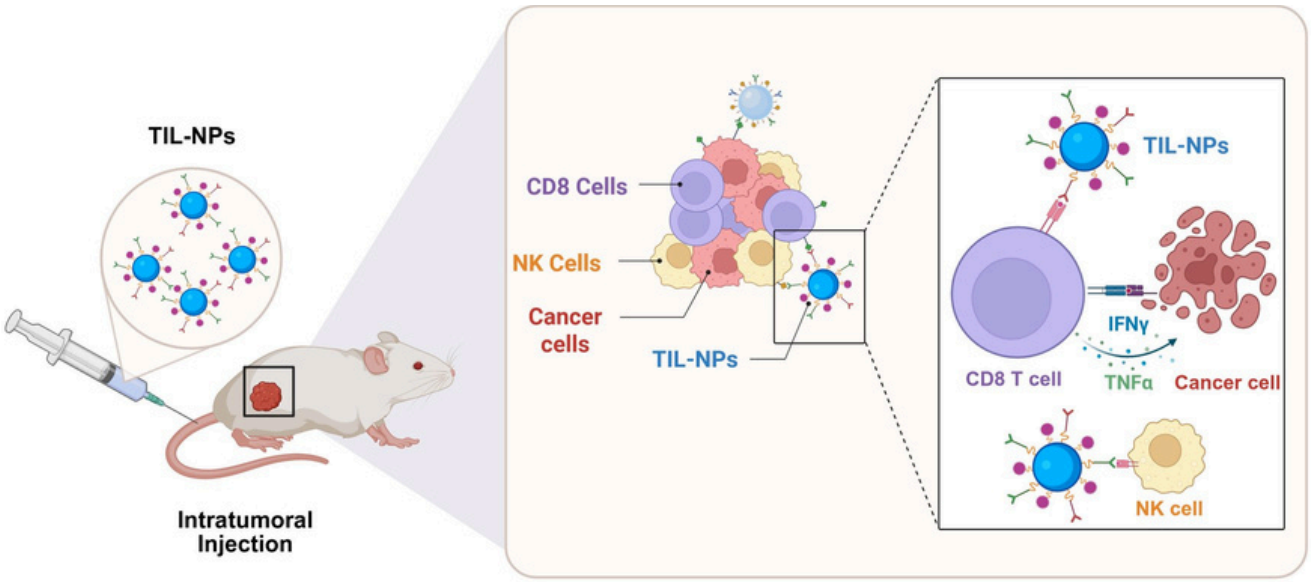


Introduction: Tumor-infiltrating lymphocyte (TIL) therapy has demonstrated clinical efficacy in melanoma, but its broader application is limited by the technically demanding manufacturing process, high cost and high toxicity profile. We developed TIL-NPs, multivalent protein-presenting nanoparticles that co-present anti-CD3, anti-4-1BB, and IL-2 on a single nanoparticle surface to spatially coordinate TCR engagement, 4-1BB co-stimulation, and cytokine support directly within tumors.

Methods: TIL-NPs were prepared by conjugating DBCO-modified anti-CD3, anti-4-1BB, and IL-2 to azide-functionalized PEG-PLGA nanoparticles. Their activity was evaluated using TILs isolated from MC38 colorectal and RENCA renal tumors and co-cultured with tumor cells. Therapeutic efficacy was assessed in bilateral tumor models following intratumoral administration into only one tumor. TIL-NPs were further evaluated in a human PBMC-engrafted NSG mouse model bearing bilateral 786-O tumors. Importantly, fresh renal cell carcinoma (RCC) specimens obtained from patients were used to establish autologous co-cultures of patient-derived TILs and matched tumor cells.

Results: TIL-NPs enhanced tumor-cell killing and increased IFN-γ and TNF-α secretion compared with untreated TILs, nanoparticle controls, and soluble molecular combinations. Intratumoral administration induced marked regression of treated tumors and inhibited contralateral tumor growth in both syngeneic models, indicating systemic antitumor immunity. TIL-NPs also enhanced the cytotoxicity and cytokine production of patient-derived TILs against matched tumor cells. In humanized mice, TIL-NPs promoted regression of treated tumors, suppressed contralateral tumor growth, and increased intratumoral $CD8^+$ T-cell infiltration.

Conclusion: Multivalent co-presentation of anti-CD3, anti-4-1BB, and IL-2 enables coordinated activation and expansion of endogenous TILs, producing local and systemic antitumor responses. This platform represents a potentially practical strategy for simplifying TIL-based immunotherapy and extending its application to solid tumors beyond melanoma.

B7 – Basic Science/Tumor Biology/Microenvironment

REGULAR ABSTRACT

# Exploiting Nucleolar Hypertrophy to Target Kidney Cancer

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Nucleolar size correlates with tumor aggressiveness, yet how nucleolar architecture is organized to sustain ribosome production and meet the heightened need for protein synthesis in tumors remains unclear. Here, we identify the ribosome biogenesis factor NOP2 as a central organizer of nucleolar structure and function in clear cell renal cell carcinoma (ccRCC), the most common type of kidney cancer. NOP2 is upregulated in tumors and associates with high-grade disease and poor patient survival. Functionally, NOP2 is required for large ribosomal subunit (60S) biogenesis. NOP2 loss disrupts nucleolar architecture, impairs ribosome production, reduces protein synthesis, and suppresses cell growth in both 2D and 3D models. Mechanistically, NOP2 forms high-molecular-weight complexes with NOP58, with which it dimerizes and co-fractionates. Interestingly, the NOP2–NOP58 complex spans nucleolar subdomains and is enriched in the dense fibrillary center. Overall, these findings define a spatially organized nucleolar module that links subdomain architecture to ribosome output and establish NOP2 as a key regulator of nucleolar function and a potential therapeutic vulnerability in ccRCC.

B8 – Basic Science/Tumor Biology/Microenvironment

REGULAR ABSTRACT

# Discovery and Development of Targeted Therapeutics in Metastatic Chromophobe Renal Cell Carcinoma

Background: Chromophobe renal cell carcinoma (ChRCC) is typically indolent, but 5-10% of cases become metastatic, where standard renal cell carcinoma regimens are less effective than in clear cell RCC and no therapy is approved specifically for ChRCC. Identifying effective therapies for metastatic ChRCC is an unmet need.

Methods: Two ChRCC-derived cell lines, UOK276 (sarcomatoid-differentiated primary tumor) and RCJ-41M (metastasis derived), were exposed to a panel of 210 compounds for 72 hours using high-throughput screening with cell toxicity imaging as an endpoint. 19 of these compounds were chosen for validation studies based on IC50 values, with compounds currently in clinical trials or FDA approved given priority. Abemaciclib, tozasertib, and zotiraciclib were further studied in both cell lines.

Results: Cell-cycle inhibitors were the most potent class in both the 210-compound and 19-compound screens, with several IC50 values below 1 μM. Guided by the high-throughput screening results, we evaluated abemaciclib, tozasertib, and zotiraciclib. Zotiraciclib was the most potent, with IC50 values of 143 nM in UOK276 and 265 nM in RCJ-41M, approximately 15 to 50 -fold lower than abemaciclib and tozasertib. At 75 nM, zotiraciclib reduced colony formation relative to vehicle after 72 hours by 75% in UOK276 and 66% in RCJ-41M ($p < 0.0001$).

Conclusion: Our results nominate zotiraciclib, an oral multi-kinase inhibitor that primarily targets CDK9, as a candidate therapy for metastatic ChRCC. The completed Phase I portion of an ongoing trial in IDH-mutant recurrent high-grade glioma (NCT05588141) established tolerability and supported FDA Fast Track designation, providing human dosing and safety data to support repurposing. Ongoing work is testing selectivity across other kidney cancer subtypes and non-malignant renal epithelium, and efficacy in ChRCC xenografts.

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B9 – Basic Science/Tumor Biology/Microenvironment

REGULAR ABSTRACT

# CG1 Promotes Acquired Resistance to HIF-2α Inhibition in Clear Cell Renal Cell Carcinoma


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HIF-2α is a critical oncogenic driver in clear cell renal cell carcinoma (ccRCC), and selective HIF-2α inhibitors have emerged as an important therapeutic strategy for patients with advanced kidney cancer. However, intrinsic and acquired resistance to HIF-2α inhibitors can limit therapeutic efficacy, highlighting the need to define resistance mechanisms and identify therapeutic vulnerabilities in resistant tumors.

To investigate mechanisms of acquired resistance to HIF-2α inhibition, we established multiple 786-O ccRCC cell lines with acquired resistance to PT2399, an analog of the clinically FDA-approved HIF-2α inhibitor belzutifan (MK-6482/PT2977). We performed RNA sequencing, ATAC-seq, and CUT&RUN sequencing to characterize transcriptional and epigenetic alterations associated with resistance. Integrative analysis identified candidate genes with coordinated changes in gene expression, chromatin accessibility, and regulatory chromatin marks.

We functionally evaluated these candidate resistance genes using complementary gain- and loss-of-function approaches. Overexpression screening identified CG1 as a potential mediator capable of reducing sensitivity to HIF-2α inhibition in 786-O cells. Independently, an sgRNA-based loss-of-function screen in an acquired-resistant 786-O-derived cell line identified CG1 as a candidate supporting growth in the resistant state. We further evaluated CG1 in vivo and found that its overexpression in parental 786-O cells conferred partial resistance to the HIF-2α inhibitor PT2977 in a subcutaneous xenograft model, supporting a functional role for CG1 in reducing tumor sensitivity to HIF-2α inhibition.

Together, these findings identify CG1 as a candidate mediator of acquired resistance to HIF-2α-targeted therapy in ccRCC. Ongoing studies are defining the molecular mechanisms underlying CG1-mediated resistance and determining whether therapeutic inhibition of CG1 can restore sensitivity to HIF-2α inhibition. These studies may reveal combination strategies to overcome acquired resistance and improve the durability of responses to HIF-2α-targeted therapy in kidney cancer.

B10 – Basic Science/Tumor Biology/Microenvironment

REGULAR ABSTRACT

# From microRNA Loss to Disrupted Nephrogenesis: Uncovering the Crucial Role of DROSHA in Kidney Development

Introduction Wilms tumor (WT) is the most common pediatric kidney cancer. The prognosis is poor for patients with blastemal predominant WT, which are composed of undifferentiated blastemal cells and lack the epithelial and stromal components associated with WT. These tumors are associated with DROSHA mutations that impair microRNA biogenesis, resulting in the failure to repress microRNA target genes. Dysregulation of these targets may interfere with the developmental programs governing nephron formation and mesenchymal-epithelial transition (MET). In this study, we investigated the impact of Drosha mutations on MET in WT and the developmental mechanisms underlying defective nephrogenesis.

Methods We engineered an inducible DroshaEK allele at the endogenous locus to mimic the WT heterozygous state. Wt1Cre mice were crossed with DroshaEK mice to obtain Wt1Cre;DroshaEK embryos, along with littermate controls. Kidneys from embryos were subjected to immunostaining for nephrogenic markers. To examine global transcriptional changes, RNA-seq was performed on nephrogenic progenitor cells from mutant and control kidneys. In parallel, scRNA-seq of nephrogenic zone cells & single-nuclie RNA-seq on whole kidneys was conducted to identify altered cell populations and characterize defects in nephrogenesis.

Results Activation of the mutation in Wt1Cre;DroshaEK developing kidney resulted in perinatal lethality, whereas littermate controls developed normally. Mutant kidneys were smaller than controls. Although early nephrogenesis appeared preserved, mutant kidneys exhibited defective maturation of epithelial nephron structures, suggesting a block in MET. Analysis of whole kidneys revealed a reduced proportion of cells within the nephrogenic lineage. Hmga2 emerged as one of the highly overexpressed genes in both RNA-seq and scRNA-seq in mutant kidneys. Persistent Hmga2 expression supports its role in defective nephrogenesis resulting from Drosha mutation activation.

Conclusion Our study demonstrates that impaired DROSHA function disrupts nephron progenitor differentiation and perturbs normal kidney development.

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B11 – Basic Science/Tumor Biology/Microenvironment

REGULAR ABSTRACT

# An Innovative Approach to Developing Syngeneic Kidney Cancer Models Harboring VHL Loss and MYC Activation


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Background: Genetically engineered mouse models (GEMMs) of kidney cancer are limited by long tumor latency, costly interbreeding, and small tumor size. Additionally, Cre-mediated activation of certain oncogenic mutations during embryonic development can lead to developmental abnormalities or lethality, limiting their use for modeling adult kidney cancer disease. We experienced this challenge while modeling concurrent VHL loss and activating MYC mutation (MycT58A), a genotype that is observed in approximately 10% of renal cell carcinoma patients.

Methods: Using a renal epithelial-specific Cre driver (Pax8-Cre) with conditional Myc activation (H11-LSL-MycT58A/+), together with additional kidney cancer-associated alterations, including VHL loss and PoleP286R, we performed timed matings to assess effects of embryonic MYC activation on kidney development. To bypass lethality, kidney tissue of defined genotypes from postnatal kidneys transplanted beneath the renal capsule of recipient mice to enable postnatal tumor development. Tumors were characterized histologically and molecularly, and derived cell lines were evaluated following transplantation into syngeneic immunocompetent mice. Functional studies were also performed on cell lines to evaluate their dependency on these pathways.

Results: Pax8-Cre-driven MYC activation was not tolerated and caused early postnatal lethality, with disrupted renal maturation, Bowman's capsule abnormalities, proximal tubular transformation, and increased proliferation. The strategy of postnatal kidney transplantation successfully bypassed this lethality, enabling MYC-driven tumor formation across multiple genetic backgrounds. Independent cell lines were established from generated tumors, and they retained renal epithelial identity with elevated MYC expression; VHL-deficient lines additionally showed dysregulation of VHL/HIF signaling and VHL reconstitution in these lines influenced the tumor growth. Transplantation of cell lines into syngeneic immunocompetent mice produced rapid tumor growth, with some models exhibiting metastatic potential.

Conclusions: Our findings demonstrate that renal subcapsular transplantation can overcome the developmental lethality associated with embryonic MYC activation and enable the generation of genetically defined kidney tumors. The establishment of VHL-deficient, MYC-driven tumor-derived cell lines that retain renal epithelial characteristics, exhibit VHL/HIF pathway dysregulation, and ability to form tumors in syngeneic immunocompetent hosts provides a reliable platform for investigating the functional consequences of VHL loss and MYC activation in kidney cancer.

B12 – Basic Science/Tumor Biology/Microenvironment

REGULAR ABSTRACT

# A Single Chromosome 3p Break Initiates Clear Cell Renal Cell Carcinoma Evolution

Chromosome 3p loss is the defining initiating event in clear cell renal cell carcinoma (ccRCC), despite the general fitness cost of large chromosomal deletions in normal cells. The mechanisms enabling renal epithelial cells to tolerate this loss during tumor initiation remain undefined. Analysis of 949 ccRCC tumors revealed two predominant patterns of chromosome 3p loss: simple arm-level deletions and localized rearrangements surrounding a terminal breakpoint, which we termed breakpoint-confined chromothripsis. To model these events, we introduced a single DNA double-strand break on chromosome 3p in non-transformed human renal proximal tubule epithelial cells. Chromosome 3p loss initially conferred a fitness disadvantage; however, rare surviving clones acquired recurrent ccRCC-specific aneuploidies, including chromosome 5q gain and 14q loss, that restored cellular fitness via metabolic reprogramming. This was sufficient to drive clonal expansion and malignant transformation, culminating in metastatic tumors with histological features of ccRCC. Clones harboring chromosome 3p loss also recapitulated the breakpoint-confined chromothripsis patterns observed in patient tumors, which we propose originate from a breakage-fusion-bridge mechanism. These findings demonstrate that a single chromosome break can initiate ccRCC evolution by generating a fitness bottleneck that selects for recurrent adaptive aneuploidies, establishing a tractable model for dissecting aneuploidy-driven tumor evolution.

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B13 – Basic Science/Tumor Biology/Microenvironment

REGULAR ABSTRACT

# Characterizing the Metabolic Consequences of VHL Missense Mutations in Clear Cell Renal Cell Carcinoma


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Clear cell renal cell carcinoma (ccRCC) is the most common form of kidney cancer and the most common cause of death from kidney cancer. Once metastatic, survival declines sharply, highlighting the need to understand mechanisms driving disease progression.

ccRCC is driven by loss of the tumor suppressor, Von Hippel–Lindau (VHL), which targets hypoxia-inducible factor α (HIF-α) for degradation. Loss of VHL stabilizes HIF signaling and shifts metabolism from mitochondrial oxidative phosphorylation toward glycolysis. Our previous work suggests that mitochondrial respiration is suppressed in primary ccRCC but reactivated in metastatic tumors, indicating that the mitochondria play an underappreciated role in cancer spread.

VHL missense mutations are common in ccRCC, but the functional consequences of individual variants are incompletely characterized. We curated public databases to identify recurrent VHL missense variants in ccRCC and VHL syndrome, then evaluated their ability to regulate HIF-α by overexpressing each variant in VHL-null 293T cells. Approximately half of the variants retained HIF-α degradation activity, with several behaving similarly to wild-type VHL. These findings reveal marked functional heterogeneity among VHL missense mutations and suggest that some pathogenic variants may promote tumorigenesis through HIF-independent mechanisms. We next generated 786-O ccRCC cell models expressing the wild-type-like VHL variants identified from the screen, together with HIF-stabilizing controls, and profiled respiration and tricarboxylic acid (TCA) cycle metabolism, two markers of mitochondrial function.

Mitochondrial activity varied markedly across the variants, with several exhibiting higher basal and maximal respiration than wild-type VHL addback. Some displayed altered respiratory chain organization and increased oxidative carbon contribution to the TCA cycle. Importantly, these metabolic phenotypes did not consistently track with HIF2α degradation, suggesting that VHL missense variants regulate mitochondrial metabolism through mechanisms beyond HIF2α regulation. We are investigating the mechanisms underlying these variant-specific metabolic phenotypes and their potential roles in tumorigenesis and metastasis.

B14 – Basic Science/Tumor Biology/Microenvironment

REGULAR ABSTRACT

# Functional interrogation of tumor-gained enhancers reveals a PLXNA1 dependency that sustains AXL signaling in clear-cell renal cell carcinoma

Epigenomic profiling studies have demonstrated that enhancer dysregulation is a prominent feature in clear cell renal cell carcinoma (ccRCC), yet the functional dependencies of the tumor-associated enhancers remain poorly understood. To dissect these dependencies, we performed a targeted dCas9-KRAB CRISPR interference (CRISPRi) screen against tumor-gained enhancers in ccRCC and identified a novel enhancer (Enh2) that is critical for tumor progression. We demonstrated that Enh2 drives the expression of PLXNA1, a gene we established for the first time as a critical dependency for ccRCC. Using CRISPR affinity purification in situ of regulatory elements followed by mass spectrometry (CAPTURE-MS), we identified HDGF as a bona fide Enh2-binding transcription factor that activates PLXNA1 transcription. Mechanistically, unbiased immunoprecipitation-mass spectrometry (IP-MS) identified the receptor tyrosine kinase AXL as a novel PLXNA1-binding protein. We further uncovered a previously unrecognized function of PLXNA1, demonstrating that it acts as an essential facilitator of AXL dimerization and autophosphorylation, thereby sustaining oncogenic AXL signaling in ccRCC. Together, our study uncovers a previously undocumented enhancer-regulated HDGF/PLXNA1/AXL signaling axis as a potential therapeutic vulnerability in kidney cancer.

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B15 – Basic Science/Tumor Biology/Microenvironment

REGULAR ABSTRACT

# Oxygen-Aware Patient-Derived Tumor Fragments as a Functional Platform to Study RCC Immunotherapy Response


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Background: Immune checkpoint blockade improves outcomes for patients with renal cell carcinoma (RCC), yet many patients fail to achieve durable benefit. Functional assays that preserve patient-specific tumor architecture and tumor-resident immune contexture may help identify early response and resistance states. Clear cell RCC is shaped by VHL/HIF-driven pseudohypoxia, but oxygen-associated tumor states and their immune consequences are heterogeneous. Recent work distinguishes pseudohypoxia from true microenvironmental hypoxia and shows context-dependent roles for hypoxia in response and resistance. Building on this concept, we developed an oxygen-aware patient-derived tumor fragment (PDTF) platform to compare normoxic and hypoxia-adapted ex vivo conditions for measuring anti–PD-1 immune reactivation.

Methods: Fresh RCC specimens from 11 clinically annotated patients were processed into matched viable tumor fragments and cultured under parallel normoxic and hypoxia-adapted conditions with control or anti–PD-1 treatment. The cohort included 6 clinical responders and 5 nonresponders to PD-1–backbone therapy. Treatment-induced immune response was assessed using multiplex soluble mediator profiling and flow cytometry-based immune/tumor-context readouts. Within-sample treatment effects compared normoxic and hypoxia-adapted anti-PD-1 responses. Data were analyzed using marker-level normalization, unsupervised clustering, dimensionality reduction, and exploratory response-score modeling.

Results: Oxygen-aware comparison identified hypoxia-sensitive anti-PD-1 response patterns that were less apparent under matched normoxic culture conditions. Marker-level analysis identified structured hypoxic response states associated with clinical response status, although unsupervised clustering alone did not fully classify all samples. An exploratory direction-aware response score derived from hypoxic anti–PD-1-induced changes improved separation of responders and nonresponders in this discovery cohort. Baseline oxygen-associated tumor-context features and selected T-cell state features were associated with ex vivo response patterns, suggesting that RCC immunotherapy responsiveness may depend on both tumor-resident immune substrate and oxygen-sensitive tumor context.

Conclusions: Oxygen-aware PDTFs provide a rapid, patient-specific platform to measure functional immune reactivation to PD-1 blockade in RCC. These preliminary findings support prospective validation of oxygen-adapted PDTF response signatures as functional biomarkers of immunotherapy response and resistance.

B16 – Basic Science/Tumor Biology/Microenvironment

REGULAR ABSTRACT

## TAZ and SRF Cooperate to Promote Immune Escape in Sarcomatoid Renal Cell Carcinoma

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Sarcomatoid renal cell carcinoma (sRCC) is an aggressive form of renal cancer associated with poor clinical outcomes. Alterations in the Hippo signaling pathway are enriched in human sRCC, and we previously demonstrated that deletion of the Hippo kinases Lats1/2 from adult renal epithelia induces aggressive, metastatic sRCC in mice.

Using genetically engineered mouse models, we investigated the roles of the Hippo effectors YAP and TAZ and the transcription factor SRF in sarcomatoid transformation and tumor progression. Although activation of either YAP or TAZ induced epithelial-to-mesenchymal transition (EMT), only activated TAZ promoted progression to sRCC, demonstrating distinct functions for these closely related transcriptional regulators.

Transcriptomic analysis of Lats1/2-deficient tumor cells identified enrichment of SRF-binding sites adjacent to TEAD-binding sites in candidate regulatory elements, suggesting cooperation between SRF and TAZ. Deletion of Srf from Lats1/2-deficient renal epithelial cells did not prevent EMT but completely blocked subsequent progression to sRCC. Transcriptomic comparison of purified Lats1/2 and Lats1/2;Srf mutant epithelial cells revealed that the pathways most strongly affected by SRF loss were associated with immune signaling. Remarkably, Lats1/2;Srf-deficient cells regained the ability to form aggressive, metastatic sRCC following transplantation into immunodeficient mice, demonstrating that SRF is dispensable for intrinsic tumorigenic potential but required for evasion of immune surveillance.

Together, these findings identify TAZ as a specific driver of sRCC progression and reveal an unexpected role for SRF in promoting tumor immune escape. We propose that TAZ and SRF cooperate transcriptionally to establish a tumor microenvironment permissive for progression of sarcomatoid RCC.

B17 – Basic Science/Tumor Biology/Microenvironment

REGULAR ABSTRACT

# Tumor Microenvironment Modulation by Cyclopamine Tartrate Enhances Immunotherapy Response in Renal Cell Carcinoma


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Immune checkpoint inhibitors (ICIs) have changed the treatment landscape for advanced renal cell carcinoma (RCC), yet durable benefit remains limited to a subset of patients, partly because vascular dysfunction and hypoxia in the RCC tumor microenvironment can restrict effective antitumor immunity. We tested whether cyclopamine tartrate (CycT), a tumor microenvironment-modulating agent, could improve tumor oxygenation and enhance ICI response. In a syngeneic RENCA-luc subcutaneous model, BALB/c mice were treated with vehicle control, CycT, dual-checkpoint blockade with anti-PD-1 plus anti-CTLA-4, or CycT plus ICIs. Tumor growth was monitored by bioluminescence imaging (BLI), oxygenation dynamics were assessed by oxygen-enhanced multispectral optoacoustic tomography (OE-MSOT), and vascular, hypoxia, and immune markers were evaluated by immunohistochemistry. Tolerability was assessed by body weight, serum chemistry, and hematology. CycT plus ICIs produced the strongest antitumor activity, with reduced BLI signal, lower endpoint tumor mass, and decreased necrotic area. OE-MSOT showed the greatest $\Delta sO_2$ response in the combination group, with reduced CA9 staining and treatment-associated vascular changes. CycT was well tolerated and also suppressed tumor growth and increased oxygenation responsiveness in an orthotopic human RCC patient-derived xenograft model. Together, these findings support tumor microenvironment modulation with CycT as a strategy to improve RCC response to immune checkpoint therapy.

B18 – Basic Science/Tumor Biology/Microenvironment

REGULAR ABSTRACT

# Partial ATG7 Loss Shapes Autophagy and Tumor Phenotype in Translocation Renal Cell Carcinoma

Translocation renal cell carcinoma (tRCC) is an aggressive kidney cancer characterized by oncogenic TFE3 fusions and no FDA approved specific therapy. Transcriptomic and proteomic analyses revealed that these tumors exhibit activation of autophagy-lysosomal pathways, indicating that autophagy may play an important role in tRCC tumorigenesis and progression. Since ATG7 is an essential component of autophagy machinery, we sought to determine how loss of Atg7 affects tumor biology in a genetically engineered mouse model of ASPSCR1-TFE3 fusion driven tRCC. We generated an ASPSCR1–TFE3-driven genetically engineered mouse model with heterozygous Atg7 loss. Tumors with heterozygous Atg7 loss were compared with tumors retaining both Atg7 alleles using histopathological and molecular analyses. Heterozygous loss of Atg7 was associated with a reduction in the expression of multiple autophagy-related genes. Our preliminary findings implicate ATG7 as a potential modulator of tumor biology in tRCC, supporting further investigation into the role of autophagy-dependent processes in TFE3 fusion-driven tumor development and progression.

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B19 – Basic Science/Tumor Biology/Microenvironment

REGULAR ABSTRACT

# Hijacking VHL-HIF signaling to prime kidney cancer cells for death

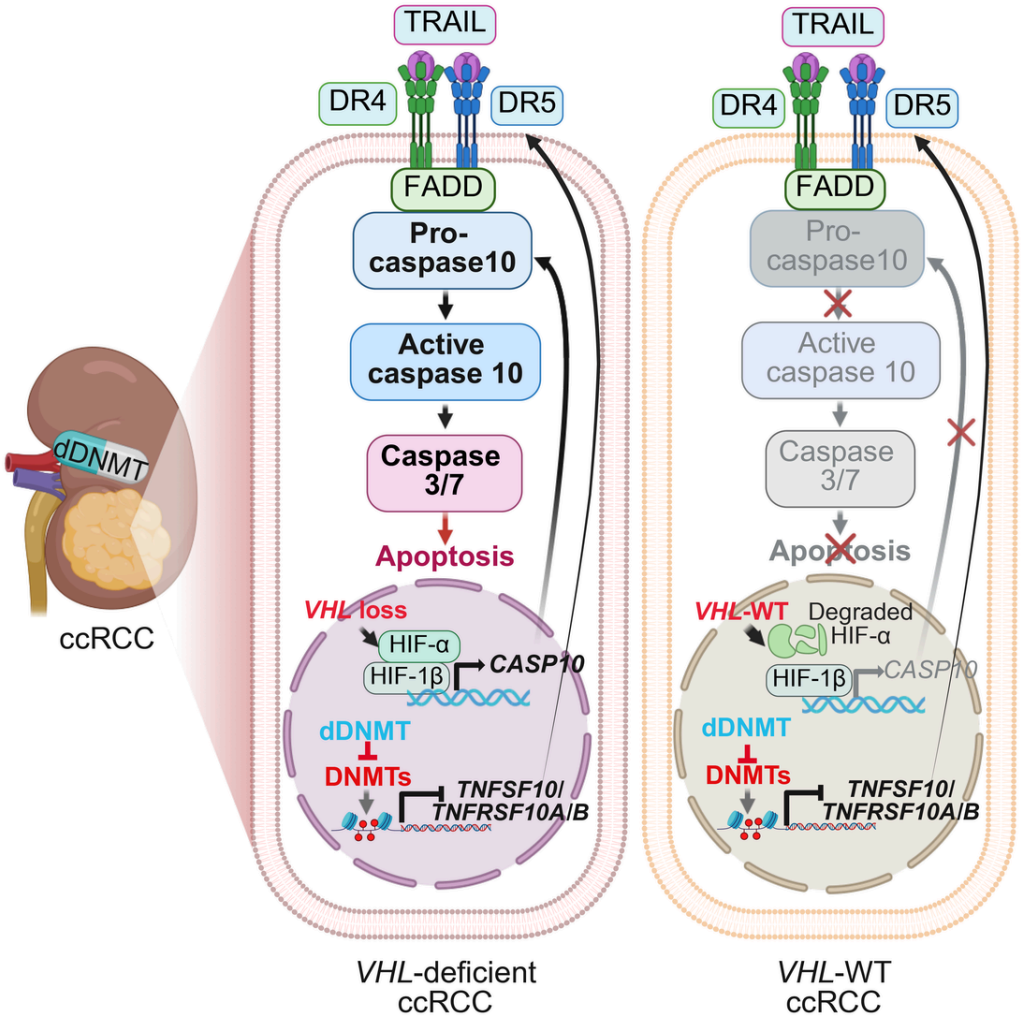

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Activation of hypoxia-inducible factors (HIFs) supports cancer cell survival, yet how HIFs govern cell death remains unclear, despite evidence that HIF-1 acts as a tumor suppressor in ccRCC. Here, we report a cell death priming role for HIF-1/2 in ccRCC. Through cell viability screens with chemical libraries, we identify SGI1027 and its analog MS1129 as HIF-1/2-dependent cell death inducers that specifically kill VHL-deficient ccRCC cells in vitro and patient-derived xenografts in mice. Mechanistically, SGI1027 and MS1129 induce proteasomal degradation of DNMT1/DNMT3A/DNMT3B proteins, leading to the loss of promoter methylation and subsequent upregulation of TRAIL, DR4, and DR5 in ccRCC cells. HIF-1/2 induce procaspase-10 expression serving a commitment point to activate TRAIL-induced apoptosis in VHL-deficient ccRCC following SGI1027 or MS1129 treatment. Notably, recombinant TRAIL protein synergizes with SGI1027 or MS1129 to kill VHL-deficient ccRCC in mice. Collectively, our study unveils an apoptosis induction strategy that involves hijacking HIFs for ccRCC treatment.

B20 – Basic Science/Tumor Biology/Microenvironment

REGULAR ABSTRACT

# Alkylating agents sensitize SLFN11-high ccRCC to PARP inhibitors PARP inhibitors demonstrated notable clinical benefit but their effectiveness is currently restricted to patients w/ BRCA1/2 mutations. How to enhance sensitivity of BRCA1/2-wildtype

PARP inhibitors have demonstrated notable clinical benefit, but their effectiveness is currently restricted to patients with BRCA1/2 mutations. How to enhance sensitivity of BRCA1/2-wildtype (WT) tumors to PARP inhibitors remains challenging. Here, we showed that BRCA1/2-WT clear cell renal cell carcinoma (ccRCC) exhibits markedly higher PARP-1 activity compared to breast cancers. A subset of alkylating agents, including Temozolomide (TMZ) and Streptozocin, is identified to induce hyperactivation of PARP-1, creating a PARP-1 dependency in ccRCC cells that renders these cells sensitive to PARP inhibitors in vitro and in mice. Mechanistically, SLFN11 is selectively upregulated and boosts proteasomal degradation of BRCA1 protein in ccRCC cells. Loss of SLFN11 increases BRCA1 levels and enhances homologous recombination repair, mitigating prolonged excessive DNA damage in ccRCC cells following combo treatment with TMZ and Olaparib. SLFN11 is also inversely correlated with BRCA1 expression and potentiates the therapeutic efficacy of TMZ and Olaparib combo treatment in ccRCC patient-derived xenograft models. Collectively, our findings reveal an intrinsic SLFN11-dependent vulnerability in ccRCC that synergizes with alkylating agents to induce an acquired PARP-1 dependency, thereby sensitizing BRCA1/2-WT tumors to PARP inhibition. Therefore, this work uncovers a potential therapeutic strategy for targeting SLFN11-high kidney cancers.

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C1 – Disparities in Cancer, Care, and Access

REGULAR ABSTRACT

# Social Vulnerability in Metastatic Renal Cell Carcinoma

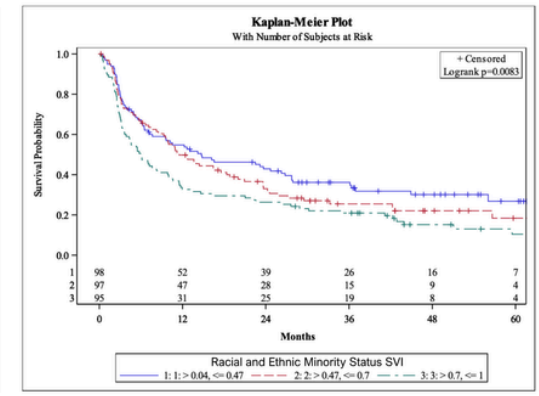

Background: High levels of social vulnerability have been shown to be associated with increased cancer mortality. The Centers for Disease Control and Prevention (CDC) Social Vulnerability Index (SVI) is a publicly available measure to evaluate social vulnerability that incorporates four main domains: socioeconomic status, household characteristics, racial and ethnic minority status, and housing type and transportation. Our study aims to explore how social vulnerability is related to survival outcomes in metastatic renal cell carcinoma (mRCC) patients in Georgia.

Methods: We performed a prospective single-center study including mRCC patients who started treatment between 2018-2023. All patient data were extracted from the electronic medical record. SVI data were extracted based off zip code from the CDC 2022 SVI Georgia dataset. SVI variables ranged from 0 to 1 with values closer to 1 indicative of higher vulnerability. Kaplan-Meier plots were utilized to assess overall survival (OS) and progression-free survival (PFS) at 12 and 60 months.

Results: There were 291 patients included. There was significantly lower 12-month PFS (32.6% in higher SVI patients vs 54.7% in lower SVI, p<0.01), as well as significantly lower 60-month PFS (10.4% for higher SVI vs 26.8% for lower SVI, p<0.01) for patients deemed highly vulnerable based on racial and ethnic minority status. 12-month and 60-month PFS and OS were similar regardless of SVI when assessed based on socioeconomic status, household characteristics, housing type and transportation, and overall SVI.

Conclusion: While there were no significant differences in survival across SVI values based on socioeconomic status, household characteristics, housing type and transportation, and overall SVI, the significant association between higher social vulnerability and worse survival outcomes based on minority status emphasizes potential disparities in cancer care that still exist, highlighting the need for community-focused interventions that can reduce these disparities in mRCC.


**Figure 1. Kaplan-Meier analysis: progression-free survival (PFS) based on racial and ethnic minority status SVI**




| Racial and Ethnic Minority Status SVI * | N | Event | Censored | Median Survival (95% CI) | 12 Month Survival | 60 Month Survival |
|---|---|---|---|---|---|---|
| 1: > 0.04, <= 0.47 | 98 | 66 (67%) | 32 (33%) | 14.7 (7.2, 26.8) | 54.7% (44.3%, 64.0%) | 26.8% (16.8%, 37.7%) |
| 2: > 0.47, <= 0.7 | 97 | 74 (76%) | 23 (24%) | 11.5 (8.5, 18.4) | 49.7% (39.4%, 59.3%) | 18.4% (9.7%, 29.3%) |
| 3: > 0.7, <= 1 | 95 | 82 (86%) | 13 (14%) | 6 (3.6, 9.9) | 32.6% (23.5%, 42.1%) | 10.4% (4.4%, 19.5%) |

* Group 1 includes patients with SVI values greater than 0.04 to 0.47 (lower SVI values are associated with lower social vulnerability; group 2 includes patients with SVI values greater than 0.47 to 0.7; group 3 includes patients with SVI values greater than 0.7 to 1 (higher SVI values are associated with higher social vulnerability)


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C2 – Disparities in Cancer, Care, and Access

REGULAR ABSTRACT

# Stage IV Kidney Cancer Non-Treatment Rates and First-Line Treatment Patterns from the National Cancer Database


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Systemic therapy for metastatic kidney cancer has changed substantially, but whether these advances reduced treatment nonreceipt is unclear. Using the National Cancer Database, we identified patients with Stage IV kidney cancer diagnosed from 2010–2023 with known first-course treatment status. Patients whose entire first-course treatment or decision not to treat occurred elsewhere (Class of Case 00), those undergoing active surveillance, and those with unknown treatment status were excluded. Treatment patterns were compared between 2010–2015 and 2018–2023. The years 2016–2017 were treated as a transition period to account for the gradual implementation of immune checkpoint inhibitor therapy into routine practice after nivolumab received FDA approval for advanced renal cell carcinoma in November 2015. Multivariable models evaluated factors associated with treatment nonreceipt and adjusted for age, insurance, comorbidity, sex, race/ethnicity, facility type, multi-facility reporting, and metastatic distribution at diagnosis.

Among 63,833 stage IV patients, 10,126 (15.9%) received no documented first-course treatment from 2010-2023. Among treated patients, registry-coded immunotherapy increased from 5.4% in 2010–2015 to 65.6% in 2018–2023. However, crude non-treatment rates remained unchanged (15.86% vs 15.92%). After adjustment for demographic, clinical, metastatic, and facility characteristics, non-treatment remained essentially unchanged between 2010–2015 and 2018–2023 (15.8% vs 15.9%; difference, +0.10 percentage points; 95% CI, −0.51 to 0.72; P=.739). Greater metastatic disease burden, including bone, brain, liver, and lung involvement, was associated with treatment nonreceipt (global P<.001), but accounting for metastatic disease burden did not alter the absence of a temporal decline.

Despite major advances in metastatic kidney cancer treatment, non-treatment rates remained unchanged. Metastatic distribution was associated with treatment nonreceipt but did not explain the stable rate over time. Expanded therapeutic options alone may be insufficient to reduce treatment nonreceipt, supporting further study of treatment eligibility, patient preferences, access, referral pathways, geography, and healthcare-system factors.


**Treatment Patterns by Era in Stage IV Kidney Cancer**

| | 2010–2015 | 2018–2023 |
|---|---|---|
| **Patients, N** | 24,734 | 29,249 |
| Treated, N (%) | 20,811 (84.1) | 24,593 (84.1) |
| **No documented treatment, N (%)** | 3,923 (15.9) | 4,656 (15.9) |
| **Treatment types among treated patients, %** | | |
| Immunotherapy | 5.4 | 65.6 |
| Targeted therapy† | 59.4 | 39.0 |
| Surgery | 50.1 | 30.8 |
| Radiation | 38.3 | 35.0 |
| **No documented treatment by care setting, n/N (% of untreated)** | | |
| Academic/Research | 1,154/3,923 (29.4) | 1,430/4,656 (30.7) |
| Community* | 2,027/3,923 (51.7) | 2,388/4,656 (51.3) |
| Integrated Network | 707/3,923 (18.0) | 809/4,656 (17.4) |
| Other‡ | 0/3,923 (0.0) | 1/4,656 (0.0) |
| Unknown/Missing | 35/3,923 (0.9) | 28/4,656 (0.6) |
| **Total** | 3,923 (100.0) | 4,656 (100.0) |
| **Charlson–Deyo among patients with no documented treatment, n/N (% of untreated)** | | |
| Score 0 | 2,395/3,923 (61.1) | 2,808/4,656 (60.3) |
| Score 1 | 949/3,923 (24.2) | 793/4,656 (17.0) |
| Score 2 | 339/3,923 (8.6) | 481/4,656 (10.3) |
| Score ≥3 | 240/3,923 (6.1) | 574/4,656 (12.3) |
| Unknown/Missing§ | 0/3,923 (0.0) | 0/4,656 (0.0) |
| **Total** | 3,923 (100.0) | 4,656 (100.0) |

* Community combines Community and Comprehensive Community Cancer Programs.

† Targeted therapy reflects the NCDB registry-coded chemotherapy field for kidney cancer.

‡ Other includes non-classifiable/other facility type codes; Unknown/Missing indicates no classifiable facility type.

§ No unknown Charlson–Deyo scores were observed in either era.

**Adjusted difference: 0.10 percentage points (95% CI, −0.51 to 0.72; P=.739).**

*Care-setting and Charlson–Deyo values are crude distributions among patients with no documented treatment; percentages sum to 100% within each era. Adjusted probabilities are marginal standardized estimates.*

D1 – Treatment Toxicities and Symptom Management

CASE REPORT ABSTRACT

# Durable Disease Control with Markedly Reduced-Dose Belzutifan in Advanced Clear-Cell Renal Cell Carcinoma


Belzutifan is a selective hypoxia-inducible factor-2α inhibitor FDA-approved for advanced clear-cell renal cell carcinoma (ccRCC). The standard dose is 120 mg daily, with recommended reductions to 80 and 40 mg for toxicity. The minimum effective dose is unknown, and activity with markedly reduced or intermittent dosing is poorly characterized.

We evaluated two patients with advanced ccRCC who maintained disease control despite significant dose reductions (40 mg qD and QOD, respectively). Whole-genome sequencing (WGS) with DRAGEN pharmacogenomic star-allele calling, and copy-number variant (CNV) analysis were performed.

Patient 1 is a 75-year-old woman with ccRCC with focal rhabdoid features with a history of pleural, osseous, brain, soft-tissue, and bowel metastases. She received multiple therapies, including sunitinib, nivolumab, axitinib, tivozanib, and a HIF-2α–directed RNA interference. Her course included paraneoplastic polycythemia and profound erythropoietin suppression with prior HIF-2α inhibition. Initiated in October 2025, belzutifan caused hypoxia, symptomatic anemia, and edema, prompting a progressive reduction to 40 mg daily. After eight months of low-dose therapy, disease remains stable without progression. WGS CNV and DRAGEN pharmacogenomic failed to identify a likely explanation.

Patient 2 is a 72-year-old man presenting with intermediate-risk metastatic ccRCC with synchronous mediastinal/hilar lymphadenopathy who, progressed on ipilimumab/nivolumab, and did not tolerate axitinib, even at low doses. He started belzutifan in February 2024 developing dyspnea, hypoxia, fatigue, and anemia. This prompted stepwise dose reductions from 120 mg daily to 40 mg every other day and, most recently, to 40 mg three times weekly. Since beginning the dose reduction, he has had stable disease for more than two years. CNV analysis identified a heterozygous UGT2B17 deletion, possibly explaining the activity at a reduced dose.

Durable disease control may occur with markedly reduced belzutifan dosing which may result at least in part from impaired drug metabolism. These observations warrant prospective exposure-response investigation.



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D2 – Treatment Toxicities and Symptom Management

CASE REPORT ABSTRACT

# Intraperitoneal Alteplase for Refractory Loculated Malignant Ascites in Advanced Renal Cell Carcinoma


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Malignant ascites is a debilitating complication of peritoneal carcinomatosis. Extensive septations and tumor implants can compartmentalize fluid, limiting the effectiveness of paracentesis and indwelling catheters. Peritoneal carcinomatosis is uncommon in renal cell carcinoma (RCC), and management of refractory loculated malignant ascites remains poorly defined. We describe intraperitoneal alteplase (tPA) for severely loculated ascites in advanced translocation RCC (tRCC).

A middle-aged woman with metastatic tRCC receiving sixth-line maintenance cabozantinib, developed progressive peritoneal carcinomatosis and symptomatic, tense, malignant ascites requiring increasingly frequent paracenteses. The patient required increasingly frequent therapeutic paracenteses with progressively diminishing drainage despite persistent symptoms. A catheter placed at an outside hospital was draining ~20 mL of thick fluid per day. At presentation, only 200 mL of thick fluid could be drained. Previous intraperitoneal catheter placement was limited by extensive septations and carcinomatosis, and her course was complicated by polymicrobial bacterial peritonitis. A 14-French percutaneous drain was placed under ultrasound and fluoroscopic guidance into a dominant locule, followed by 4 mg intraperitoneal tPA with one hour dwell time. The drain subsequently yielded 3 L over 24 hours with symptomatic improvement and no bleeding, hemodynamic instability, or immediate infectious complications. Additional tPA doses produced minimal drainage. Subsequent placement and exchange of larger drains yielded an additional 1.8 L. The patient later developed shock and altered mental status in the setting of advanced disease and inferior vena cava compression and was transitioned to hospice care.

Large-bore peritoneal drainage with intraperitoneal tPA produced rapid but transient restoration of drainage in severely loculated RCC-associated malignant ascites. Further studies are needed to define patient selection, dosing, safety, and durability.

E1 – Patient-reported Outcomes

REGULAR ABSTRACT

# Navigating Uncertainty: Shared Decision-Making, Patient Priorities, and Decisional Regret in Adjuvant Renal Cell Carcinoma


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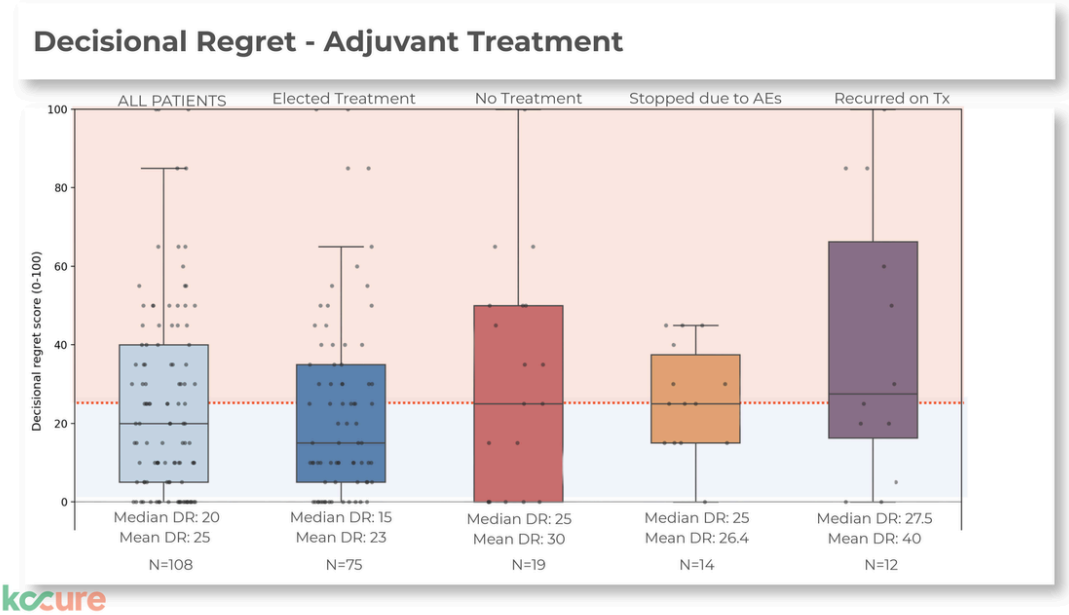
Adjuvant treatment decisions in renal cell carcinoma (RCC) require patients to weigh uncertain benefit against known treatment burden. We evaluated shared decision-making, treatment priorities, perceived recurrence risk, and decisional regret among patients offered adjuvant therapy.

KCCure conducted a patient survey from June–September 2022. Among 632 respondents with localized RCC, 111 were offered adjuvant treatment; 75 (67.6%) received or were receiving treatment and 21 (18.9%) declined. Complete Decision Regret Scale (DRS) data were available for 108 respondents; the received-versus-declined comparison included 94 (75 and 19, respectively). The five-item DRS ranges from 0–100, with higher scores indicating greater regret and scores ⩾25 considered meaningful. Shared decision-making was assessed using the nine-item SDM-Q-9 (0–100).

Mean DRS was 24.8 (median 20); 46% had scores ⩾25 and 21% reported no regret. Patients declining therapy had higher mean regret than those receiving treatment (30.3 vs 23.4), but were also more likely to report no regret (31.6% vs 20.0%). Regret was highest among patients whose disease recurred during therapy (mean 40.0; median 27.5). Patients discontinuing because of side effects had moderate regret (mean 26.4; median 25.0).

Shared decision-making scores were high and similar among patients receiving versus declining therapy (78.0 vs 79.4), as was perceived recurrence risk (62.2% vs 63.3%). Patients receiving therapy prioritized the risk of dying from cancer, whereas those declining therapy prioritized treatment-related side effects and burden.

Decisional regret varied by subsequent treatment experience, even among patients reporting high shared decision-making. As combination therapies enter the adjuvant setting and potentially increase risks and burden, incorporating patient priorities becomes increasingly important. Although limited by sample size, these findings highlight the need to communicate benefits, risks, and uncertainty and understand how subsequent outcomes reshape regret over time.

F1 – Post-treatment Surveillance

CASE REPORT ABSTRACT

# Late, Imaging-Occult Gastrointestinal Metastases from Renal Cell Carcinoma


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Gastrointestinal (GI) metastases from renal cell carcinoma (RCC) are rare, occurring in 0.2% to 1.6% of patients with metastatic disease, and may present years to decades after nephrectomy with iron deficiency anemia or GI bleeding. FDG-PET sensitivity for distant RCC metastases is approximately 64%, and small or intraluminal bowel lesions may be difficult to detect on conventional imaging.

We reviewed clinical, imaging, endoscopic, pathologic, and immunohistochemical findings from two patients at our institution with biopsy-proven GI metastases from RCC and searched PubMed, Embase, and Scopus for reported RCC metastases to the stomach, jejunum, and ileum.

Patient 1, a 54-year-old man, developed iron deficiency anemia more than 3 years after right nephrectomy. Capsule endoscopy and jejunal biopsy confirmed metastatic RCC. CT enterography demonstrated three jejunal and one ileal lesion. PET/CT could not distinguish intraluminal activity from physiologic bowel uptake, and MRI showed no definite small bowel lesion. Patient 2, a 73-year-old man with pT3bNxG2 clear cell RCC with IVC invasion resected in 2008, underwent resection of a lung metastasis in 2023. Seventeen years after nephrectomy, multiple 5 to 15 mm gastric polyps were confirmed as metastatic clear cell RCC. PET/CT one month later still showed no evidence of disease.

Approximately 73 to 80 gastric cases have been reported, with median intervals of 5.4 to 6.7 years after nephrectomy; jejunal metastases remain exceedingly rare. In the largest multicenter cohort (GETUG, n=74), 70% were symptomatic at diagnosis. To our knowledge, these are the first reported RCC GI metastases missed by both PET/CT and MRI.

RCC survivors with unexplained iron deficiency anemia or GI symptoms warrant endoscopic evaluation despite negative imaging. Very late recurrence supports continued symptom-driven vigilance well beyond routine surveillance intervals.

F2 – Post-treatment Surveillance

REGULAR ABSTRACT

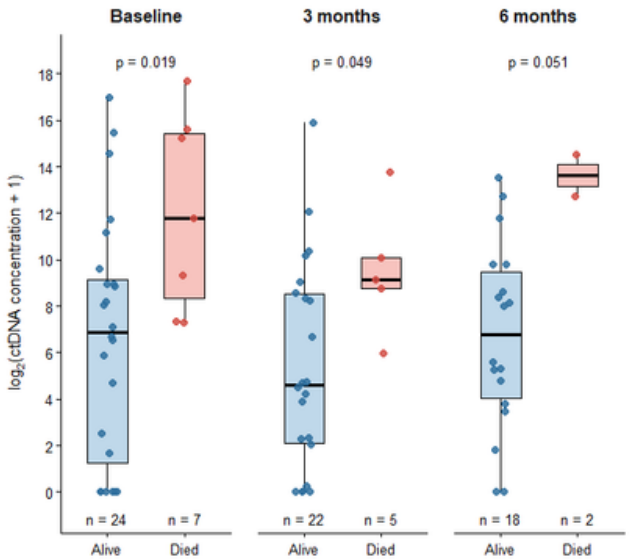
# Ultrasensitive ctDNA Kinetics and Association with Survival in Oligoprogressive Renal Cell Carcinoma Patients Treated with Metastasis Directed Therapy


Background: Metastasis-directed therapy (MDT) in oligoprogressive disease aims to control resistant lesions while preserving the current systemic therapy, but guiding biomarkers are lacking. We characterized longitudinal ultrasensitive circulating tumor DNA (ctDNA) kinetics and survival associations in a prospective cohort with oligoprogressive renal cell carcinoma (RCC) receiving MDT.

Methods: Patients with oligoprogressive RCC ([⩽5] progressing lesions) were prospectively enrolled on protocol 2023-0751 and received definitive radiotherapy to all progressing sites. Plasma was collected before MDT and at 3, 6, 9, and 12 months. Patient-specific panels (⩽1,000 somatic variants from tumor whole-genome sequencing; Myriad Genetics) quantified tumor fraction in parts per million (PPM). Exploratory Cox regression related log2 tumor fraction to overall survival (OS) from MDT start.

Results: Thirty-one patients enrolled between June through September 2026 had oligoprogressed on surveillance (n=11), first-line (n=2), or later-line (n=18) therapy. Median follow-up was 14.7 months (range, 9.2–16.8); 7 patients died. ctDNA was detectable before MDT in 26/31 (84%; median 262 PPM among positives, IQR 4.8–3463) and at 3 months in 21/27 (78%; median 62 PPM, IQR 3.9–558) (Figure 1); (3/27) baseline-positive patients cleared ctDNA by 3 months. Around 52% of patients (14/27) had ctDNA decline. All 7 deaths occurred in baseline ctDNA-positive patients (7/26 vs 0/5). Higher baseline tumor fraction was associated with shorter OS (HR 1.20 per doubling, 95% CI 1.11–1.40, p=0.033), with a similar 3-month estimate (HR 1.24, 95% CI 0.98–1.57; 0/6 deaths among 3-month negatives).

Conclusion: Ultrasensitive ctDNA was detectable in most patients, declined after MDT, and higher baseline tumor fraction was associated with shorter OS. With 7 deaths, estimates are imprecise and require validation in larger cohorts, where ctDNA kinetics after MDT warrant evaluation as a monitoring biomarker.



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G1 – Prevention and Screening

REGULAR ABSTRACT

# Body weight history during the adult lifespan and survival in renal cell carcinoma patients


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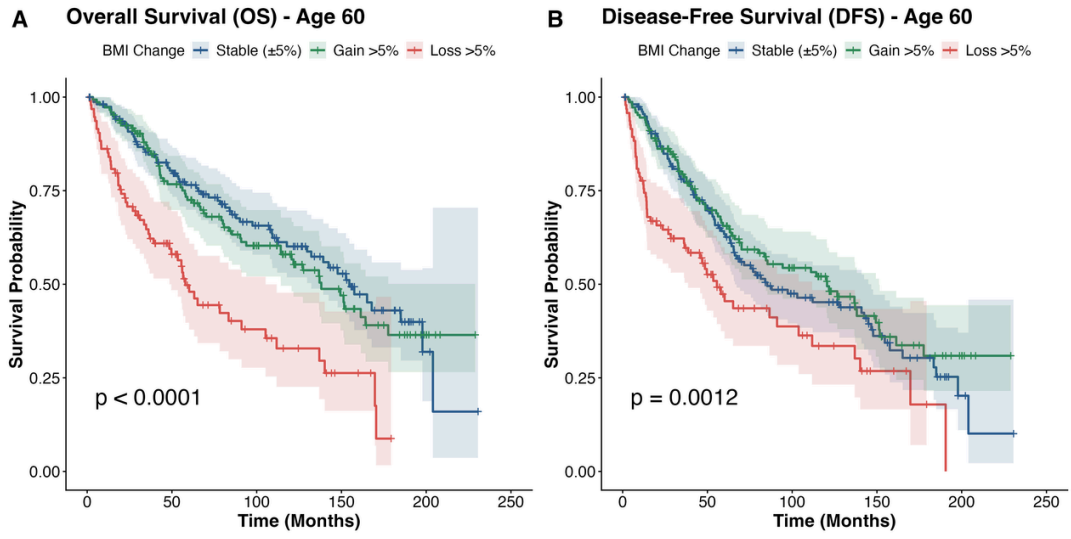


Background: Obesity, based on body mass index (BMI) at diagnosis, is associated with better survival in patients with renal cell carcinoma (RCC), but the relationship between pre-diagnostic lifetime body weight pattern and survival remains largely unknown. This study investigated associations of pre-diagnostic body weight patterns across the adult lifespan with overall survival (OS) and disease-free survival (DFS).

Methods: A retrospective cohort study of patients from the Roswell Park Comprehensive Cancer Center was performed. Pre-diagnostic lifetime body weight patterns were characterized using latent class trajectory modeling (LCTM), weighted years overweight and obese (WYO), and BMI change from ages 18, 30, 45, and 60 to the time of diagnosis or treatment initiation. Associations with OS and DFS were tested using multivariable Cox proportional hazards models.

Results: A total of 670 cases (mean age 62.3, 63.3% males, and 34.1% advanced-stage) were included. Many patients experienced >5% BMI increase (87.9% from age 18 years and 74.1% from age 30 years to diagnosis). Compared with normal weight, obesity at diagnosis was associated with better OS (HR 0.49, 95% CI 0.32-0.75) and DFS (HR 0.50, 95% CI 0.34-0.73), and obesity at age 45 years was associated with better DFS (HR 0.65, 95% CI 0.43-0.98). From age 60 years to diagnosis, 24.2% of patients experienced >5% BMI reduction, and compared with those who remained stable weight, patients with >5% loss had worse OS (HR 1.94, 95% CI 1.20-3.14) and DFS (HR 1.59, 95% C: 1.02-2.48) (Figure 1). Lifetime body weight patterns evaluated by LCTM and WYO were not associated with survival.

Conclusion: Pre-diagnostic body weight patterns were not consistently associated with RCC survival, and weight loss occurring later in life was associated with worse survival potentially due to cachexia or sarcopenia. These findings suggest that weight history of patients may offer prognostic information beyond BMI at diagnosis.

H1 – Quality of Care and Quality Improvement

TRIALS IN PROGRESS ABSTRACT

# Subcutaneous versus Intravenous Immune Checkpoint Inhibitors, Treatment Burden, and Care Delivery for Patients with Renal Cell Carcinoma


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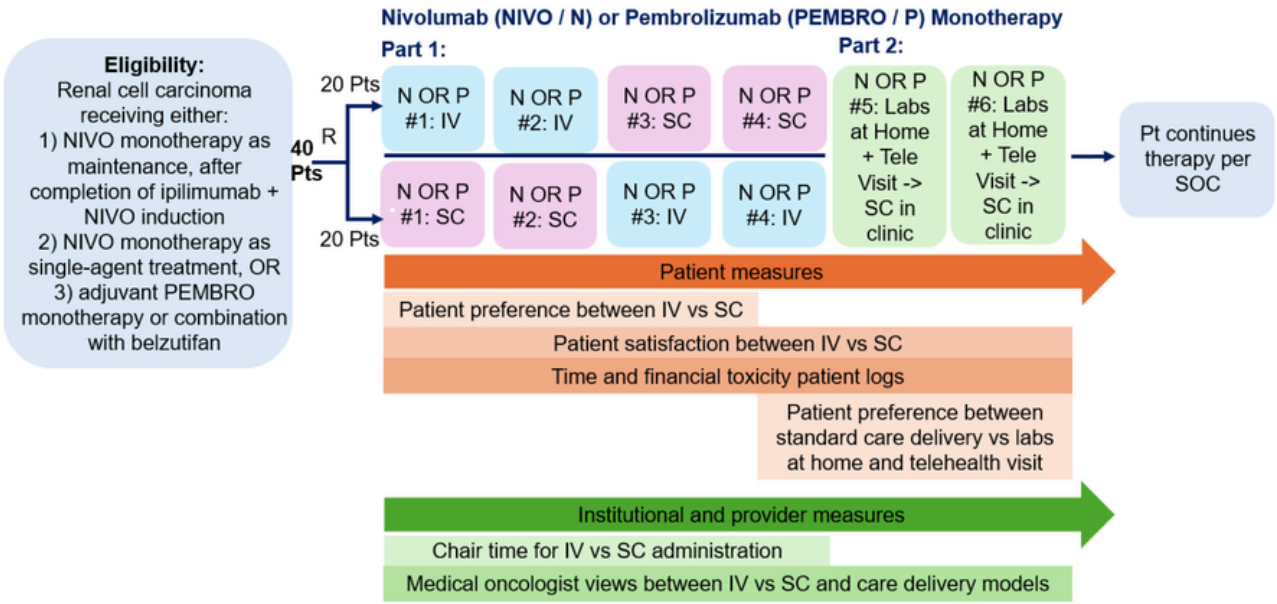
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Background: There has been an increasing appreciation of the "time toxicity" of cancer care for patients with renal cell carcinoma (RCC) – the lost time spent coordinating, waiting, and receiving care. This has sparked a heightened interest in improving care delivery in the clinic and bringing care closer to home with the use of telehealth technology. The approval of subcutaneous immune checkpoint inhibitors (ICI) in RCC provides an opportunity to minimize time burden for patients through shorter in-person visits and provides a research opportunity to investigate novel care delivery models through labs at home and telehealth visits.

Methods: This is a single-institution clinical trial enrolling 40 patients with RCC receiving nivolumab or pembrolizumab as the backbone of approved regimens, on a standard schedule. In Part 1, patients will be randomized to receive their next 2 ICI doses as intravenous versus subcutaneous formulation, followed by 2 doses of the alternative formulation. Patients will complete surveys on time toxicity, treatment satisfaction, and preference between the two formulations. After concluding the 4 ICI doses of Part 1, patients advance to Part 2. Here, they will receive the next 2 ICI doses of the subcutaneous formulation. We will evaluate if obtaining labs at home and conducting a telehealth visit with the oncologist 1-2 days prior to treatment will improve their experience. Patients will complete surveys on time toxicity, treatment satisfaction, and preference for this home-based care delivery model.

Significance / Vision: The approval of subcutaneous ICI therapies presents an opportunity to improve treatment care delivery. There is limited data about patient preferences regarding IV vs SC ICI in the real-world setting. Further, while SC ICI may reduce the time of administration, there is significant wait time associated with lab draws, an in-person visit, and clearance for treatment. We hypothesize that bringing care to the home prior to the day of administration will lessen this burden and improve patient experience.

I1 – Real-World Evidence

REGULAR ABSTRACT

# A RISK-ADAPTED FRAMEWORK FOR ADJUVANT PEMBROLIZUMAB PLUS BELZUTIFAN IN RESECTED CLEAR CELL RENAL CELL CARCINOMA


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## INTRODUCTION

KEYNOTE-564 established adjuvant pembrolizumab over observation for patients at increased risk of recurrence following nephrectomy. LITESPARK-022 demonstrated improved disease-free survival (DFS) with pembrolizumab+belzutifan versus pembrolizumab alone; however, higher toxicity was reported in the combination arm (42.2% versus 17.9% grade ⩾3 adverse events). We sought to estimate the absolute benefit of each adjuvant strategy across baseline recurrence-risk scenarios.

## METHODS

We used pembrolizumab as the common comparator between KEYNOTE-564 and LITESPARK-022 to indirectly estimate the DFS effect of pembrolizumab+belzutifan versus surveillance, assuming that the relative effect of pembrolizumab was sufficiently similar across trial populations. We made this assumption given the two trials' broadly overlapping eligibility criteria and clinical populations. We then translated these relative treatment effects into estimated 24-month DFS across clinically relevant baseline-risk scenarios using the ASSURE nomogram.

## RESULTS

The published DFS hazard ratios from KEYNOTE-564 and LITESPARK-022 were both 0.72. Using pembrolizumab as the common anchor, we chained the two relative treatment effects on the log-hazard-ratio scale, yielding an indirect hazard ratio of 0.52 (95% CI 0.39-0.68) for pembrolizumab+belzutifan versus surveillance. Absolute benefit of adjuvant therapy increased substantially with baseline recurrence risk. Across clinical scenarios, the incremental 24-month DFS benefit of adding belzutifan to pembrolizumab increased from 1.7% in the lowest-risk scenario to 10.3% in the highest-risk scenario (Table). Using a 10% improvement in 24-month DFS as a benchmark, pembrolizumab monotherapy would reach this benefit when baseline DFS with surveillance was approximately 55.1% or lower. The corresponding threshold for pembrolizumab+belzutifan was approximately 77.8% or lower.

| Representative patient characteristics | 24-month DFS with surveillance (%)* | 24-month DFS with pembrolizumab (%) | Absolute benefit with pembrolizumab (%, 95% CI)† | 24-month DFS with pembrolizumab + belzutifan (%) | Absolute benefit with pembrolizumab + belzutifan (%, 95% CI)‡ | Incremental benefit of adding belzutifan (%, 95% CI)§ |
|---|---|---|---|---|---|---|
| Low-risk: 75 y/o F; 4.6cm ccRCC; perinephric fat invasion; grade 3; no sarcomatoid features; no coagulative necrosis; no renal vein involvement; no pathologic nodal involvement; no distant metastasis | 91.2 | 93.6 | 2.4 (1.1 to 3.5) | 95.3 | 4.1 (2.7 to 5.2) | 1.7 (0.8 to 2.6) |
| Intermediate-risk: 70 y/o F; 10.7cm ccRCC; pT3a; grade 2; no sarcomatoid features; no coagulative necrosis; renal vein involvement present; no pathologic nodal involvement; no distant metastasis | 73.5 | 80.1 | 6.6 (3.0 to 9.9) | 85.2 | 11.7 (7.6 to 15.1) | 5.1 (2.3 to 7.6) |
| High-risk: 63 y/o M; 5.0cm ccRCC; grade 4; sarcomatoid features present; no coagulative necrosis; no renal vein involvement; lymph node metastasis present; no distant metastasis | 60.4 | 69.6 | 9.2 (4.1 to 13.9) | 77.0 | 16.6 (10.5 to 21.6) | 7.4 (3.4 to 11.2) |
| Very-high-risk: 48 y/o M; 10.6cm ccRCC; pT3a; grade 4; sarcomatoid features present; coagulative necrosis present; renal vein involvement present; no pathologic nodal involvement; no distant metastasis | 41.4 | 53.0 | 11.6 (5.0 to 18.0) | 63.3 | 21.9 (13.4 to 29.3) | 10.3 (4.6 to 15.8) |

*Baseline 24-month DFS with surveillance was estimated using the ASSURE nomogram. Estimated 24-month DFS with pembrolizumab was calculated using the KEYNOTE-564 DFS hazard ratio for pembrolizumab versus placebo/observation of 0.72. Estimated 24-month DFS with pembrolizumab plus belzutifan was calculated using the indirect hazard ratio for pembrolizumab plus belzutifan versus surveillance of 0.52. Absolute benefit reflects the percentage-point difference compared with surveillance. Incremental benefit reflects the percentage-point difference between pembrolizumab plus belzutifan and pembrolizumab monotherapy.
† Intervals derived from the KEYNOTE-564 disease-free survival hazard ratio of 0.72 (95% CI, 0.59 to 0.87).
‡ Intervals derived from the indirect chained hazard ratio of 0.52 (95% CI, 0.39 to 0.68), obtained by summing the variances of the two component log hazard ratios.
§ Intervals for the incremental benefit are conditional on the pembrolizumab estimate and derived from the LITESPARK-022 hazard ratio of 0.72 (95% CI, 0.59 to 0.87); this contrast corresponds to the directly randomized comparison in LITESPARK-022 and is therefore the least assumption-dependent quantity in the table.
All intervals reflect uncertainty in the hazard ratios only and are conditional on the nomogram-estimated baseline. They do not incorporate uncertainty in the baseline recurrence-risk estimate itself, which is not quantified by the nomogram and which may be substantial, particularly at the extremes of the risk spectrum. ccRCC = clear cell renal cell carcinoma; CI = confidence interval; DFS = disease-free survival.

**Table 1:** Representative patient scenarios and estimated 24-month disease-free survival benefit by adjuvant strategy

## CONCLUSIONS

The absolute benefit of adjuvant therapy depends on individual baseline risk. These findings support a two-step, risk-adapted approach: first determining whether recurrence risk justifies adjuvant therapy, and then whether the additional DFS benefit of belzutifan justifies added toxicity.

I2 – Real-World Evidence

REGULAR ABSTRACT

# Clinical Characteristics and Systemic Therapy in Birt-Hogg-Dubé Patients with Renal Tumors


Purpose: Birt-Hogg-Dubé (BHD) is an inherited cancer predisposition syndrome caused by pathogenic variants (PV) in the FLCN gene and marked by fibrofolliculomas, pulmonary cysts/pneumothorax, and renal tumors. Renal neoplasms occur in approximately one-third of affected individuals, but the clinical characteristics and outcomes of these tumors remain poorly described, especially in the advanced setting. We characterize the clinical presentation of patients with BHD syndrome at our institution who developed renal cell carcinoma.

Methods: We queried an institutional database of patients with cancer who consented to germline sequencing through MSK-IMPACT, a tumor-normal next-generation sequencing platform. Patients with germline PV in FLCN were identified. Patient and tumor characteristics were collected through medical record review.

Results: Among 55,871 cancer patients, 27 (0.048%) had a PV in FLCN diagnostic of BHD. Of these, 9 (33%) were diagnosed with renal tumors (median age 54 years; range 31-71; M:F 2:7) with a median tumor size of 5.5cm. Six (67%) of the patients reported a family history of RCC. Pulmonary cysts were observed in all 9 patients and pneumothorax in 4. Renal tumor histology was heterogeneous, including unclassified, chromophobe, clear cell, hybrid oncocytic/chromophobe, oncocytoma, and epithelioid angiomyolipoma (Table 1). Four patients received systemic therapy. Patient 4 was treated with CTLA4/PD1/TKI (best response stable disease), then progressed on multiple other therapies. Notably, patient 8 (previously reported) had a locally advanced renal tumor, and showed a complete pathologic response after treatment with ipilimumab plus nivolumab.

Conclusion: This case series expands the clinicopathologic spectrum of BHD-associated renal tumors by demonstrating substantial histologic diversity and the potential for aggressive clinical behavior. The complete pathologic response to neoadjuvant immunotherapy in one patient warrants further investigation. These findings support broader histologic characterization and prospective evaluation of systemic treatments for patients with advanced BHD-associated renal tumors.


Table 1. Clinical Presentation of BHD Patients with Renal Tumors

| Pt | Age at diagnosis (years) | Sex | Histology | Size (Largest mass; cm) | Grade/ Variant | Staging at Diagnosis | Tumor NGS | Advanced/ Metastatic Disease | Disposition | Systemic Therapy (best response) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 35 | F | Unclassified | 2.8 | 2 | T1aN0M0 | FLCN | No | Alive; NED | N/A |
| 2 | 54 | F | Unclassified, Eosinophilic | 5.3 | Unknown | T1bN0M0 | No somatic mutations | No | Alive; NED | N/A |
| 3 | 59 | F | Unclassified, Eosinophilic | 5.7; 12 | 4; N/A | T3cN0M0; pT2bNX | KEAP1, KMT2C, RAD52, SDHB, SETD2; AGO2, KMT2A | No | Alive; NED | N/A |
| 4 | 57 | M | Clear Cell | 14.4 | 3 | T3aN1M1 | MET, FLT4, CKN2A/B loss TERT, TRIP13, SDHAN | Yes | Deceased; PD | CTLA4/PD1/TKI (SD) Tivozanib (PD) Cabozantinib (PD) Everolimus (PD) |
| 5 | 33 | M | Oncocytoma | 2.8 | Unknown | T1aNXM0 | No somatic mutations | No | Alive | N/A |
| 6 | 66 | F | Chromophobe, Eosinophilic | 6 | Unknown | TXNXMX | N/A | No | Alive | Bevacizumab (ongoing) |
| 7 | 43 | F | Unclassified, Rhabdoid | 5.5 | 4 | T3aN0M0 | ARID1A, CBL, DOT1L, FLCN, FLT4, HSP90AA1, KDR, NLPR1, STAT6, TNFRSF11A (unmatched) | Yes | Alive | IO+anti-VEGF on clinical trial (ongoing) |
| 8 | 71 | F | Epithelioid Angiomyolipoma | 10 | High | T3N0M0 | N/A | Yes | Alive; NED | Ipilimumab + Nivolumab (CR) |
| 9 | 31 | F | Hybrid oncocytic/ chromophobe | 3.3 | Unknown | T1aNXMX | No somatic mutations | No | Alive; NED | N/A |


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I3 – Real-World Evidence

REGULAR ABSTRACT

# Short-Term Healthcare Utilization Following Percutaneous Thermal Ablation Versus Partial and Radical Nephrectomy for Kidney Cancer: A Real-World Medicare Analysis


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BACKGROUND

Percutaneous thermal ablation (PTA) is a minimally invasive alternative to surgical resection for select patients with kidney cancer. However, comparative real-world data on healthcare utilization remain limited. This study compared index encounter costs, length of stay (LOS), and 30-day inpatient hospitalizations following PTA, partial nephrectomy (PN), and radical nephrectomy (RN) among Medicare beneficiaries.

METHODS

A retrospective cohort study was conducted using the Medicare 5% Standard Analytical Files. Patients aged ⩾65 years with kidney cancer who underwent PTA, PN, or RN from January 1, 2017 to December 1, 2024 with ⩾12 months of continuous Medicare Fee-for-Service enrollment prior to the index procedure were identified. Patient counts were extrapolated to the Medicare Fee-for-Service population using a standard multiplier of 20. Index encounter costs reflected inflation-adjusted Medicare payments from admission through discharge. LOS was calculated as days from admission to discharge. Means were compared using unpaired t-tests and medians using Mann–Whitney tests.

RESULTS

The extrapolated cohort included 25,740 PTA, 41,520 PN, and 71,440 RN patients (mean age, 73.2; mean Charlson Comorbidity Index, 4.6). Mean ± standard deviation costs were lower for PTA ($7,295 ± $18,447) than PN ($13,339 ± $16,696) or RN ($19,558 ± $19,325; both $p<0.01$). Median (interquartile range [IQR]) costs were $6,977 ($3,523-$8,429), $12,146 ($2,218-$16,871), and $15,708 ($12,566-$21,403), respectively (both $p<0.01$). Median (IQR) LOS was 0 (0-0) days for PTA versus 2 (0-3) for PN and 3 (2-5) for RN, and 4.6% of PTA patients had a LOS >1 day compared to 54.4% for PN and 79.7% for RN (all $p<0.01$). Additionally, 30-day inpatient hospitalizations were lower following PTA (6.5%) than PN (9.0%) or RN (9.2%; both $p<0.01$).

CONCLUSION

Among Medicare beneficiaries with kidney cancer, PTA was associated with lower index encounter costs, shorter LOS, and fewer 30-day inpatient hospitalizations than PN or RN, highlighting differences in short-term healthcare utilization across treatment approaches.

I4 – Real-World Evidence

REGULAR ABSTRACT

# Clinical Outcomes of Extended-Interval Pembrolizumab Dosing in Metastatic Renal Cell Carcinoma: A Real-World Analysis from the Canadian Kidney Cancer Information System (CKCis)

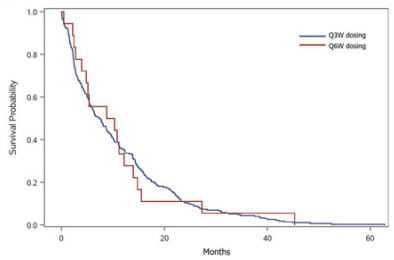

Background: Pembrolizumab in combination with Axitinib or Lenvatinib is a standard first-line treatment option for metastatic renal cell carcinoma (mRCC) following the demonstration of superior efficacy over sunitinib in the pivotal KEYNOTE-426 and CLEAR trials. The conventional pembrolizumab dosing schedule of 200mg every 3 weeks (Q3W) was based on these clinical trials, whereas the alternative 400mg every 6 weeks (Q6W) was subsequently approved across tumor types based primarily on pharmacokinetic analyses, supported by findings from KEYNOTE-555. However, real-world data evaluating the effectiveness of Q6W in mRCC remain scarce. Using the Canadian Kidney Cancer Information System (CKCis), we compared clinical outcomes between Q6W and conventional Q3W pembrolizumab dosing in combination with Axitinib or Lenvatinib.

Methods: Patients with mRCC treated with first-line pembrolizumab plus Axitinib or Lenvatinib were identified from CKCis. The primary endpoint was IMDC-adjusted progression-free survival (PFS). Secondary endpoints included time-to-treatment failure (TTF) and overall survival (OS).

Results: A total of 535 patients were evaluated. Of these, 495 patients were treated with Q3W dosing and 40 patients were treated with Q6W dosing. In the Q3W and Q6W cohorts, pembrolizumab/axitinib was used in 428 patients (86.5%) and 22 patients (55.0%), respectively, while pembrolizumab/lenvatinib was used in 67 patients (13.5%) and 18 patients (45.0%), respectively. For primary endpoint, the IMDC-adjusted hazard ratio (HR) for progression for Q6W administration was 0.93 (95% CI 0.56-1.53; p=0.764), suggesting no statistically significant difference in PFS between dosing intervals. Similarly, no significant difference in IMDC-adjusted TTF was observed (HR 1.20, 95% CI 0.79-1.82; p=0.385). In contrast, adjusted OS favored the Q6W cohort, with an HR of 4.15 (95% CI 1.32-12.99; p=0.015) for Q3W relative to Q6W. However, these findings should be interpreted with considerable caution given treatment regimen imbalance and the small sample size of the Q6W cohort.

Conclusion: No statistically significant differences in PFS or TTF were detected between Q6W and Q3W pembrolizumab dosing in this multicenter real-world CKCis cohort. The observed OS difference should be interpreted cautiously given the small Q6W cohort, shorter follow-up, and treatment regimen imbalance. Further follow-up and larger cohorts are needed to clarify outcomes with Q6W dosing.


**Figure 1.** Kaplan–Meier estimates of IMDC-adjusted progression-free survival according to pembrolizumab dosing schedule (Q3W vs Q6W).





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I5 – Real-World Evidence

REGULAR ABSTRACT

# Real-world effectiveness and tolerability of first-line cabozantinib + nivolumab (CaboNivo) in patients with bone metastases (BM): CaboCombo post-hoc analysis


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First-line CaboNivo is approved for advanced renal cell carcinoma (aRCC), having demonstrated improved overall survival (OS) versus sunitinib in CheckMate 9ER (CM9ER; NCT03141177). BM are common in RCC; in CM9ER, 24.4% of patients had BM, and median progression-free survival (PFS) with CaboNivo was 13.8 (95% CI: 8.3–20.1) months.1

CaboCombo (NCT05361434) is a prospective, real-world study of first-line CaboNivo in adults with clear-cell aRCC. This post hoc analysis assessed effectiveness and tolerability in patients with BM.

Of 311 patients enrolled, 101 (32.5%) had baseline BM. Patients with or without BM showed similar baseline characteristics; ECOG PS 2–3 was more common in patients with BM (Table). In patients with and without BM, 18-month OS rates were 63.0% (95% CI: 52.0–72.0%) and 80.0% (74.0–85.0%), respectively; ORRs were 49.4% (38.4–60.5%) and 67.7% (60.6–74.2%). Median PFS was similar between groups (13.5 [9.1–17.3] vs 14.3 [12.2–16.8] months), as were other outcomes (Table). Patients with BM had more severe baseline pain and reported significant pain reductions due to treatment from baseline to month 13 (mean NPRS change: –1.2 [95% CI: –2.3, –0.2]; p=0.0264), whereas those without BM did not (0.3 [–0.2, 0.8]; p=0.2991). Similarly, disease-related symptom scores significantly improved in patients with BM (p=0.0378) but not in those without (p=0.7759). AE rates were similar between groups (Table).

In this real-world study, a greater proportion of patients had baseline BM than in CM9ER. CaboNivo was effective regardless of BM status, with PFS consistent with the CM9ER BM subgroup. Significant improvements in pain and disease-related symptoms were observed in patients with BM, with no new safety signals.


Apolo A. et al. J Clin Oncol 2026, 44(suppl 16); abstract 4528.


| | With BM (n = 101) | Without BM (n = 210) |
|---|---|---|
| Age, yr, median (IQR) | 67.0 (58.0—73.0) | 67.0 (60.0–74.0) |
| Male, n (%) | 71 (70.3) | 154 (73.3) |
| ECOG PS 2–3, n (%) | 19 (21.4) | 15 (8.2) |
| IMDC intermediate/poor risk, n (%) | 59 (83.1) | 104 (78.2) |
| Prior nephrectomy, n (%) | 51 (50.5) | 127 (60.5) |
| **Other effectiveness outcomes** | | |
| Disease control rate, % (95% CI) | 89.4 (80.8–95.0) | 92.8 (88.2–96.0) |
| Duration of response, mo, median, (95% CI) | 19.6 (13.3–23.2) | 17.2 (12.6–24.0) |
| Time to response, mo, median (IQR) | 3.2 (2.7–3.9) | 3.0 (2.5–4.0) |
| **Safety** | | |
| Any TEAE, n (%) | 95 (94.1) | 205 (97.6) |
| Serious TEAE, n (%) | 46 (45.5) | 92 (43.8) |
| Cabo- or Nivo-related TEAE, n (%) | 89 (88.1) | 193 (91.9) |
| Grade 3/4 Cabo- or Nivo-related TEAE, n (%) | 42 (41.6) | 89 (42.4) |
| Any TEAE associated with BM, n (%) | 22 (21.8) | 15 (7.1) |
| **Treatment patterns** | | |
| CaboNivo duration, mo, median (IQR) | 12.6 (5.3–20.4) | 16.4 (7.6–22.1) |
| Cabo reduction, n (%) | 57 (57.0) | 140 (67.3) |
| Cabo interruption, n (%) | 72 (72.0) | 158 (76.0) |
| Cabo discontinuation, n (%) | 78 (78.0) | 136 (65.4) |
| Owing to AEs, n (%) | 40 (51.3) | 64 (47.1) |
| Owing to disease progression, n (%) | 23 (29.5) | 41 (30.1) |
| Nivo discontinuation, n (%) | 79 (79.0) | 147 (70.7) |

AE, adverse event; BM, bone metastases; Cabo, cabozantinib; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IQR, interquartile range; mo, months; Nivo, nivolumab; TEAE, treatment-emergent adverse event; yr, years

16 – Real-World Evidence

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REGULAR ABSTRACT

# Real world evidence of belzutifan use in patients with Von Hippel-Lindau (VHL) disease

Background:
Belzutifan, a HIF-2α inhibitor, is FDA-approved for VHL-associated renal cell carcinoma (RCC), central nervous system hemangioblastomas (CNS-Hb), and pancreatic neuroendocrine tumors. Extending an earlier 2016-2023 analysis, this refreshed data cut characterized real-world use of belzutifan and tumor reduction procedure (TRP) rates in VHL patients.

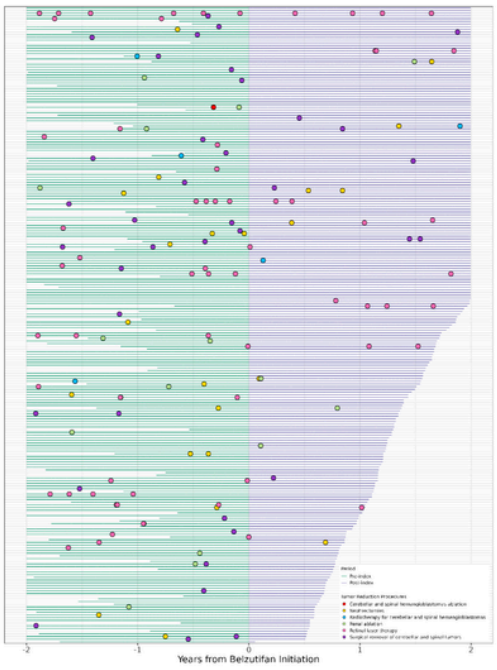
Methods:
This retrospective cohort study used administrative claims from Komodo Research Data (January 2016 – September 2025), selecting adult VHL patients who filled first belzutifan prescription (index date) on or after August 2021. Time on belzutifan was estimated using Kaplan-Meier analysis. Per person-month TRP counts across the 24 months preceding and following index were compared using generalized linear mixed models with random effects, adjusted for key variables.

Results:
The analysis included 237 patients; mean age 40.9 [SD 14.5] years, 53.6% female, and 54.4% white. Median follow-up was 21.9 months. More than 1 VHL-associated tumor was observed in 83. 5% patients with the most commontumor being RCC (67.5%), followed by CNS-Hb (44.3%) and pheochromocytomas (21.1%); CNS-Hb and RCC co-occurred in 30.4%. Using a ⩾90-day gap to define treatment break, median time on belzutifan was not reached, with 60.1% of patients remaining on belzutifan at 24 months. Among those with a break, 46.4% reinitiated belzutifan after a median of 4.7 months.

Post-index date, the rate for any TRP declined by 58% (adjusted incidence rate ratio [95% CI] 0.42 [0.30, 0.59], p<0.01), with 70% and 46% reductions in surgery for cerebellar/spinal hemangioblastomas (p<0.01) and retinal laser therapy (p<0.05), respectively. The figure shows pre- and post-index TRP distributions.

Conclusions:
In this larger, longer-horizon cohort, belzutifan continued to demonstrate high treatment persistence and lower rates of tumor reduction procedures following initiation. These findings add to the real-world evidence of belzutifan's effectiveness in managing VHL disease.

**Figure: Distribution of all TRPs During the 2-Year Periods Before and After Belzutifan Initiation for Individual Patients**



I7 – Real-World Evidence

REGULAR ABSTRACT

# Patient Characteristics and Survival Outcomes of Early-Stage Relapsed, Metastatic Renal Cell Carcinoma

Background: The standard of care for clinically localized renal cell carcinoma (RCC) remains surgical resection, followed by consideration of adjuvant pembrolizumab for high-risk cases. Many predictive models exist to predict postoperative recurrence, though patients (pts) with early-stage RCC are thought to have low recurrence rates. We describe characteristics and outcomes of pts with initially early-stage RCC who relapsed with metastatic disease.

Methods: A prospectively maintained RCC database at Indiana University was queried for pts with localized, either stage I or II, RCC who were treated with surgery (partial or radical nephrectomy) and later had relapse with metastatic disease. Baseline characteristics, including disease characteristics and genomic alterations identified by NGS, were summarized. The Kaplan-Meier method was used to analyze progression-free survival (PFS) and overall survival (OS).

Results: 38 pts were included. Histology was 71.1% clear cell, 10.5% chromophobe, 7.8% papillary, 5.3% mixed, and 5.3% unclassified. Rhabdoid/sarcomatoid features were present in 10.6% of pts. Pathologic T staging was T1 in 65.8% and T2 in 34.2%. IMDC risk was good in 47.4% of pts, intermediate in 50%, and unknown in 2.6%. Fuhrman grade was 4 in 3.4%, 3 in 4.2%, 2 in 47.4%, 1 in 2.6%, and unknown in 42.4%. Metastasis sites included lung 52.6%, regional lymph nodes (LN) 36.8%, bone 36.8%, distant LN 23.7%, liver 15.8%, and brain 10.5%. Most common genomic alterations included VHL 50.0%, PBRM1 34.2%, TP53 21.1%, SETD2 18.4%, and PTEN 10.5%. 2-year PFS was 20.2% and 2-year OS was 82.4%.

Conclusion: In this cohort, almost two-thirds of pts had initially T1 resected disease. The majority of pts had Fuhrman grade 2 disease, and there was a surprisingly low rate of sarcomatoid/rhabdoid features. 2-yr OS was high, likely reflective of slower disease biology.

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J1 – Surgery & Localized Interventions

REGULAR ABSTRACT

# Clinical Features, Genomic Alterations, and Outcomes of Patients Undergoing Cytoreductive Nephrectomy for Renal Cell Carcinoma


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Background: In the era of targeted therapies (TT) and immune checkpoint inhibitors (ICI) for metastatic renal cell carcinoma (RCC), cytoreductive nephrectomy (CN) may improve survival compared to systemic therapy alone, particularly for IMDC favorable and intermediate-risk patients. The prognostic implications of genomic biomarkers for CN are less studied. Here, we describe the clinical features, genomic alterations, and outcomes of patients with metastatic RCC undergoing CN.

Methods: A prospectively maintained RCC database at Indiana University was queried for patients with metastatic RCC who underwent CN. Baseline characteristics, including disease characteristics and genomic alterations identified by next-generation sequencing, were summarized. Kaplan-Meier method was used to analyze progression-free survival (PFS) and overall survival (OS), using the log-rank test to compare groups.

Results: 47 patients were included. The most common sites of metastasis were lungs (74.5%), regional LNs (42.6%), and bone (42.6%). Sarcomatoid features were present in 17 patients (36.2%) and rhabdoid in 13 patients (27.7%). 13 patients (27.7%) had IMDC poor-risk disease. Most patients received first-line systemic therapy with an IO-IO (n=15, 31.9%) or IO-tyrosine kinase inhibitor (TKI) (n=13, 27.7%). The most common genomic alterations were VHL (n=31, 66.0%), PBRM1 (n=17, 36.2%), SETD2 (n=13, 27.7%), and BAP1 (n=10, 21.3%). Median PFS and OS were 0.8 yr (0.5-1.1) and 3.6 yr (2.7-7.3), respectively. There were no significant differences in PFS or OS for the most common genomic alterations.

Conclusion: In this cohort of patients with metastatic RCC undergoing CN, median OS was 3.6 yrs with most patients receiving first-line systemic therapy of IO-IO or IO-TKI. A significant proportion had sarcomatoid or rhabdoid features and/or poor-risk disease. Survival did not differ based on genomic alteration. Further data is needed to determine prognostic implications of genomic alterations for CN.

J2 – Surgery & Localized Interventions

REGULAR ABSTRACT

# KEYNOTE-564 Criteria Provide Less Prognostic Discrimination Than Multilevel Risk Models After Nephrectomy for Renal Cell Carcinoma

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Background: Adjuvant treatment decisions after nephrectomy for renal cell carcinoma (RCC) increasingly use the KEYNOTE-564 inclusion criteria. These criteria select patients for treatment but were not developed for individualized prognostication. We compared their prognostic discrimination with established and exploratory risk models in a tertiary referral-center cohort.

Methods: We retrospectively analyzed surgically treated, nonmetastatic RCC in a prospective longitudinal institutional database. Metastasis-free/disease-free survival (MFS/DFS) was measured from surgery to first documented postoperative metastasis; patients without metastasis were censored at last follow-up. Death without documented metastasis was not an event. In an identical complete-case cohort, we compared binary KEYNOTE-564-oriented risk status, the continuous Leibovich 2003 score, and an exploratory Cox-oriented score incorporating tumor size, pathological T and N stage, grade/sarcomatoid differentiation, and favorable histology (Munich Score). Discrimination was quantified using Harrell's C-index. Internal validation comprised 50 repetitions of stratified 10-fold out-of-fold cross-validation and 1,000 bootstrap resamples.
Results: The comparison included 580 patients and 154 MFS/DFS events. Apparent C-indices were 0.684 (95% confidence interval [CI], 0.646–0.722) for KEYNOTE-564-oriented classification, 0.756 (95% CI, 0.715–0.797) for Leibovich, and 0.763 (95% CI, 0.725–0.802) for the Munich score. Mean out-of-fold C-indices were 0.676, 0.749, and 0.751, respectively. The optimism-corrected C-index of the Munich score was 0.762. Its apparent advantage over Leibovich was 0.007; the bootstrap 95% CI for this difference was −0.013 to 0.034. The proportional-hazards assumption was violated for KEYNOTE-oriented risk status.

Conclusions: KEYNOTE-564-oriented criteria had lower prognostic discrimination than Leibovich and the exploratory multivariable score. Trial-derived treatment eligibility should not be used as a stand-alone prognostic system in high-risk RCC. Established multilevel scores provide finer recurrence-risk stratification, while the exploratory model requires independent external validation.

K1 – Survivorship

REGULAR ABSTRACT

# Outcomes of Involuntary Active Surveillance for Small Renal Masses


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Background
Active surveillance (AS) has become an accepted management strategy for selected patients with small renal masses (SRMs), particularly elderly patients and those with significant competing comorbidity. We evaluated patient characteristics, tumor kinetics, surveillance patterns, and clinical outcomes in a contemporary institutional cohort of patients experiencing involuntary AS (iAS) due to missed or underreported findings on imaging.

Methods
A retrospective analysis was performed using a prospectively maintained institutional renal mass database including patients in whom previous abdominal imaging could have been retrieved at baseline presentation for the evaluation of a newly detected renal mass. Patient demographics, histology, baseline tumor characteristics, serial imaging measurements, surveillance intervals, duration of follow-up, and reasons for discontinuation of involuntary iAS were analyzed. Continuous variables are reported as median and interquartile range (IQR), and categorical variables as frequencies and percentages.

Results
A total of 177 patients underwent iAS for localized renal masses. Median age was 68.2 years (range 30.3–90.7), and 67% were male. Median baseline tumor diameter was 2.0 cm (range 0.0–8.9). Histologic confirmation was available in 18% of patients. Among biopsied lesions, benign pathology predominated, including angiomyolipoma (8.5%) and oncocytoma (4.0%), while clear-cell and papillary renal cell carcinoma accounted for 3.4% and 1.1% of the cohort, respectively. Most patients (82%) continued iAS without tissue diagnosis.

Among patients with evaluable serial imaging, median tumor diameter increased from 1.8 cm (range 0.3–8.9) at baseline to 2.2 cm (range 0.4–9.5) at last follow-up. Median tumor growth rate was 1.25 mm/year (range −4.8 to 24.7 mm/year), demonstrating slow growth in the majority of lesions. One year after enrollment (9–15 months), 76.7% demonstrated <20% tumor growth from baseline.
Median follow-up was 9.4 months (range 0.0–250.3). The median surveillance interval was 12 months (range 6–24). Seventeen patients (9.7%) discontinued AS and underwent definitive treatment, while the remainder continued surveillance.
Estimated intervention-free survival was 92.9% at 1 year, 91.5% at 3 years, and 76.2% at 5 years. Median intervention-free survival was not reached.
At last follow-up, 91% of patients remained on iAS. Conversion to active treatment occurred infrequently and consisted primarily of stereotactic radiosurgery (n=9) and surgery (n=6).

Conclusions
Involuntary Active surveillance for SRMs was associated with slow tumor growth. More than 90% of patients opted to remain intervention-free through 3 years, supporting AS as an effective management strategy for appropriately selected patients. Longer follow-up will further define long-term oncologic outcomes and identify clinical predictors of progression requiring intervention.

L1 – Therapeutics

REGULAR ABSTRACT

# Darlifarnib+cabozantinib in renal cell carcinoma (RCC): Updated FIT-001 Ph1a results


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VEGFR- and IO-targeted therapies for metastatic RCC have limitations, and disease progression remains common, highlighting the need for effective, well-tolerated combination strategies. Darlifarnib–a potent next-generation farnesyl transferase inhibitor–blocks RHEB farnesylation to selectively inhibit mTORC1 while sparing mTORC2. Here, we report safety and preliminary antitumor activity of darlifarnib+cabozantinib from the FIT-001 Ph1a RCC cohort.

FIT-001 (NCT06026410) is an ongoing, first-in-human, multicenter, open-label, Ph1a/b study evaluating darlifarnib in advanced solid tumors. In the Ph1a RCC cohort, darlifarnib 3, 5, or 8mg QD was administered (Days 1–7, 15–21) with cabozantinib 40 or 60mg QD. Primary objectives: safety/tolerability; secondary: preliminary antitumor activity, PK.

As of 25-March-2026, 72 RCC (58 clear cell [cc]RCC) patients received darlifarnib+cabozantinib in Ph1a; median age: 67y (range 24–83), 76% male, 75% White. 53% of patients had ⩾2 prior lines (65% IO+TKI, 38% cabozantinib). Darlifarnib+cabozantinib was well-tolerated; any-Gr TEAEs (⩾25% incidence): diarrhea (64%), fatigue (50%), neutropenia (47%), nausea (43%). The only Gr⩾3 TEAE in ⩾10% of patients was neutropenia (36%). Darlifarnib-related TRAEs led to darlifarnib discontinuations in 3% of patients. Median follow-up in all RCC patients: 7.8 months (range 0.9–19.2); 30 patients (42%) remained on treatment. Antitumor activity was observed across dose levels (Table). In cabozantinib-naive ccRCC patients receiving darlifarnib 5 or 8mg+cabozantinib 60mg, ORRs were 33%–50%. 6/19 response-evaluable ccRCC patients with prior cabozantinib exposure responded to the combination; 3/6 responders had immediate prior cabozantinib exposure. Across all RCC patients, darlifarnib exposure was approximately dose-proportional and similar to monotherapy. Additional data, including a TKI-exposed patient vignette, will be presented.

Darlifarnib+cabozantinib was well-tolerated with a manageable safety profile. Encouraging antitumor activity was seen in cabozantinib-naive and -exposed ccRCC. These results support further evaluation of the combination in cabozantinib-naive ccRCC patients in Ph1b, which is ongoing/enrolling.


**Table. Antitumor activity in response-evaluable[a] patients with ccRCC**

| n (%) [95%CI] | Cabozantinib 40 mg | | | Cabozantinib 60 mg[b] | | |
|---|---|---|---|---|---|---|
| | Darlifarnib 3 mg n=8 | Darlifarnib 5 mg n=7 | Darlifarnib 8 mg n=6 | Darlifarnib 3 mg n=10 | Darlifarnib 5 mg n=10 | Darlifarnib 8 mg n=12 |
| **ORR (CR+PR+uPR)** | 2 (25) [3.2–65.1] | 2 (29) [3.7–71.0] | 2 (33) [4.3–77.7] | 3 (30)[c] [6.7–65.2] | **5 (50)[d]** [18.7–81.3] | **4 (33)** [9.9–65.1] |
| Cabozantinib-naive, n/N (%) | 0/1 [0–97.5] | 1/1 (100) [2.5–100] | 1/4 (25) [0.6–80.6] | 1/6 (17)[e] [0.4–64.1] | **5/10 (50)[d]** [18.7–81.3] | **4/12 (33)** [9.9–65.1] |
| Cabozantinib-exposed, n/N (%) | 2/7 (29) [3.7–71.0] | 1/6 (17) [0.4–64.1] | 1/2 (50) [1.3–98.7] | 2/4 (50)[e] [6.8–93.2] | - | - |
| **DCR (CR+PR+uPR+SD)** | 7 (88) [47.3–99.7] | 7 (100) [59.0–100] | 5 (83) [35.9–99.6] | 8 (80)[c] [44.4–97.5] | 8 (80)[d] [44.4–97.5] | 12 (100) [73.5–100] |
| **Median DOR**, months | 8.4 [5.7–NE] | NE [3.7-NE] | NE [NE–NE] | NE [NE–NE] | NE [6.2–NE] | NE [3.4–NE] |

[a]Response-evaluable patients had ≥1 post baseline scan. [b]Cabozantinib 40 mg cohorts were enrolled before cabozantinib 60 mg cohorts. [c]Includes 2 uPRs pending confirmatory scan. [d]Includes 1 uPR due to withdrawal of consent due to non-related adverse event. [e]Includes 1 uPR pending confirmatory scan.
ccRCC, clear cell renal cell carcinoma; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; NE, not evaluable; ORR, objective response rate; PR, partial response; SD, stable disease, uPR, unconfirmed partial response.

L2 – Therapeutics

REGULAR ABSTRACT

# Efficacy and safety of cabozantinib plus nivolumab (C+N) versus sunitinib (SUN) by baseline liver metastasis status in patients with advanced renal cell carcinoma (aRCC)


Background: In the phase 3 CheckMate 9ER trial in patients with previously untreated aRCC, C+N significantly improved progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) compared with SUN, including in patients with baseline liver metastases. Exploratory analyses further evaluated outcomes in patients without liver metastases and those with liver and concomitant metastatic sites.

Methods: In CheckMate 9ER, patients with aRCC were randomized 1:1 to cabozantinib (40 mg QD) plus nivolumab (240 mg Q2W) or SUN (50 mg QD; 4 weeks of 6-week cycles). In this exploratory analysis, PFS, OS, ORR, time to response, duration of response (DOR), and safety were evaluated in patients with or without liver metastases at baseline and in patients with concomitant liver plus bone or lung metastases.

Results: Of 651 randomized patients, 129 (20%) had baseline liver metastases. Baseline characteristics were generally consistent between treatment arms and across liver metastasis subgroups. With a median follow-up of 67.6 months, the ORR was higher, and PFS, OS, and DOR were prolonged with C+N versus SUN in both liver metastasis subgroups. Although liver metastases were associated with poorer clinical outcomes, the benefit of C+N versus SUN was consistent across all subgroups (Table). The safety profile of C+N was similar regardless of liver metastasis status. In patients with and without liver metastases, the median daily dose of cabozantinib was 31.8 mg and 26.3 mg, respectively.

Conclusions: First-line C+N improved efficacy outcomes versus SUN regardless of liver metastasis status, including in patients with liver plus bone or lung metastases. The safety profile of C+N was consistent among patients with and without liver metastases, with no increase in hepatotoxicity.


**Table. Efficacy/safety by sites of metastases**

| | Patients with liver metastases[a] | | Patients without liver metastases | | Patients with liver and bone metastases | | Patients with liver and lung metastases | |
|---|---|---|---|---|---|---|---|---|
| | C+N (n=73) | SUN (n=56) | C+N (n=250) | SUN (n=272) | C+N (n=15) | SUN (n=17) | C+N (n=46) | SUN (n=43) |
| **ORR, %** | 52[b] | 21[b] | 57 | 29 | 40 | 18 | 52 | 23 |
| CR, % | 10 | 2 | 15 | 5 | 7 | 0 | 9 | 2 |
| PR, % | 42 | 20 | 42 | 24 | 33 | 18 | 43 | 21 |
| SD, % | 21 | 27 | 36 | 44 | 20 | 18 | 22 | 28 |
| PD, % | 14 | 27 | 4 | 12 | 20 | 47 | 17 | 30 |
| UTD, % | 14 | 25 | 3 | 15 | 20 | 18 | 9 | 19 |
| **mTTR, mo** | 2.8 | 4.0 | 2.8 | 5.4 | 2.9 | 3.0 | 2.8 | 3.5 |
| **mDOR, mo** | 20.7 | 17.8 | 22.1 | 15.2 | 12.6 | 6.4 | 23.1 | 15.8 |
| **mPFS, mo** | 10.9[b] | 6.2[b] | 18.4 | 9.2 | 6.9 | 3.8 | 9.1 | 4.1 |
| HR (95% CI) | 0.55 (0.37–0.82)[b] | | 0.59 (0.48–0.71) | | 0.77 (0.33–1.76) | | 0.50 (0.32–0.80) | |
| **mOS, mo** | 37.6[b] | 22.1[b] | 49.5 | 39.7 | 20.9 | 12.7 | 40.1 | 13.4 |
| HR (95% CI) | 0.65 (0.43–0.97)[b] | | 0.83 (0.66–1.03) | | 0.57 (0.26–1.24) | | 0.49 (0.30–0.79) | |
| **Grade 3/4 TRAEs, %** | 68 | 55 | 68 | 55 | — | | | |

[a]Seven patients had liver-only disease (C+N, n=2; SUN, n=5), precluding meaningful analysis of this subgroup.
[b]As reported in Motzer R, et al. *Ann Oncol* 2026;37:33–43.
**C+N**, cabozantinib plus nivolumab; **CI**, confidence interval; **CR**, complete response; **HR**, hazard ratio; **mDOR**, median duration of response; **mo**, months; **mOS**, median overall survival; **mPFS**, median progression-free survival; **mTTR**, median time to response; **ORR**, objective response rate; **PD**, progressive disease; **PR**, partial response; **SD**, stable disease; **SUN**, sunitinib; **TRAE**, treatment-related adverse event; **UTD**, unable to determine.


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L3 – Therapeutics

REGULAR ABSTRACT

# XmAb819, a novel ENPP3 x CD3 bispecific, in advanced clear cell renal cell carcinoma (ccRCC): Interim Phase 1 results


Background

Advanced ccRCC lacks differentiated options beyond immune checkpoint inhibition (ICI), VEGFR-TKIs, and HIF2α inhibition. XmAb819 (ENPP3 x CD3) is a mechanistically novel 2+1 bispecific antibody engineered for tumor-selective T-cell engagement via the tumor-associated antigen ENPP3, which is highly expressed in ccRCC and minimally in normal tissues.

Methods

XmAb819-01 (NCT05433142) is a Phase 1 multicenter study in patients with advanced ccRCC previously treated with ⩾1 ICI and ⩾1 VEGFR-TKI. XmAb819 was given intravenously (IV) with weekly priming, then Q2W from Cycle 2 until progression or unacceptable toxicity. Adverse events (AEs) were graded per CTCAE v5.0, cytokine release syndrome (CRS) per ASTCT, and efficacy assessed per RECIST v1.1.

Results

As of 02-Apr-2026, 101 patients received XmAb819 IV; median age 61 years, median 3 prior lines (range, 1-10), 60% with ⩾2 prior VEGFR-TKIs, 34% prior HIF2α inhibitor. Among patients treated at the target dose range (n=60), objective response rate (ORR, including unconfirmed) was 27% and disease control rate (DCR) 68%; ORR and DCR were consistent in subgroups receiving ⩾2 prior VEGFR-TKIs (n=33; 30%, 73%) and prior HIF2α inhibitor (n=23; 26%, 70%). Fifteen of 16 responders remained on treatment at the data cutoff, with median follow-up of 21 weeks (range, 7-87). In the safety population (n=101), Grade ⩾3 treatment-related AEs occurred in 61% of patients, AEs led to discontinuation in 7%, and there were no Grade 5 events. ENPP3 was expressed in >95% of tumor samples, and tumor regression was observed across all expression levels.

Conclusions

XmAb819 showed meaningful antitumor activity in heavily pretreated ccRCC, including after HIF2α inhibition. AEs were manageable and did not prevent delivery of active target doses. These data support continued development in ccRCC and other ENPP3-expressing tumors.



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L4 – Therapeutics

REGULAR ABSTRACT

# Characterization and Clinical Development of PF-08634404, a Tetravalent PD-1/VEGF Bispecific Antibody, in Locally Advanced or Metastatic Renal Cell Carcinoma (la/mRCC)


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PF-08634404 is an investigational tetravalent anti–PD-1/VEGF bispecific antibody designed to simultaneously inhibit PD-1-mediated T-cell dysfunction and VEGF-A-driven angiogenesis and immune suppression. Preclinical studies demonstrated simultaneous nanomolar binding to PD-1 and VEGF-A, showing more potent and deeper VEGF inhibition than relevant benchmarks, and the same or superior for PD-1 inhibition. Cooperative binding enhanced target engagement through VEGF-mediated multimerization, increasing PD-1 avidity (>100-fold), receptor internalization, and functional inhibition of PD-1 (>10-fold). This differentiates PF-08634404 from anti–PD-1 and VEGF inhibitor combinations as it may enhance antitumor activity and minimize toxicity.

RCC is characterized by an immunogenic tumor microenvironment and frequent activation of angiogenic pathways. Therefore, combining immune checkpoint blockade with VEGF pathway inhibition is a rational therapeutic approach. Phase 1 and 2 studies of PF-08634404 have demonstrated encouraging antitumor activity with a manageable safety profile in solid tumors. Based on this and the potential for improved efficacy and safety, PF-08634404 is being evaluated in la/mRCC.

Symbiotic-GU-08 (NCT07227415) is an ongoing phase 1b/2, three-cohort study evaluating PF-08634404 as monotherapy or in combination with ipilimumab (anti–CTLA-4) or axitinib (VEGF tyrosine kinase inhibitor) in ≈224 adults with untreated la/mRCC. Patients included must have measurable disease (RECIST 1.1), ECOG PS 0/1, and no prior systemic therapy for la/mRCC (except adjuvant immunotherapy if given >12 months prior enrollment). Patients excluded include those at risk of VEGF inhibition-associated toxicity or with active central nervous system disease. Study treatments and endpoints are shown in the Table. The study is open for enrollment.


| Cohort | A (n≈40) | B[b] (n≈92) | C[b,c] (n≈92) |
|---|---|---|---|
| Regimens[a] | PF-08634404 | PF-08634404 + ipilimumab[d] | PF-08634404 + axitinib |
| Primary endpoints | • Investigator-assessed objective response rate<br>• Safety<br>• Dose-limiting toxicities (dose escalation only; Cohorts B and C) | | |
| Secondary endpoints | • Investigator-assessed duration of response<br>• Investigator-assessed progression-free survival<br>• Overall survival<br>• Laboratory abnormalities<br>• Pre- and post-dose PF-08634404 concentration<br>• Incidence of antidrug antibodies | | |

Q3W, every 3 weeks.
[a]Treatment until investigator-assessed progression (RECIST 1.1), intolerable toxicity, or other protocol-specified criteria for discontinuation.
[b]Cohorts B and C comprise a dose-escalation part with PF-08634404, starting at 5 mg/kg Q3W (Bayesian Optimal Interval design to guide escalation to 10 mg/kg Q3W; N≈3-6 patients/dose level) and a dose-optimization/-expansion part (≈40 patients/dose level; randomized 1:1, stratified by the International Metastatic RCC Database Consortium score).
[c]Initiated after ≥12 patients in Cohort A complete 1 treatment cycle and safety review.
[d]For the first 4 cycles.

L6 – Therapeutics

TRIALS IN PROGRESS ABSTRACT

# Belzutifan plus zanzalintinib versus belzutifan for advanced renal cell carcinoma (RCC) during or after anti–PD-(L)1 and VEGF-TKI therapy: Phase 3 LITESPARK-034 study


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Background: Despite treatment advances for advanced RCC, an unmet need remains to improve outcomes for patients who progress after anti–PD-(L)1 and VEGF-TKI therapy. Belzutifan is a potent, selective hypoxia-inducible factor 2α inhibitor approved for treatment of patients with advanced clear cell RCC following a PD-(L)1 inhibitor and VEGF-TKI therapy (US: 1 prior VEGF-TKI; EU: ⩾2 prior VEGF-TKIs). Zanzalintinib is a multitargeted kinase inhibitor of VEGF receptors, MET, and TAM kinases. The randomized, double-blind, phase 3 LITESPARK-034 study (NCT07489495) is designed to evaluate the efficacy and safety of belzutifan plus zanzalintinib versus belzutifan in participants with advanced clear cell RCC who experienced recurrence during or after anti–PD-(L)1 and VEGF-TKI therapy.

Trial design: Eligible participants are aged ⩾18 years with histologically confirmed diagnosis of unresectable, advanced RCC with clear cell component with or without sarcomatoid features and measurable disease per RECIST v1.1 by investigator assessment, who received ⩽3 prior systemic regimens (including only 1 prior anti–PD-[L]1 therapy) and experienced disease progression during or after having received both anti–PD-(L)1 (⩾2 doses) and VEGF-TKI therapy for metastatic disease. Approximately 758 participants will be randomly assigned 1:1 to receive belzutifan 120 mg orally once daily plus zanzalintinib 60 mg orally once daily or belzutifan 120 mg orally once daily plus placebo. Treatment will continue until unacceptable toxicity or disease progression. Randomization will be stratified according to International Metastatic RCC Database Consortium risk (favorable vs intermediate vs poor), number of prior TKIs (1 vs 2-3), and prior cabozantinib (yes vs no). Primary end points are progression-free survival per RECIST v1.1 by blinded independent central review (BICR) and overall survival. Key secondary end point is objective response per RECIST v1.1 by BICR. Secondary objectives include duration of response per RECIST v1.1 by BICR and evaluating safety and tolerability of belzutifan plus zanzalintinib.

L7 – Therapeutics

TRIALS IN PROGRESS ABSTRACT

# Modulation of the Bone Immune Microenvironment by Cabozantinib plus Nivolumab in Bone-Metastatic Clear Cell Renal Cell Carcinoma: Proof of Concept Study

Background: Bone metastases (BM) in clear cell renal cell carcinoma (RCC) carry a high risk of skeletal related events (SRE) and are an adverse prognostic factor. The BM immune micro-environment remains poorly defined because tissue is difficult to collect and requires decalcification. Preclinical animal modeling of RCC BM has established important interactions between tumor, bone stromal resident cells, and immune populations.Cabozantinib treatment led to treatment response of BM, influenced influx of immune cell populations, altered tumor vasculature, and reduced osteolysis in RCC BM. Additionally, our group has successfully performed single cell RNA sequencing (scRNA seq) in over 80 patients with RCC BM using both biopsy and surgical specimens in both the treatment naïve and treatment experienced patients. Cabozantinib plus nivolumab (cabo+nivo) is an established front-line regimen in metastatic RCC. We hypothesize that cabo+nivo favorably alters the tumor immune microenvironment through modulation of the macrophage and other immune cell populations with RCC BM.

Methods: NCT07187869 is an investigator-initiated, tissue-rich, single-center study, of cabo+nivo in patients with RCC BM. This trial will enroll up to 16 patients who will have BM and non-bone tumor collected at baseline and after 8 weeks of treatment with surgical or biopsy specimens. The study will stop once 10 patients have successful baseline and on treatment scRNA seq of BM. Primary endpoints are safety of serial bone sampling, success rate of serial scRNA sequencing of BM, and quantification of fold changes of macrophage subsets (among other immune cell subsets) comparing baseline to on treatment BM samples. Key secondary endpoints include comparing bone and non-bone scRNA, SRE rate, bone turnover markers, objective response rate, and progression free survival.Funded by Exelixis with philanthropic support from Stomp Out Cancer, The Dan Hund Family Fund, and Bill and LuAnn Hoffman fund. Accrual is ongoing.

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L8 – Therapeutics

TRIALS IN PROGRESS ABSTRACT

# Oncorella-1: a Phase I/II study of orellanine in patients with metastatic clear-cell or papillary renal cell carcinoma and ESKD requiring hemodialysis


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Background
Patients with metastatic RCC and ESKD requiring chronic hemodialysis are typically excluded from clinical trials and face limited treatment options. Novel therapies are urgently needed for this underserved patient population.
ONC175 (orellanine) is a first-in-class, highly kidney-specific synthetic cytotoxin derived from Cortinarius mushrooms. Accidental ingestion in humans causes irreversible renal injury without major systemic toxicity. Preclinical studies have shown that ONC175 induces apoptosis and ferroptosis in clear-cell RCC (ccRCC) and papillary RCC (pRCC), achieving >90% tumor volume reduction in xenograft models. Its tumor selectivity is mediated by orellanine transporters. The FDA approved the IND (167761) in March 2025.

Methods
Oncorella-1 (NCT05287945) is a multipart, adaptive trial enrolling patients with metastatic ccRCC or pRCC on maintenance hemodialysis who have progressive disease following standard-of-care therapies.

Part A: Intra-patient dose escalation at a single site—completed (N=5).

Part B: Inter-patient dose-exposure expansion across multiple sites to define the recommended Phase 2 dose (RP2D)—ongoing (N=20-25).

Part C: Planned dose expansion based on Part B findings.

After a 30-minute IV infusion of ONC175, patients undergo 1–3 days of controlled drug exposure with intensive monitoring.
The primary endpoints are safety, tolerability, and pharmacokinetics; secondary endpoints include preliminary antitumor activity and dialysis-specific safety parameters.

This trial addresses a rare and underserved population of patients with advanced RCC on dialysis, for whom no approved systemic therapies currently exist.

L9 – Therapeutics

REGULAR ABSTRACT

# The First Sequential Multiple Assignment Randomized Trial (SMART) in Metastatic Renal Cell Carcinoma: Response Rate Did Not Identify the Optimal Survival Strategy

Background: Overall survival (OS) time reflects every line of therapy, including salvage treatments given after first-line therapy has failed. Because conventional trials randomize only first-line treatment, they cannot identify an optimal sequence of agents. Sequential multiple assignment randomized trials (SMARTs) can, but none have been reported in renal cell carcinoma (RCC).

Methods: In this open-label SMART (NCT01217931), 175 patients with metastatic clear cell RCC were randomized among six two-stage strategies, each a (first-line, second-line) pair obtained from everolimus (E), pazopanib (P), and bevacizumab (B). Randomizing patients among two-stage strategies that include the agents given as first salvage enables OS comparisons between the sequences, rather than confounding first-line treatments with non-randomized post-progression therapies. The primary endpoint was time to overall treatment failure; OS and objective response rate (ORR) were secondary endpoints. Cox regression models were fit using everolimus-then-pazopanib (E, P) as the reference strategy, adjusted for risk category and prior cytokine/vaccine therapy. Median follow-up was 73.2 months (6.1 years).

Results: Everolimus-first strategies were most favorable (Table): (E, P) had the longest median time to overall treatment failure (25.4 months) and OS (70.6 months). Bevacizumab-then-pazopanib (B, P) was least favorable (10.7 and 32.3 months); adjusted hazards versus (E, P) were elevated for overall treatment failure (HR 2.09, 95% CI 1.25–3.50, p = 0.005) and death (HR 2.05, 1.10–3.84, p =0.024), with 95% CIsentirely above 1 and consistent across MSKCC- and IMDC-adjusted models. Discordantly, pazopanib produced the highest first-line ORR (48.2% vs 10.9% bevacizumab, 6.3% everolimus), yet pazopanib-first strategies did not achieve the longest survival.

Conclusions: In the first RCC SMART, an everolimus-first sequence was most favorable for long-term outcomes, while the agent with highest response did not give the best two-stage strategy for survival. These findings support guiding sequencing decisions by salvage-aware OS rather than by early response.

**Table. Six two-stage treatment strategies in metastatic clear cell RCC, ordered by median overall survival.**

| Two-stage strategy | Time to overall treatment failure, median (mo) | Overall survival, median (mo) | Adjusted HR for death vs E-P (95% CI) | First-line ORR (%) |
|---|---|---|---|---|
| **E-P (reference)** | 25.4 | 70.6 | 1.00 (reference) | 6.3 |
| **E-B** | 23.8 | 56.4 | 0.90 (0.46–1.78) | 6.3 |
| **P-B** | 21.3 | 47.0 | 1.04 (0.53–2.02) | 48.2 |
| **P-E** | 13.5 | 44.6 | 1.19 (0.63–2.27) | 48.2 |
| **B-E** | 14.5 | 40.1 | 1.25 (0.65–2.39) | 10.9 |
| **B-P** | 10.7 | 32.3 | 2.05 (1.10–3.84) | 10.9 |

*Strategies are ordered by median overall survival (OS). Hazard ratios (HRs) are from a multivariable Cox model with everolimus-then-pazopanib (E-P) as the reference, adjusted for MSKCC risk category and prior cytokine/vaccine therapy; the pattern was consistent in IMDC-adjusted models. First-line ORR reflects the first-line agent (everolimus 6.3%, bevacizumab 10.9%, pazopanib 48.2%): the highest-responding agent, pazopanib, did not define the best survival strategy. Open-label single-institution trial; N = 175; median follow-up 73.2 months. B, bevacizumab; E, everolimus; ORR, objective response rate (RECIST v1.1); P, pazopanib.*

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L10 – Therapeutics

REGULAR ABSTRACT

# Updated analysis of cabozantinib plus nivolumab (C+N) versus sunitinib (SUN) in patients with advanced renal cell carcinoma (aRCC) by baseline bone metastasis status


Background: In the phase 3 CheckMate 9ER trial, first-line treatment with C+N significantly improved progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) versus SUN in patients with aRCC. In an exploratory subgroup analysis with a median follow-up of 23.5 months, treatment benefits were observed regardless of baseline bone metastasis status. This updated analysis assessed outcomes by baseline bone metastasis status and additional sites of metastases using the final 5-year follow-up data from CheckMate 9ER.

Methods: In CheckMate 9ER, patients with clear-cell aRCC were randomized 1:1 to cabozantinib (40 mg QD) plus nivolumab (240 mg Q2W) or SUN (50 mg QD; 4 weeks of 6-week cycles). In this exploratory subgroup analysis (median follow-up of 67.6 months), PFS, OS, ORR, time to response, duration of response (DOR), and safety were evaluated in patients with or without bone metastases at baseline and in patients with bone plus liver or lung metastases.

Results: Of 651 randomized patients, 154 (24%) had baseline bone metastases. Baseline characteristics were generally balanced between treatment arms regardless of bone metastasis status. Compared with SUN, C+N improved ORR and prolonged PFS, OS, and DOR in patients with and without bone metastases, including those with bone plus liver or lung metastases (Table). Although bone metastases were associated with poorer clinical outcomes, the benefit of C+N over SUN was maintained across metastatic site subgroups. The safety profile of C+N was comparable across bone metastasis subgroups and generally consistent with the overall population.

Conclusions: With extended follow-up, C+N continued to demonstrate benefit versus SUN in patients with or without bone metastases, including those with bone plus liver or lung metastases.


**Table. Efficacy/safety by sites of metastases**

| | Patients with bone metastases[a] | | Patients without bone metastases | | Patients with bone and liver metastases | | Patients with bone and lung metastases | |
|---|---|---|---|---|---|---|---|---|
| | C+N (n=79) | SUN (n=75) | C+N (n=244) | SUN (n=253) | C+N (n=15) | SUN (n=17) | C+N (n=57) | SUN (n=58) |
| **ORR, %** | 49[b] | 9[b] | 58 | 33 | 40 | 18 | 51 | 10 |
| CR, % | 11 | 0 | 15 | 6 | 7 | 0 | 9 | 0 |
| PR, % | 38 | 9 | 43 | 27 | 33 | 18 | 42 | 10 |
| SD, % | 32 | 44 | 32 | 41 | 20 | 18 | 28 | 41 |
| PD, % | 11 | 25 | 5 | 11 | 20 | 47 | 12 | 28 |
| UTD, % | 8 | 21 | 5 | 15 | 20 | 18 | 9 | 21 |
| **mTTR, mo** | 2.9 | 7.3 | 2.8 | 4.3 | 2.9 | 3.0 | 2.8 | 5.7 |
| **mDOR, mo** | 18.0 | 6.9 | 22.9 | 15.4 | 12.6 | 6.4 | 18.0 | 6.7 |
| **mPFS, mo** | 13.8[b] | 5.3[b] | 16.6 | 9.5 | 6.9 | 3.8 | 10.0 | 4.4 |
| HR (95% CI) | 0.43 (0.30–0.64)[b] | | 0.60 (0.49–0.74) | | 0.77 (0.33–1.76) | | 0.45 (0.29–0.70) | |
| **mOS, mo** | 34.8[b] | 20.7[b] | 49.5 | 41.0 | 20.9 | 12.7 | 31.6 | 22.1 |
| HR (95% CI) | 0.66 (0.45–0.95)[b] | | 0.85 (0.68–1.06) | | 0.57 (0.26–1.24) | | 0.72 (0.47–1.10) | |
| **Grade 3/4 TRAEs, %** | 75 | 42 | 66 | 59 | — | | | |

[a]Nine patients had bone-only disease (C+N, n=7; SUN, n=2), precluding meaningful analysis of this subgroup.
[b]As reported in Motzer R, et al. *Ann Oncol* 2026;37:33–43.
**C+N**, cabozantinib plus nivolumab; **CI**, confidence interval; **CR**, complete response; **HR**, hazard ratio; **mDOR**, median duration of response; **mo**, months; **mOS**, median overall survival; **mPFS**, median progression-free survival; **mTTR**, median time to response; **ORR**, objective response rate; **PD**, progressive disease; **PR**, partial response; **SD**, stable disease; **SUN**, sunitinib; **TRAE**, treatment-related adverse event; **UTD**, unable to determine.


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L11 – Therapeutics

TRIALS IN PROGRESS ABSTRACT

# EXPLORE-RCC: A Phase II Trial of Neoadjuvant Zanzalintinib Plus Nivolumab in Locally Advanced and/or Surgically Challenging Clear Cell Renal Cell Carcinoma


Background:
The role of immunotherapy-based combinations in perioperative clear cell renal cell carcinoma (ccRCC) remains uncertain. EXPLORE-RCC evaluates neoadjuvant zanzalintinib, a novel vascular endothelial growth factor receptor tyrosine kinase inhibitor with a short half-life, plus nivolumab in patients with locally advanced or surgically challenging ccRCC. This approach may reduce tumor burden, facilitate resection, and enable partial nephrectomy or minimally invasive surgery.

Methods:
EXPLORE-RCC is a multisite, phase II, open-label, single-arm trial coordinated by the Hoosier Cancer Research Network. Participants receive zanzalintinib 60 mg orally daily plus intravenous nivolumab at standard dosing for 12 weeks, followed by restaging. Operable participants proceed to resection (Cohort A). Those remaining inoperable may continue treatment for up to 48 weeks, with resection if operability is achieved (Cohort B1). Participants with progression discontinue protocol therapy (Cohort B2).

Eligible participants are age >=18 years, ECOG performance status 0-1, histologically confirmed ccRCC, locally advanced (cT3/4, N0-1, with or without tumor thrombus) and/or has surgically challenging disease. Nonmeasurable metastatic disease by RECIST v1.1 is permitted, including soft-tissue metastases measuring <10 mm in longest diameter or distant lymph nodes measuring <15 mm in short axis. Key exclusion criteria include non-clear cell histology, measurable metastatic disease by RECIST v1.1, and prior systemic therapy for ccRCC.

The primary endpoint is objective response rate after 12 weeks. The study will evaluate improvement from a historical 30% to 45% response rate, with 80% power and one-sided $\alpha$=0.05. Planned enrollment is 69 participants. Secondary and exploratory endpoints include conversion to operability, disease-free and overall survival, pathologic response, safety, surgical complications, and biomarker correlatives. The trial is actively enrolling or opening at six US centers (NCT06794229).



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L12 – Therapeutics

REGULAR ABSTRACT

# Final Analysis of the TiNivo-2 Phase 3 Trial: Long-term Outcome of Tivozanib (Tivo) in patients with metastatic renal cell carcinoma (mRCC)


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Background
TiNivo-2 results showed that immune checkpoint inhibitor (ICI) rechallenge did not offer benefit to patients with mRCC, regardless of treatment sequencing (Lancet, 2024; 404:1309). However, the data highlighted activity for Tivo monotherapy in the post-ICI setting. Long term outcomes of the TiNivo-2 are reported here.

Methods
TiNivo-2 (NCT04987203) trial design and primary-endpoint results were previously reported: patients with mRCC were randomized to Tivo 0.89 mg once daily for 21/28 days plus Nivolumab (Nivo) at 480 mg every four weeks (Tivo/Nivo) or Tivo 1.34 mg once daily for 21/28 days. Here, long term progression free survival (PFS), overall survival (OS), and the safety profile are reported at final analysis.

Results
At the final database lock on January 30, 2026, 172 patients were randomized to Tivo (171 treated) and 171 patients were randomized to Tivo/Nivo (168 treated); median (m) follow up was 28.5 months (mo) (95% CI 27.0-30.6) in Tivo versus 27.2 mo (95% CI 26.1-28.6) in Tivo/Nivo. Survival outcomes and hazard ratios (HR) for the ITT population, 2L, and 3L populations are summarized in Table 1. In 2L, mPFS favored Tivo over Tivo/Nivo (9.23 mo [7.29, 11.04] vs 5.95 mo [4.37, 7.66]). Across subgroups, there were no differences in mOS.

No new safety signals were observed with prolonged administration; in the Tivo and Tivo/Nivo groups respectively the most common ⩾ Grade 3 TEAE was hypertension occurring in 39 (22.8%) and 38 (22.6%) and of patients; other ⩾ Grade 3 TEAEs included diarrhea (2.3% and 3.6%) and palmar-plantar erythrodysaesthesia (0.6% and 1.2%); and treatment-related SAEs occurred in 15 (8.8%)and 18 (10.7%) of patients.

Conclusions
This final analysis of patients in the TiNivo-2 study highlights sustained Tivo efficacy and consistent safety profile in mRCC in the post-ICI treatment setting, an area of high unmet need.




**Table 1**

| Parameter | By ITT | | 2L setting | | 3L setting | |
|---|---|---|---|---|---|---|
| | Tivo (0.89mg) /Nivo (n=171) | Tivo (1.34mg) (n=172) | Tivo(0.89mg) /Nivo (n=111) | Tivo (1.34mg) (n=105) | Tivo(0.89mg) /Nivo (n=60) | Tivo (1.34mg) (n=67) |
| mPFS, months (95% CI) | 5.72 (4.37–7.43) | 7.43 (5.52–9.23) | 5.95 (4.37–7.66) | 9.23 (7.29–11.04) | 5.45 (3.42–9.56) | 5.44 (2.10–7.36) |
| mPFS HR | 0.95 (0.75, 1.21) | | 1.11 (0.82, 1.50) | | 0.74 (0.51, 1.08) | |
| mOS, months (95% CI) | 23.85 (19.71–NR) | 22.93 (18.14–NR) | 29.50 (21.06–NR) | 23.52 (18.33–NR) | 19.71 (10.87–31.90) | 22.70 (11.79–NR) |
| mOS HR | 0.95 (0.70, 1.28) | | 0.88 (0.60, 1.30) | | 1.15 (0.73, 1.83) | |

NR, not reached

L13 – Therapeutics

TRIALS IN PROGRESS ABSTRACT

# Phase 3 study to assess the safety and efficacy of 177Lu-girentuximab in advanced, relapsed or recurrent ccRCC (LUTEON)


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Background: [177Lu]Lu-girentuximab enables targeted delivery to CAIX+ tumor cells (expressed on >95% ccRCC; limited expression in healthy tissues). Phase 1/2 data suggest favorable safety, tolerability, and efficacy profile. LUTEON is a Phase 3 study to assess safety and efficacy of 177Lu-girentuximab in patients with advanced, relapsed or recurrent ccRCC.

Methods: LUTEON is a 2-part, randomized, open-label, multicenter Phase 3 study, including initial dose-optimization (Part 1) followed by efficacy and safety evaluation (Part 2). Eligible patients are ⩾18y; have relapsed or recurrent, locally advanced or metastatic, histologically or cytologically confirmed ccRCC; and have received 2-3 prior lines of systemic therapies for locally advanced or metastatic ccRCC. Patients must have CAIX+ cancer on [89Zr]Zr-girentuximab PET.
In Part 1, patients are randomized 1:1 (⩽20/arm) to receive either 3 infusions of 1887MBq [177Lu]Lu-girentuximab every 8wks or 6 infusions of 1258MBq [177Lu]Lu-girentuximab every 4wks. In Part 2, patients will be randomized 1:1 to receive [177Lu]Lu-girentuximab at recommended Phase 3 dose (RP3D; identified in Part 1) or SOC.

In both parts, end of treatment (EOT) visit occurs 3±1wk after the last infusion of [177Lu]Lu-girentuximab or within 30d of discontinuing. After EOT, efficacy assessments occur every 8±2wks for 6m; patients will undergo tumor assessments according to RECIST 1.1 and will receive ceCT and/or MRI of chest, abdomen, and pelvis. In Part 2, after first 6-m follow-ups, patients continue follow-up every 12±2wks for up to 24m after EOT visit or until progression, death, or initiation of new systemic therapies.

Primary objective of Part 1 is to select RP3D. Primary objective of Part 2 is to compare median PFS of treatment with [177Lu]Lu-girentuximab to SOC as assessed by blinded independent central review.
Results: This trial is ongoing.

Conclusions: Previous study results support further investigation into efficacy of [177Lu]Lu-girentuximab in these patients in late-line ccRCC.



Disclosure: Sponsored by Telix Pharmaceuticals.

L14 – Therapeutics

TRIALS IN PROGRESS ABSTRACT

# Phase 1b Dose Escalation of a Multicenter, Open-Label Trial of Tivozanib Plus HC-5404 in Patients With Metastatic Clear Cell Renal Cell Carcinoma (ccRCC)


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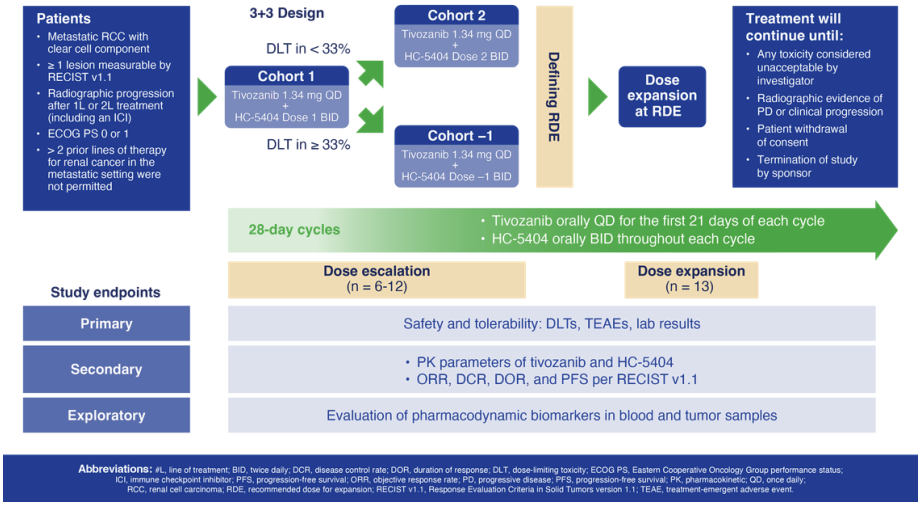


Background: Protein kinase RNA-like endoplasmic reticulum kinase (PERK) mediates the endoplasmic reticulum stress response and promotes tumor angiogenesis. In preclinical models, PERK inhibition reduces tumor growth and vascular density (Atkins 2013). HC-5404 is a highly selective, potent PERK inhibitor that has been explored as a monotherapy in phase 1a testing. In advanced solid tumors, HC-5404 was well tolerated; grade ⩾3 TRAEs occurred in 17.4% of patients (Dudek 2024).

Tivozanib, a potent and selective VEGFR-TKI, is FDA-approved for adults with relapsed/refractory advanced ccRCC following ⩾2 prior systemic therapies. Tivozanib was well-tolerated in patients with metastatic RCC, with a low incidence of class-related adverse events and dose adjustments (Rini 2020).

Tumors adapt to VEGFR-TKI-induced hypoxia through the PERK-mediated stress response (Fels 2006), providing a rationale for combining PERK inhibition with tivozanib to delay resistance. This phase 1b study will examine the safety and tolerability of tivozanib plus HC-5404 in patients with metastatic ccRCC.

Methods: The phase 1b study has two stages: a 2-cohort dose-escalation phase with a standard 3+3 design, followed by a single-cohort dose-expansion phase at the recommended dose for expansion (Figure). Enrollment will include ~6-12 patients in dose escalation and 13 in dose expansion. Key eligibility criteria include adults with measurable metastatic ccRCC and ECOG PS 0-1. All patients will receive tivozanib 1.34mg orally once daily for 21 days of each 28-day cycle, per the approved US prescribing information. During dose escalation, cohort 1 will receive HC-5404 Dose 1 orally BID, with a dose-limiting toxicity (DLT) evaluation period of 28 days. Escalation to HC-5404 Dose 2 (cohort 2) or de-escalation to HC-5404 Dose −1 (cohort −1) depends upon the DLT rate in cohort 1. Primary endpoints are safety, tolerability, and DLTs; secondary endpoints include objective response rate and progression-free survival per RECIST v1.1, and pharmacokinetics.


**Abbreviations:** #L, line of treatment; BID, twice daily; DCR, disease control rate; DOR, duration of response; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; ICI, immune checkpoint inhibitor; PFS, progression-free survival; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetic; QD, once daily; RCC, renal cell carcinoma; RDE, recommended dose for expansion; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TEAE, treatment-emergent adverse event.

M1 – Treatment Toxicities and Symptom Management

REGULAR ABSTRACT

# Immune-related toxicities of first-line ipilimumab/nivolumab in older versus younger patients with metastatic clear cell renal cell carcinoma: An expanded multi-institutional analysis


Background: Ipilimumab plus nivolumab (I/N) is a standard first-line treatment for metastatic clear cell renal cell carcinoma (mccRCC), but older adults remain underrepresented in pivotal immunotherapy trials, and age-related differences in treatment tolerance are incompletely characterized. We previously reported retrospectively that patients aged ⩾70 years had lower rates of I/N induction completion and higher incidence of treatment discontinuation due to adverse event (AE) than younger patients, despite comparable outcomes. Here, we present an expanded analysis to characterize incidence and clinical consequences of immune-related adverse events (irAEs) by age.

Methods: We retrospectively analyzed 514 patients with mccRCC treated with first line I/N at Memorial Sloan Kettering Cancer Center and MD Anderson Cancer Center. Individual charts were reviewed, and irAEs that occurred during the first 12 weeks of treatment were retrospectively adjudicated and categorized by organ system. Outcomes included development of irAE of special interest per prespecified organ-based categories, irAE-related hospitalizations, treatment discontinuation, need for systemic corticosteroids and nonsteroidal immunosuppression. Patients were stratified by age at treatment initiation (<70 vs ⩾70 years). Multivariable logistic regression (MLR) evaluated associations between age ⩾70 and toxicity outcomes after adjustment for sex, IMDC risk, sarcomatoid/rhabdoid features, and BMI.

Results: Among 514 patients, 98 (19%) were aged ⩾70 years. irAEs were numerically more frequent in older patients (65.3% vs 54.3%), but age ⩾70 was not independently associated with irAE development on MLR (aOR 1.45, 95% CI 0.89–2.40). Among patients who developed an irAE, the frequency of multiple irAE types was similar by age; however, patients ⩾70 had approximately two-fold higher adjusted odds of irAE-related treatment discontinuation (aOR 2.15, 95% CI 1.20–3.88) and a greater risk to require corticosteroids (aOR 2.13, 95% CI 1.18–3.93). Hospitalization rates and additional immunosuppression did not differ significantly after adjustment, and no organ-specific differences remained significant after multiple-testing correction.

Conclusions: Patients aged ⩾70 years did not have a significantly higher adjusted incidence of irAEs with first line I/N. However, among patients who developed an irAE, older adults had approximately two-fold higher adjusted odds of both irAE-related treatment discontinuation and corticosteroid requirement. Whether these differences reflect greater irAE severity or differences in clinical management could not be determined in the absence of standardized toxicity grading. These findings highlight the importance of careful toxicity assessment and individualized management of older adults receiving I/N.


**Table 1. Immune-related adverse events and clinical consequences by age group**

| Toxicity domain | Outcome | <70 years | ≥70 years | p-value |
|---|---|---|---|---|
| Overall irAE burden | Any irAE | 226/416 (54.3%) | 64/98 (65.3%) | 0.054 |
| | ≥2 distinct irAE categories | 80/416 (19.2%) | 23/98 (23.5%) | 0.400 |
| Selected organ-specific irAEs | Dermatitis | 64/416 (15.4%) | 26/98 (26.5%) | 0.012 |
| | Thyroid | 59/416 (14.2%) | 10/98 (10.2%) | 0.329 |
| | Hepatitis | 41/416 (9.9%) | 14/98 (14.3%) | 0.206 |
| | Colitis | 31/416 (7.5%) | 15/98 (15.3%) | 0.019 |
| | Pneumonitis | 27/416 (6.5%) | 3/98 (3.1%) | 0.237 |
| | Hypophysitis | 18/416 (4.3%) | 3/98 (3.1%) | 0.779 |
| | Arthritis | 10/416 (2.4%) | 7/98 (7.1%) | 0.027 |
| | Cardiac | 7/416 (1.7%) | 6/98 (6.1%) | 0.023 |
| Clinical consequences among patients with an irAE | irAE-related hospitalization | 74/226 (32.7%) | 27/64 (42.2%) | 0.182 |
| | **irAE-related treatment discontinuation** | 71/226 (31.4%) | 33/64 (51.6%) | 0.005 |
| | **Corticosteroid requirement** | 104/226 (46.0%) | 41/64 (64.1%) | 0.016 |
| | Additional immunosuppression | 25/226 (11.1%) | 12/64 (18.8%) | 0.135 |

Values are n/N (%). P-values are from Fisher exact tests. Overall irAE burden and selected organ-specific irAEs use the full cohort (n=416 aged <70 years; n=98 aged >=70 years). Clinical consequence analyses are restricted to patients who developed an irAE (n=226 aged <70 years; n=64 aged >=70 years). Corticosteroid requirement includes both therapeutic corticosteroids and physiologic steroid replacement.


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M2 – Treatment Toxicities and Symptom Management

CASE REPORT ABSTRACT

# Pembrolizumab-Induced Vogt-Koyanagi-Harada-Like Disease in a Patient with Metastatic Renal Cell Carcinoma


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Ophthalmologic immune-related adverse events (irAEs) occur in 1-3% of patients treated with immune checkpoint inhibitors (ICIs) and most commonly present as ocular surface disease or anterior uveitis. Posterior segment cases with retinal/choroidal involvement often are associated with more severe vision loss. Vogt-Koyanagi-Harada (VKH)-like disease, a bilateral granulomatous panuveitis with exudative retinal detachment mirroring idiopathic VKH syndrome, is a rare but vision-threatening ICI-associated irAE. It has been reported with anti-CTLA-4 and anti-PD-1 therapy across melanoma, lung, and gastric cancers, but renal cell carcinoma (RCC) remains underrepresented in this literature.

We describe a 54-year-old man with metastatic, poorly differentiated RCC who developed bilateral blurry vision approximately seven weeks after starting pembrolizumab with axitinib. Evaluation revealed reduced visual acuity (20/60 OD, 20/100 OS) with bilateral exudative retinal detachment on OCT. Infectious and autoimmune workup was negative. Pembrolizumab was held and topical, then systemic, corticosteroids were initiated, with vision worsening notably during a prednisone taper from 40 to 30 mg. Bilateral sub-Tenon's triamcinolone injections (35 mg) improved right-eye vision, while the left eye developed a full-thickness retinal tear requiring laser retinopexy.

This case illustrates that ocular irAEs, though rare, can permanently alter oncologic treatment plans. This highlights two practical management challenges: patients' functional ability to adhere to topical regimens, and the narrow therapeutic window between adequate immunosuppression and taper-associated flare. It also demonstrates the need for early multidisciplinary recognition, patient education, and close ophthalmologic follow-up, and treatment in patients on checkpoint inhibitor therapy who report vision changes.

N1 – Translational Research

REGULAR ABSTRACT

# Chromatin-Enabled HIF-2α Regulation of PTHrP Is a Therapeutically Actionable Driver of Paraneoplastic Hypercalcemia in Clear Cell Renal Cell Carcinoma

Hypercalcemia (HC) is a marker of poor prognosis in patients with renal cell carcinoma (RCC) and is most often driven by parathyroid hormone–related protein (PTHrP). Yet the upstream mechanisms controlling PTHrP expression, and the contribution of hypoxia-inducible factor-2 (HIF-2), the principal oncogenic driver in clear cell RCC (ccRCC), have not been well defined. We investigated whether HIF-2 directly regulates PTHLH, the gene encoding PTHrP, and whether pharmacologic HIF-2 inhibition could reverse HC. Using patient-derived tumorgraft (TG) models generated from hypercalcemic ccRCC, we measured serum calcium and circulating PTHrP and mapped chromatin accessibility at the PTHLH locus by ATAC-seq. HIF-2 was targeted pharmacologically with PT2399 in TG models and with belzutifan (PT2977) in patients. HIF-2α inhibition significantly reduced PTHLH expression ($p<0.01$) and diminished HIF-2α binding at the PTHLH promoter. Notably, the PTHLH locus was more accessible in hypercalcemic tumors and remained accessible following HIF-2α inhibition. Although HIF-2α blockade altered chromatin accessibility at other HIF-2 target loci, including EPO, no comparable changes were observed at PTHLH. These findings suggest that a HIF-2-independent chromatin program establishes or maintains the PTHrP-secretory state, while HIF-2α acts on this permissive chromatin landscape to drive PTHLH transcription and hypercalcemia. PT2399 rapidly normalized serum calcium in most hypercalcemic TG models ($p<0.01$), independent of tumor regression. Hypercalcemia was associated with clear-cell histology and aggressive sarcomatoid/rhabdoid differentiation ($p<0.001$), and hypercalcemic TGs showed preferential sensitivity to HIF-2α inhibition (odds ratio 3.03; 95% CI, 0.96–9.58). Consistent with these findings, belzutifan suppressed circulating PTHrP and corrected hypercalcemia in patients, including cases inadequately controlled by anti-resorptive therapy.

Together, these findings identify HIF-2α as a direct transcriptional regulator of PTHLH and establish the HIF-2α-PTHrP axis as a therapeutically actionable mechanism of paraneoplastic hypercalcemia in ccRCC. Furthermore, a HIF-2 independent chromatin landscape might maintain the hypercalcemia state.

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N2 – Translational Research

TRIALS IN PROGRESS ABSTRACT

# Diet and the gut microbiome among patients receiving cabozantinib-based regimens for advanced renal cell carcinoma: a prospective, multicenter, observational cohort study

Background: The gut microbiome is associated with response to immune checkpoint blockade (ICB); in randomized trials in metastatic renal cell carcinoma (mRCC), adding the butyrate-producing live bacterial product CBM588 to ICB-based regimens, including nivolumab plus cabozantinib, improved outcomes. Diet is a modifiable determinant of the microbiome, and high dietary fiber intake was associated with longer progression-free survival (PFS) in our prior prospective cohort study which included patients with RCC receiving ICB. Whether diet influences outcomes on cabozantinib with or without ICB remains unknown.
Methods: This prospective, observational, non-interventional, multicenter cohort study is enrolling 120 patients with advanced RCC (stage T4 or M1) receiving standard-of-care cabozantinib (n=60) or cabozantinib plus nivolumab (n=60). Assessments including biomarker collection occur once, 90–120 days after cabozantinib initiation: the Harvard Willett Food Frequency Questionnaire; a questionnaire assessing antibiotic use, probiotic use, and Charlson Comorbidity Index; and a single stool collection for metagenomic sequencing of the gut microbiome, including butyrate-producing bacteria and fiber-fermentation pathways. Clinical characteristics and outcomes are abstracted from the health record. The primary objective is to estimate improvement in PFS for high (⩾median) versus low (<median) fiber intake within and across cohorts, with day 120 after cabozantinib initiation as time zero, using Kaplan-Meier and one-sided log-rank methods. Power exceeds 80% to detect hazard ratios of 0.47 within the two cohorts and 0.59 combined (one-sided $\alpha$=5%); multivariable Cox models will adjust for confounders such as age, sex, body mass index, antibiotic use, probiotic use, Charlson Comorbidity Index score, prior therapies, kilocalories/day, concurrent therapies, brain metastases, histologic features, laboratory values, smoking status, alcohol use, and IMDC score. Exploratory objectives include associations of diet and the gut microbiome with one another, treatment response, overall survival, grade ⩾3 treatment-related adverse events, and grade ⩾3 diarrhea. Enrollment is ongoing; target accrual is anticipated within 2 years.

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N3 – Translational Research

REGULAR ABSTRACT

# Utilizing circulating tumor cells (CTCs) and cytokines to predict immunotherapy treatment response in patients with renal cell carcinoma (RCC)


Background:
While immunotherapies (IO) have contributed to improved outcomes in patients with clear cell renal cell carcinoma (ccRCC), molecular alterations contribute to treatment resistance over time. Characterization of circulating tumor cells (CTCs) can potentially provide a non-invasive approach to identifying druggable targets. We previously described a highly sensitive CTC capture method for RCC; this study evaluated CTCs and circulating cytokines in patients with metastatic RCC.

Methods:
Patients with RCC and starting IO-based treatments were prospectively enrolled at UT Southwestern Medical Center. Peripheral blood samples were collected at baseline, 4 weeks, and 12 weeks of treatment. CTCs were isolated using a dendrimer-based microfluidic chip assay functionalized with antibodies against EpCAM, EGFR. C-Met, CA-9 identifying nucleated CTCs (DAPI+/CK+, CD45-). CTC changes were considered concordant if they decreased >10% in pts with complete or partial response (CR or PR), remained within 10% of baseline in pts with stable disease (SD), or increased >10% in pts with progressive disease (PD), as defined by RECIST 1.1. Anti-human ALEXA 594 conjugated NECTIN-4 antibody was used to detect surface expression of NECTIN-4 via immunofluorescence. 52-plex cytokine profiling screening was performed using a 48-plex Bio-Plex Pro Human Cytokine Screening Panel and 6-plex R&D Custom Cytokine Screening Panel. Descriptive statistics were used, and unpaired multiple T-tests with a welch correction was performed for all three time points. For single time points, an unpaired, two-tailed T test with Welch correction was performed.

Results:
31 patients with RCC were enrolled with median age 63 years, predominately male (27/31, 87.05%), and Caucasian (22/31, 70.9%). All patients had clear cell renal cell carcinoma (ccRCC). Significant increases in CTC were associated with PD (p= 0.009). Notably, surface nectin-4 expression was detected on ccRCC CTCs for one patient after Ipi/Nivo treatment. Comparing circulating cytokines in patients with PR vs SD/PD, there was a statistically significant decrease at week 12 in the median concentrations of Kim-1 (69.1 pg/mL vs 291.2 pg/mL), VCAM-1 (3.47e5 pg/mL vs 4.46e5 pg/mL), IL-7 (10.3 pg/mL vs. 33.6 pg/mL), IL-10 (1.8 pg/mL vs 7.6 pg/mL), PIGF (0.6 pg/mL vs. 2.2 pg/mL) IL-12 (59.0 pg/mL vs 65.5 pg/mL). IL-2Ra decreased at week 4 in patients with PR versus SD/PD (14.0 pg/mL vs 23.8 pg/mL).

Conclusion:
CTC enumeration and staining can reveal valuable insights about the post-treatment proteomic expression in patients with RCC. Circulating cytokines changes, particularly in Kim-1, VCAM-1, IL-7, IL-10, and IL-12, can provide correlates for those responding to IO regimens. Further work is ongoing to evaluate the surfaceome on CTCs.



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N4 – Translational Research

REGULAR ABSTRACT

# SPATIAL AND MOLECULAR LANDSCAPE IN CLEAR CELL RENAL CELL CARCINOMA BONE METASTATIC PATIENTS

Background: Bone metastases (BMs) in metastatic clear cell renal cell carcinoma (mccRCC) occur in 30-40% of patients. BMs are an adverse prognostic factor associated with skeletal related events that impact patients' quality of life. Although combinations of tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs) have substantially improved outcomes in mccRCC, patients with symptomatic bone metastases are often unrepresented on clinical studies due to impaired performance status. The mechanisms underlying therapy response and resistance in BMs are poorly understood, in part because of the complexity of the bone microenvironment, challenges associated with processing bone tissue, and limited enrollment of patients with symptomatic BMs in clinical trials.

Methods: A prospective study over 3 years was conducted for patients undergoing a standard of care bone biopsy or bone surgery for mRCC. Single-cell RNA sequencing and spatial biology analyses on biospecimens collected from 63 patients with bone-metastatic ccRCC were collected on MD Anderson IRB approved protocol PA17-0577. Of these, 52 samples were eligible for integrated clinical and molecular analyses. Single-cell analysis revealed a treatment-associated remodeling of the bone microenvironment, characterized by an increase in myeloid populations and a decrease in lymphoid and endothelial populations. Gene-set enrichment analysis further identified increased TNF-α signaling and IFNα/IFNγ response pathways in treated patients.

To characterize the spatial organization of the metastatic niche, we performed multiplex immunofluorescence using COMET™, evaluating 20 tumor, immune, and stromal markers, followed by automated cell segmentation and phenotyping using Visiopharm. Spatial analysis demonstrated an overall reduction in immune-cell infiltration in patients previously treated with TKI+ICI therapy.
Together, these findings provide a comprehensive characterization of the immune and stromal landscape of ccRCC BMs and reveal treatment-associated changes that may contribute to therapeutic resistance. Ongoing analyses will integrate spatial, molecular, and clinical data to identify cellular and molecular determinants of resistance and potential therapeutic targets.

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N5 – Translational Research

REGULAR ABSTRACT

# The DNA Damage Immune Response Signature Associates with Benefit from Atezolizumab Plus Bevacizumab in RCC

Background: Advanced renal cell carcinoma (RCC) is characterized by an immune-permissive tumor microenvironment, yet biomarkers predicting immune checkpoint blockade (ICB) benefit remain limited. The DNA Damage Immune Response (DDIR) signature – previously validated in breast cancer – reflects activation of DNA damage-associated pathways that promote interferon signaling, immune-cell recruitment, and antitumor immunity. We evaluated associations between DDIR status, tumor immune features, and clinical outcomes to ICB in patients enrolled in the phase III IMmotion151 trial.

Methods: A validated 44-gene DDIR signature was applied to RNA sequencing data from 822 patients enrolled in IMmotion151 who received either atezolizumab plus bevacizumab or sunitinib. Patients were classified as DDIR-high or DDIR-low according to their DDIR score. Associations between DDIR status, clinical outcomes, and tumor immune features were evaluated. Progression-free survival (PFS) was analyzed using Kaplan-Meier estimates and Cox proportional hazard models, while the relationship between DDIR scores and objective response rates (ORR) alongside NMF-based microenvironment phenotypes were compared by ANOVA.

Results: DDIR scores were significantly enriched in patients with RCC exhibiting sarcomatoid differentiation ($p = 0.001$) and in PD-L1-positive tumors ($p < 0.001$). DDIR-high tumors were also enriched for the T-effector/proliferative NMF cluster, consistent with an activated antitumor immune microenvironment ($p < 0.001$). Across the overall population, PFS did not differ significantly between DDIR-high and DDIR-low patients. However, among DDIR-high patients, treatment with atezolizumab plus bevacizumab was associated with prolonged PFS compared with sunitib ($p = 0.007$), whereas no significant difference in PFS was observed between treatment arms in the DDIR-low subgroup. DDIR-high patients treated with atezolizumab plus bevacizumab also achieved higher ORR than those treated with sunitib.

Conclusion: DDIR-high tumors were associated with immune-enriched phenotypes and improved ICB outcomes. These findings support further evaluation of DDIR as a predictive biomarker for selecting patients with advanced RCC most likely to benefit from atezolizumab plus bevacizumab.

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N6 – Translational Research

REGULAR ABSTRACT

# Mechanistic investigation of paraneoplastic anemia in renal cell carcinoma through integrated clinical and preclinical models

Paraneoplastic anemia (PA) is frequently observed in renal cell carcinoma (RCC) and can improve following nephrectomy, suggesting a tumor-mediated mechanism. However, the tumor-derived factors responsible remain poorly understood. We hypothesize that a subset of RCC tumors secretes inflammatory mediators that suppress erythropoiesis and impair compensatory hematopoietic responses.

Using the Kidney Cancer Explorer (KCE) platform, we established a clinically annotated cohort of >4,500 patients who underwent nephrectomy at UT Southwestern Medical Center. Among 1,733 patients with paired pre- and post-nephrectomy hemoglobin measurements, approximately 30% had preoperative anemia, with a subset demonstrating improvement or normalization following nephrectomy after exclusion of hematuria-associated cases. We evaluated hematologic parameters across >100 RCC tumorgraft-bearing mice. Several tumorgrafts derived from patients with clinically suspected PA reproducibly induced reduced hemoglobin levels across serial passages and were provisionally classified as PA-associated tumorgrafts (TGPA), whereas selected control tumorgrafts maintained comparatively normal hemoglobin levels. In a matched patient–tumorgraft model, anemia developed during tumor growth and improved following nephrectomy, paralleling the clinical course of the originating patient. Tumor-bearing anemic mice lacked the expected compensatory increase in reticulocytes, while reticulocyte counts transiently increased during recovery after tumor removal.

These findings support the feasibility of PDX models that recapitulate reversible RCC-associated anemia and suggest impaired erythropoietic compensation as a potential mechanism. We will integrate tumor transcriptomic and plasma proteomic profiling to identify candidate tumor-derived soluble mediators. Candidates will be evaluated using ex vivo erythropoiesis assays and targeted using neutralizing antibodies, pharmacologic inhibitors, and genetic perturbation. Defining tumor–bone marrow signals underlying PA may identify biomarkers and therapeutic strategies to restore erythropoietic homeostasis and provide a framework for investigating other RCC-associated paraneoplastic syndromes.

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N7 – Translational Research

REGULAR ABSTRACT

# Development and Characterization of Patient-Derived Xenograft Models of Clear Cell Renal Cell Carcinoma with Spontaneous Venous Tumor Thrombus.

Invasion of the renal vein and inferior vena cava (IVC) by tumor thrombus is a distinctive and clinically challenging complication of renal cell carcinoma (RCC). However, the mechanisms underlying tumor thrombus formation remain poorly understood, partly due to the lack of experimental models that faithfully recapitulate vascular invasion and dissemination. Here, we characterized two patient-derived xenograft (PDX) models of clear cell RCC (ccRCC) that spontaneously develop venous tumor thrombi and metastases. Tumor fragments were orthotopically implanted under the renal capsule of immunodeficient NOD scid gamma (NSG) mice. Tumor growth and thrombus formation were monitored longitudinally by computed tomography (Albira Si PET/SPECT/CT, Bruker) and ultrasound (Vega Preclinical Ultrasound System, Revvity). Histopathological and immunohistochemical characterization, cryopreservation, and genomic profiling were performed to assess model fidelity and stability across passages. Both PDX models originated from high-grade tumors containing sarcomatoid and rhabdoid components and extensive necrosis. One patient presented with renal vein, IVC and both iliac veins tumor thrombus (Figure 1). The PDX models reproduced the vascular invasion and metastatic phenotype observed clinically, with in vivo thrombus formation detected at 2 and 3 weeks, respectively. Metastases were identified in the peritoneum, lymph nodes, and lungs. Both models remained viable following cryopreservation and preserved tumor characteristics across successive passages. PAX8, carbonic anhydrase IX (CAIX), and cytokeratin 7 (CK7) expression patterns were maintained in PDX tumors and derived cell lines. Genomic profiling identified alterations in VHL, BAP1, and FAT1, recapitulating key molecular features of the parental tumors. These PDX models faithfully reproduce the histological, immunophenotypic, genomic, vascular-invasive, and metastatic characteristics of the original tumors. Their defined kinetics of tumor growth and venous thrombus formation provide a robust platform for investigating the mechanisms underlying RCC-associated tumor thrombus and for evaluating neoadjuvant therapies aimed at reducing thrombus burden.

Keywords: Patient-derived xenografts; Tumor thrombus formation; kidney cancer

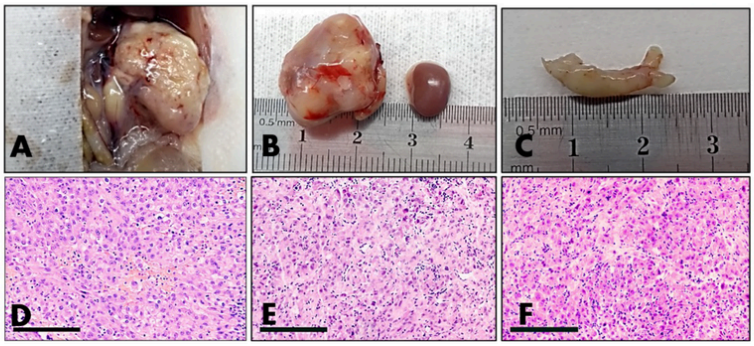



**Figure 1-Establishment of a ccRCC PDX model with tumor thrombus formation. (A)** Tumor growth with thrombus formation in the renal vein and inferior vena cava. **(B)** Comparison between the tumor-affected kidney and the remaining kidney. **(C)** Resection of the inferior vena cava and part of the iliac veins. **(D)** Histology of the primary tumor. **(E)** Histology of the PDX tumor. **(F)** Histology of the inferior vena cava thrombus. Scale bar = 200 µm.

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N8 – Translational Research

REGULAR ABSTRACT

# Cluster of Differentiation 70 (CD70) Expression Predicts Benefit from Adjuvant Checkpoint Inhibition in Renal Cell Carcinoma


Background:
CD70 is a costimulatory cell-surface protein transiently expressed on immune cells to promote immune activation. In renal cell carcinoma (RCC), CD70 is overexpressed on tumor cells and associated with T-cell exhaustion and immune evasion, making it a promising therapeutic target (Srour et al., JCO 2026). We evaluated clinical outcomes and molecular characteristics according to CD70 expression in patients with RCC at high risk of recurrence enrolled in IMmotion010.

Methods:
Normalized transcripts-per-million gene expression matrices and clinical data from 533 patients were analyzed. Patients were stratified into CD70-high and low expressors using the cohort median expression value. Previously defined non-negative matrix factorization (NMF) transcriptional clusters were identified and compared between groups using the chi-square test. Immune cell populations were estimated with xCell deconvolution and then correlated with CD70 using Pearson's correlation coefficient. Disease-free survival (DFS) was estimated using the Kaplan-Meier method, with hazard ratios calculated using Cox proportional hazards models.

Results:
Baseline characteristics were comparable between groups. In matched tumor samples, CD70 expression decreased at progression in both arms. CD70 status defined distinct NMF cluster distributions, with CD70-high tumors enriched for the angiogenic subtype and CD70-low tumors enriched for the proliferative subtype ($p<0.00001$). CD70 negatively correlated with Tregs, while positively correlated with activated myeloid dendritic cells and Tcells (CD4+ and CD8+). CD70 was not prognostic in the intention-to-treat population or placebo arm, although CD70-low tumors trended toward worse DFS with placebo (HR 1.43, $p=0.062$). Conversely, CD70-low was associated with improved DFS in the checkpoint inhibitor (CPI) arm (HR 0.57, $p=0.008$). CPI only improved DFS in CD70-low patients (placebo HR 1.93, $p=0.001$).

Conclusions:
CD70 expression was not consistently prognostic across groups. CPI improved DFS exclusively among CD70-low patients, highlighting a potential predictive role for CD70. This suggests that CD70-targeted therapies might not benefit from CPI combination strategies in the adjuvant setting.



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N9 – Translational Research

REGULAR ABSTRACT

# Rewiring Nitrogen Metabolism to Sustain Pyrimidine Biosynthesis in Human clear cell RCC


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Clear cell RCC (ccRCC) exhibits extensive metabolic reprogramming and dependence on glutamine as a carbon and nitrogen source. Clinical efforts to inhibit glutaminase, which provides glutamine carbon to the mitochondria, have been disappointing. A more recent investigational agent, DRP-104, blocks amidotranferases that transfer glutamine's amide group to nucleotides, hexosamines, amino acids, and other biosynthetic precursors. However, we currently do not know which amidotransferases are active in human ccRCC.

To investigate glutamine-derived nitrogen metabolism in vivo, we performed the first intra-operative infusions of [amide-15N]glutamine in eight ccRCC patients. [15N] labelling was measured in plasma, tumor, and adjacent normal kidney (NK). The infusions were complemented with a slice culture platform using fresh human tissue samples, supporting ex vivo isotope tracing. Together these approaches allowed us to study tumor-intrinsic glutamine metabolism and metabolism of glutamine by-products synthesized remotely and delivered to the tumor by the circulation (Figure 1A,B).

Intraoperatively infused ccRCC tumors exhibited greater [15N] labelling in asparagine and uridine nucleotides but lower labelling in guanosine nucleotides and select amino acids compared to NK (Figure 1C,D). In culture, tumor slices utilized [amide-$^{15}$N]glutamine for asparagine and nucleotide synthesis, and both pathways were blocked by DRP-104, demonstrating tumor-intrinsic glutamine utilization that was susceptible to inhibition.

Unexpectedly, tumors and NK exhibited substantial enrichment of [15N]-orotate despite low labeling of precursors. The plasma also contained enriched [$^{15}$N]-orotate, suggesting uptake of circulating orotate by renal tissues. Ex vivo, although both NK and tumor slices generated orotate from [amide-15N]glutamine, the tumors also took up extracellular orotate and incorporated it into pyrimidine synthesis. Notably, DRP-104 treatment increased [15N2]orotate incorporation into pyrimidine nucleotides, indicating enhanced contribution of extracellular orotate when glutamine metabolism is inhibited. Collectively, these findings reveal a previously underappreciated metabolic flexibility in ccRCC, where circulating orotate supports pyrimidine nucleotide production and may compensate for glutamine pathway inhibition.

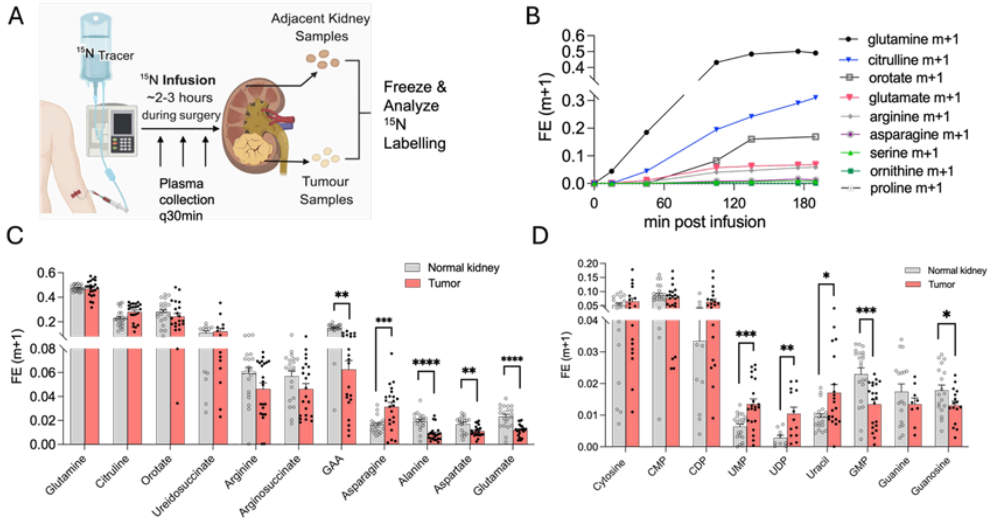




Figure 1. Intraoperative infusion of [amide-$^{15}$N]glutamineein patients with ccRCC. (A) Schematic of the intraoperative isotope infusion. (B) $^{15}$N labelling of plasma metabolites. (C and D) Fraction enrichment (FE) of [$^{15}$N]-labelled metabolites from 8 ccRCC patients. unpaired test, *p<0.05, **p<0.01, ***p<0.005, ****p<0.001.

O1 – Tumor Biomarkers and Pathology

REGULAR ABSTRACT

# Utility of Circulating Tumor DNA in Patients with Renal Cell Carcinoma at High Clinical Risk of Recurrence After Resection


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Despite approval of adjuvant pembrolizumab for high-risk renal cell carcinoma (RCC), risk of disease recurrence persists after surgical resection. Circulating tumor DNA (ctDNA) is utilized in multiple solid tumors to identify molecular residual disease (MRD) and monitor treatment response. However, evidence in RCC is sparse. Here we aim to investigate whether detection of ctDNA in high-risk RCC can predict disease recurrence and guide management.

We conducted a retrospective analysis of RCC patients at high-risk for recurrence after resection who underwent ctDNA testing 2022-2025. Inclusion criteria were pT2 with grade 4 or sarcomatoid features, pT3, pT4, pN1, or M1 without evidence of disease after resection. Post-operative ctDNA testing was performed using the commercially available, tumor-informed, next-generation sequencing-based SignateraTM assay. Disease-free survival (DFS) analysis was performed using Kaplan-Meier and univariable Cox-regression analyses.

A total of 128 patients underwent ctDNA testing with Signatera Exome with a median follow up of 26.2 months. Of these, 123 (96.1%) were pT3, 113 (88.3%) were clear cell RCC, and 39 (30.5%) received adjuvant therapy. Anytime postoperative ctDNA positivity was seen in 33 (25.8%) patients. In this ctDNA-positive cohort, 27 (81.8%) had disease recurrence, vs 15 (15.8%) in the ctDNA-negative cohort (p<0.001). Post-operative ctDNA positivity was associated with a significantly shorter DFS than observed in the serially ctDNA-negative group (HR 8.03; 95%CI: 4.2-15.3; p<0.001). DFS benefit from adjuvant therapy was not significant across postoperative ctDNA subgroups: ctDNA+ (HR 0.53, 95%CI: 0.21-1.3, p=0.17), ctDNA- (HR 0.47, 95%CI: 0.13-1.7, p=0.24, Figure 1).

Postoperative ctDNA positivity is a significant predictor of disease recurrence for RCC after resection, defining a true high-risk population with MRD. Prospective clinical trials are needed to determine whether ctDNA-guided treatment escalation improves outcomes in this high-risk population.

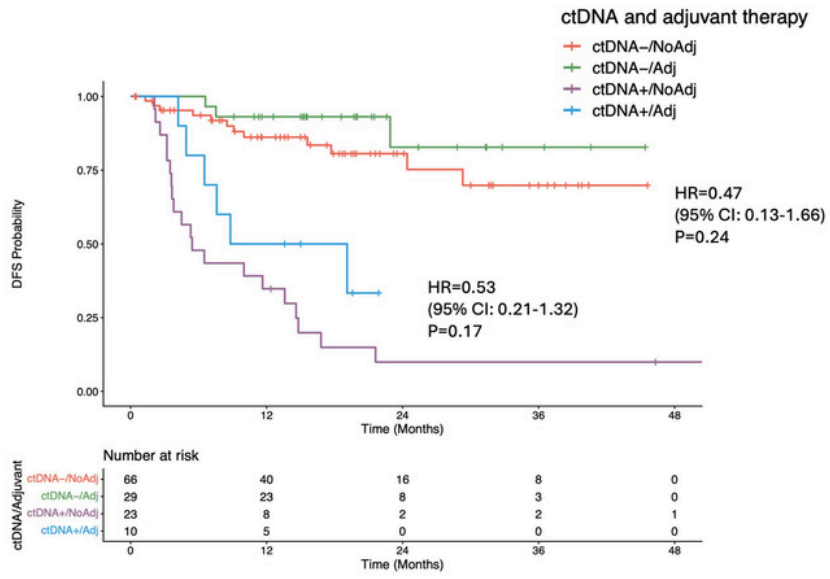




Figure 1. Kaplan-Meier estimates of DFS in patients with RCC stratified by ctDNA status and receipt of adjuvant therapy.

O2 – Tumor Biomarkers and Pathology

REGULAR ABSTRACT

# FASN expression is associated with tyrosine kinase inhibitor resistance in advanced renal cell carcinoma

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Background: Fatty acid synthase (FASN) drives de novo lipogenesis and is a potential adverse prognostic biomarker in renal cell carcinoma (RCC). Whether FASN expression predicts treatment response is unknown. We evaluated the relationship between FASN expression and outcomes on tyrosine kinase inhibitor (TKI)-based therapy in RCC.

Methods: RNA sequencing and clinical data were analyzed from patients with advanced RCC in the phase III JAVELIN Renal 101 trial (NCT02684006; sunitinib, n=377; avelumab plus axitinib, n=366). Genes associated with resistance in the sunitinib or combination (IO/TKI) arms were identified using Kaplan-Meier analysis and Cox proportional hazards regression models. Progression-free survival (PFS) was compared across FASN expression tertiles (low-T1, intermediate-T2, high-T3). Published JAVELIN Renal 101 and IMmotion151 (NCT02420821) gene signatures were scored by ssGSEA and correlated with FASN expression.

Results: In the sunitinib arm, higher FASN expression was associated with progressively shorter PFS (median PFS 11.1, 8.3, and 6.9 months for T1/T2/T3); the detrimental association was confirmed in continuous FASN analysis (HR 1.19 per 1-SD, p=0.0015). In the combination arm, FASN was not associated with PFS (median PFS 14.6, 14.1, and 14.7 months for T1/T2/T3). However, the relative benefit of combination therapy compared with sunitinib increased with FASN expression (HR 0.81, 0.72, and 0.49 in T1/T2/T3; arm x FASN interaction p=0.0073). FASN showed no association with IMDC risk (P=1.00). FASN expression correlated positively with the published IMmotion151 proliferative-stromal NMF6 (Spearman ρ =0.34, p=5.15e-21) and proliferative-anabolic NMF5 signatures (Spearman ρ=0.2, p=9.3e-8), but negatively with the angiogenic NMF2 signature (Spearman ρ=-0.43, p=1.4e-34).

Conclusion: High FASN identified an angiogenesis-low, metabolic RCC phenotype with TKI resistance. FASN expression may reflect resistance biology not captured by standard clinical risk stratification, supporting further investigation of lipogenic metabolism as a potential mechanism of treatment resistance.

| FASN tertile | Patients (N) | IMDC int/poor (%) | Sunitinib median PFS (months) | Avelumab + axitinib median PFS (months) | Combination vs sunitinib | |
|---|---|---|---|---|---|---|
| | | | | | PFS HR (95% CI) | P value |
| T1 (low) | 248 | 80.2% | 11.1 | 14.6 | 0.81 (0.61–1.07) | 0.140 |
| T2 | 247 | 81.4% | 8.3 | 14.1 | 0.72 (0.55–0.96) | 0.025 |
| T3 (high) | 248 | 75.3% | 6.9 | 14.7 | 0.49 (0.37–0.66) | 2.0e-06 |

**Table 1.** Progression-Free Survival by FASN Expression Tertile and Treatment Arm

O3 – Tumor Biomarkers and Pathology

REGULAR ABSTRACT

## Ribosomal Proteins and Wilms Tumorigenesis


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Wilms tumor (WT) is the most common pediatric kidney cancer, arising from aberrant nephrogenesis and affecting approximately 1 in 10,000 children worldwide. Although current multimodal therapies achieve high overall survival, 5–10% of patients relapse and have poor outcomes, and survivors often experience significant long-term treatment-related toxicities. Therefore, there remains an urgent need to identify biologically driven therapeutic targets.

Ribosomal proteins (RPs), beyond their canonical roles in ribosome assembly, are increasingly recognized as regulators of selective mRNA translation and modulators of oncogenic pathways, including MYC and p53 signaling. RP dysregulation has been implicated in ribosomopathies and developmental disorders associated with increased cancer susceptibility; however, its role in Wilms tumor pathogenesis remains incompletely defined.

SIX2, a master regulator of nephron progenitor self-renewal during kidney development, is highly expressed in the blastemal compartment of WT and is associated with poor prognosis. Persistent SIX2 activity is thought to maintain tumor-initiating cells in an undifferentiated, stem-like state. To explore a potential link between SIX2 function and translational control, we performed SIX2 immunoprecipitation followed by mass spectrometry in embryonic mouse kidneys and human kidney tumor cells, identifying multiple ribosomal proteins as SIX2-interacting partners.

To further evaluate translational dysregulation in WT, we analyzed Wilms tumor datasets from the TARGET (Therapeutically Applicable Research to Generate Effective Treatments) cohort using gene set enrichment analysis (GSEA). Ribosome biogenesis pathways were significantly enriched in WT compared with normal kidney tissue. Notably, specific ribosomal protein genes, including RPS17, RPS24, and RPL35A, were markedly upregulated in tumors, in some cases more than threefold relative to normal controls. In parallel, SIX1 and SIX2 were among the most highly upregulated developmental regulators, whereas genes associated with kidney differentiation were significantly downregulated. Analysis of independent human WT specimens further confirmed dysregulation of selected ribosomal proteins relative to adjacent normal kidney tissue.

Together, these findings support a model in which aberrant SIX2 signaling cooperates with ribosomal protein dysregulation to drive translational reprogramming and sustain Wilms tumor growth. Targeting RP-associated translational dependencies may therefore represent a promising strategy for biomarker development and therapeutic intervention in Wilms tumor.

O4 – Tumor Biomarkers and Pathology

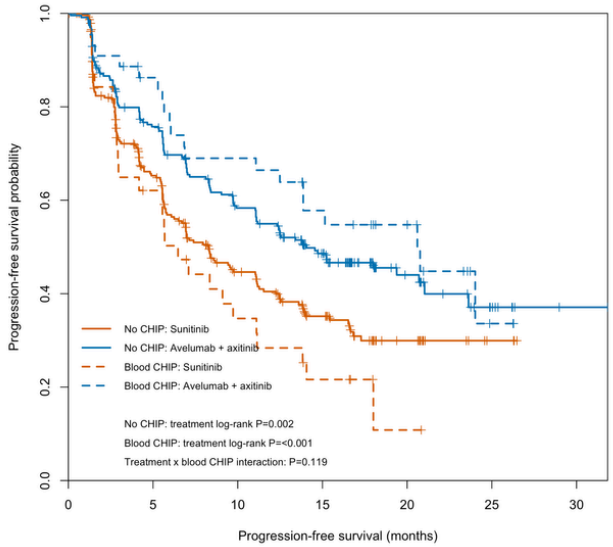
REGULAR ABSTRACT

# Clonal hematopoiesis, treatment associations, and germline TERT architecture in renal cell carcinoma (RCC)


Background: Clonal hematopoiesis of indeterminate potential (CHIP) is linked to cancer and cardiovascular disease; CHIP-mutant cells can infiltrate solid tumors as tumor-infiltrating clonal hematopoiesis (TI-CH). Although reported in renal cell carcinoma (RCC) and associated with adverse outcomes in lung cancer, the clinical relevance and germline determinants of TI-CH in RCC remain unclear.
Methods: Genetic correlation and colocalization were evaluated across GWAS of RCC, coronary artery disease, CHIP, and telomere length (TL). Paired blood/tumor exome sequencing in phase 3 JAVELIN Renal 101 identified blood CHIP and defined TI-CH by exact variant concordance. Cox models assessed progression-free survival and treatment-by-CHIP interaction; prespecified TERT variants were tested for CHIP/TI-CH.

Results: RCC–CHIP genetic correlation was positive (rg=0.182, P=0.023), and a TERT promoter haplotype colocalized across TL–RCC, TL–CHIP, CHIP–RCC, and TL–coronary artery disease (PP4≈1.00). Among 596 participants with classifiable TI-CH, 84 had blood CHIP and 8 (9.5%) had TI-CH. Avelumab plus axitinib versus sunitinib showed a numerically larger progression-free survival benefit among blood CHIP carriers (HR 0.37, 95% CI 0.21–0.68) than among patients without CHIP (HR 0.68, 95% CI 0.54–0.87), although interaction testing was inconclusive (P=0.119, Figure 1). Objective response was directionally similar. TI-CH-specific predictive effects were not evaluable because 7/8 TI-CH-positive participants received avelumab plus axitinib. Prespecified TERT variants showed nonsignificant TI-CH associations, with concordant directions across blood CHIP and TI-CH for four of five variants. rs2736100-A was associated with lower blood CHIP odds (adjusted OR 0.62, 95% CI 0.42–0.90).

Conclusions: TERT is a candidate germline determinant of CHIP/TI-CH in RCC. The numerically larger treatment effect among blood CHIP carriers is hypothesis-generating. Larger treatment-stratified studies should assess whether TI-CH is prognostic or predictive of benefit from immune checkpoint inhibitor-based therapy.



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O6 – Tumor Biomarkers and Pathology

CASE REPORT ABSTRACT

# POSTOPERATIVE CTDNA ELEVATION REVEALS PERSISTENT SYSTEMIC DISEASE IN ADVANCED CLEAR CELL RENAL CELL CARCINOMA


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Introduction

Circulating tumor DNA (ctDNA) has emerged as a potential adjunct for assessing systemic disease activity in metastatic malignancies. In renal cell carcinoma (RCC), its clinical utility remains investigational due to variable tumor DNA shedding and genomic heterogeneity. The clinical implications of postoperative ctDNA changes in high-risk, immunotherapy-resistant clear cell RCC remain undefined.

Methods

A 69-year-old male initially presented with a neck mass and underwent thyroidectomy, revealing metastatic clear cell renal cell carcinoma (ccRCC). Radical nephrectomy demonstrated pT3aN0M1 grade 3 ccRCCwith renal sinus and major vein invasion. After completing adjuvant pembrolizumab, recurrent cervical lymphadenopathy was confirmed as metastatic RCC and subsequently treated with nivolumab and ipilimumab. After four cycles, imaging demonstrated progressive cervical disease with internal jugular vein tumor thrombus and new pulmonary nodules. Radical neck dissection was performed. Pre- and postoperative ctDNA was obtained, and the resected tissue underwent molecular profiling.

Results

Preoperative ctDNA measured 1.31 MTM/mL and increased to 2.56 MTM/mL following neck dissection. Pathology revealed metastatic ccRCC involving 1 of 40 lymph nodes with extranodal extension, rhabdoid features, and BAP1 loss. Chromosomal analysis demonstrated loss of chromosomes 3p and 9p. In the context of suspected radiologic pulmonary metastases, rising postoperative ctDNA was consistent with persistent systemic disease despite locoregional resection. Post-operative radiation therapy and/or systemic therapy is being considered.

Conclusion

Postoperative ctDNA elevation in this aggressive, immunotherapy-resistant case suggests potential utility for monitoring systemic disease activity. Integration of ctDNA kinetics with genomic risk features may enhance risk stratification and inform systemic management in advanced RCC.

O7 – Tumor Biomarkers and Pathology

REGULAR ABSTRACT

# Proteome-Wide Profiling Reveals Remodeling of Humoral Immunity Following Immune Checkpoint Inhibition in Renal Cell Carcinoma


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Background: Immune checkpoint inhibitors (ICIs) have transformed the treatment of renal cell carcinoma (RCC), but their effects on humoral immunity remain incompletely understood. We investigated how ICI therapy alters circulating antibody responses in patients with RCC.

Methods: We identified 34 patients with RCC treated with ICIs for whom longitudinal plasma specimens were available. A total of 81 samples collected before and after ICI treatment were analyzed using a human proteomic microarray containing more than 21,000 full-length human proteins and isoforms. Antibody antigen-recognition profiles were compared across patients and treatment time points.

Results: RCC patient sera exhibited broad antibody reactivity, recognizing hundreds of human proteins. The overall repertoire of antibody-recognized proteins remained relatively stable following ICI treatment, without a substantial global increase in antigen-recognition diversity. However, comparative analysis of longitudinal samples identified a subset of antibody reactivities that were selectively altered following ICI therapy. These findings demonstrate that checkpoint blockade can remodel specific components of the circulating humoral immune response in patients with RCC.

Conclusions: Proteome-wide profiling reveals selective changes in antibody antigen recognition following ICI treatment in RCC. Ongoing studies are integrating these treatment-associated humoral responses with clinical outcomes and cellular immune profiling to determine their relationship with antitumor efficacy and immune-related adverse events.

P1 – Surgery & Localized Interventions

REGULAR ABSTRACT

# Stereotactic body radiation therapy for renal cell carcinoma with inferior vena cava thrombus: an international multi-institutional cohort


Surgical thrombectomy for renal cell carcinoma (RCC) with inferior vena cava tumor thrombus (IVC-TT) carries significant morbidity, leaving poor surgical candidates with limited options. We evaluated the safety, oncological outcomes, and palliative efficacy of stereotactic body radiation therapy (SBRT) for RCC IVC-TT in the largest international cohort to date.

We retrospectively analyzed 50 patients treated at 10 institutions worldwide. Treatment indications were non-mutually exclusive and included definitive treatment in 20 (40%), palliation in 31 (62%), and adjunctive therapy in 25 (50%) (neoadjuvant/adjuvant/salvage). Median SBRT dose was 40Gy in 5 fractions (range, 12-50Gy in 1-10 fractions). The primary endpoint was local IVC-TT control, defined as radiographic stability or regression on post-SBRT imaging. Secondary endpoints included adverse events (AEs), symptom palliation, and overall survival (OS).

Among 50 patients, 36 (72%) were male, 40 (80%) had clear cell RCC, and 29 (58%) had mayo level III-IV thrombus. After a median follow-up of 35 months, median OS was 43 months (95% CI 27.0–not reached), with 1-year OS of 82.7%. Local control was 97% among the 35 patients with evaluable post-SBRT imaging. Of 31 patients treated for symptoms, 77% achieved palliation. SBRT-related AEs occurred in 46%, predominantly Grade 1–2 nausea, fatigue; no Grade ⩾3 SBRT-related AEs occurred. Survival differed by treatment indication, with adjunctive SBRT associated with improved OS compared with palliative SBRT on multivariable analysis (HR 0.1; 95%CI 0.01-0.68; p=0.01; table 1), although this finding is subjective to treatment-selection bias.

SBRT for RCC IVC-TT demonstrated high local control, meaningful symptom palliation, and minimal high-grade toxicity. These findings support SBRT as a noninvasive option for patients who are not surgical candidates and warrant prospective evaluation of its role both as definitive therapy and within multimodality treatment.


Table 1 – Cox regression univariate and multivariate analysis for overall survival.

| | | Univariate HR (95% CI) | Univariate p-value | Multivariate HR (95% CI) | Multivariate p-value |
|---|---|---|---|---|---|
| **Age** | | 1.02 (0.98-1.06) | 0.35 | 1.01 (0.97-1.06) | 0.47 |
| **Sex** | Male | Ref | | | |
| | Female | 0.64 (0.23-1.78) | 0.39 | | |
| **Symptoms** | No | | | | |
| | Yes | 1.59 (0.64-3.93) | 0.3 | | |
| **Thrombus Level** | III-IV | Ref | | | |
| | I-II | 0.52 (0.21-1.26) | 0.15 | | |
| **Metastasis** | No | Ref | | | |
| | Yes | 1.2 (0.49-2.9) | 0.68 | 0.95 (0.35-2.53) | 0.92 |
| **Lymph Nodes** | No | Ref | | | |
| | Yes | 1.16 (0.41-3.24) | 0.77 | | |
| **Surgical Treatment** | No | Ref | | | |
| | Yes | 0.73(0.30-1.77) | 0.49 | | |
| **Systemic Therapy** | No | Ref | | | |
| | Yes | 1.09 (0.35-3.32) | 0.87 | | |
| **Treatment indication** | palliative | Ref | | | |
| | definitive | 0.44 (0.14-1.39) | 0.16 | 0.26 (0.06-1.179) | 0.08 |
| | adjunctive | 0.22 (0.06-0.70) | 0.01 | 0.10 (0.01-0.68) | 0.01 |
| **Total dose (Gy)** | <20 | Ref | | | |
| | 20-30 | 1.09 (0.12-9.58) | 0.93 | 0.2 (0.01-2.80) | 0.23 |
| | 30-40 | 0.61 (0.07-4.81) | 0.64 | 0.42 (0.04-3.81) | 0.44 |
| | >40 | 0.23 (0.02-2.64) | 0.24 | 0.08 (0.00-1.25) | 0.07 |

HR – Hazard ratio; CI – Confidence interval; Ref – reference, Gy - Gray


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P2 – Surgery & Localized Interventions

CASE REPORT ABSTRACT

# Multidisciplinary management of Renal Cell Carcinoma with Intravascular Recurrence


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Up to 10% of renal cell carcinoma (RCC) patients will have a venous tumor thrombus. In the absence of widespread metastasis, surgical resection is recommended. Intravascular tumor recurrence following resection presents a unique challenge with limited literature to guide clinicians. We describe a patient who underwent radical nephrectomy with inferior vena cava (IVC) thrombectomy, received immunotherapy, and subsequently developed intravascular recurrence in the supradiaphragmatic IVC and pulmonary arteries. We detail multidisciplinary management of recurrent intravascular disease with novel endovascular excision and pulmonary bilobectomy to achieve no evidence of disease.

A 66 y/o woman with minimal medical comorbidities presented with an 8.8cm right renal mass with tumor thrombus extending into the cavo-atrial junction. She underwent successful radical nephrectomy with IVC tumor thrombectomy. Postoperative imaging demonstrated pulmonary and adrenal metastasis. She initiated immunotherapy with excellent regression of all metastatic disease but developed a growing, recurrent mass in the supradiaphragmatic IVC as well as pulmonary tumor emboli. Multi-disciplinary discussions considered surgical resection, radiation, systemic therapy options, and endovascular procedures. After weighing risks, the patient underwent a novel endovascular procedure to remove the caval tumor in which a basket retrieval device was introduced through the internal jugular vein to secure the tumor while an electrified wire transected the tumor stalk via femoral access. She underwent pulmonary bilobectomy for removal of tumor emboli.At 18 month follow up after her radical nephrectomy, she has no evidence of disease.

This case highlights multidisciplinary management of RCC with IVC tumor thrombus and intravascular recurrence and introduces endovascular resection as a potential option in select cases

P3 – Surgery & Localized Interventions

REGULAR ABSTRACT

# Intraoperative Sodium Acetate Infusion to Mitigate Acute Kidney Injury After Robotic Partial Nephrectomy: A Nomogram-Guided Risk-Stratified Analysis

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Background. Acute kidney injury (AKI) after partial nephrectomy may contribute to chronic renal dysfunction. Intraoperative sodium acetate (SA) has biologic plausibility as a renoprotective agent, but its effect may depend on baseline AKI risk.WE evaluated whether SA was associated with lower-than-expected AKI after robotic-assisted partial nephrectomy (RAPN), overall and across validated risk strata.

Methods. We retrospectively analyzed consecutive RAPNs from January 2023 through August 2025. SA was infused from anesthesia induction until robot undocking. AKI within 14 postoperative days was defined by RIFLE Injury criteria using peak serum creatinine. Predicted AKI probabilities after RAPN were calculated using the validated Soputro nomogram incorporating age, sex, race, BMI, CKD stage, RENAL nephrometry score, and age-adjusted CCI. Patients were categorized as low (< 128 points on nomogram), moderate (128-169), or high risk (>= 170). Observed-to-expected (O/E) event ratios were compared by SA exposure.

Results. Among 263 patients, 144 received SA and 119 did not. Baseline clinical and operative characteristics were comparable, including CKD prevelence, tumor complexity, clamp time, and EBL. Overall AKI occurred in 13.2% with SA vs. 16.6% without SA; expected rates were 8.9% and 10% respectively, yielding O/E ratios of 1.48 and 1.66. No benefit was observed in low-risk patients. In moderate-risk patients, AKI occurred in 13% with SA versus 20% without SA (O/E 1.2 vs. 2.2). In high-risk patients, AKI occurred in 25% versus 28.6% (O/E 0.76 vs. 0.90).

SA was not associated with lower AKI incidence in the overall RAPN cohort. More favorable observed and risk-adjusted outcomes in moderate- and high-risk patients suggest that any benefit may be concentrated in patients with elevated preoperative risk. Prospective protocolized evaluation in a risk-enriched population is warranted.

P4 – Surgery & Localized Interventions

REGULAR ABSTRACT

# Clinical Predictors of Progression and Survival After Pre-Surgical Systemic Therapy and Nephrectomy for Renal Cell Carcinoma


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Background: In the immune checkpoint inhibitor (ICI) era, there has been renewed interest in neoadjuvant systemic therapy prior to nephrectomy for locally advanced or metastatic renal cell carcinoma (RCC). However, predictors of progression and survival after surgery remain poorly defined. We aimed to evaluate if clinical markers, including pathologic response, may be used as surrogate prognostic endpoints.

Methods: We retrospectively reviewed patients who received presurgical ICI and/or tyrosine kinase inhibitor (TKI) therapy before nephrectomy. We generated logistic regression models for progression and death adjusted for age, sex, baseline clinical TNM stage, duration/type of pre-surgical therapy, tumor necrosis, and complete pathologic response. Kaplan-Meier curves with log-rank testing assessed PFS and OS, stratified by baseline stage, regimen type, and complete pathologic response

Results: The cohort included 113 patients with a median age of 62. The cohort was 78% male, 85% white, and the most common clinical T stage was T3a. 38% had cN1 disease at baseline, and 62% with metastatic at presentation. ICI/TKI combinations were more common than ICI/ICI combinations. 70% of the cohort underwent a radical nephrectomy +/- lymph node dissection, with 20% undergoing partial nephrectomy and 13% requiring IVC thrombectomy. 38% were pathologically downstaged, with a 10.6% complete pathologic response rate. At a median follow up of 30.3 months, 46 (41%) progressed and 24 (21%) died. On multivariate logistic regression (Table 1), baseline clinical M1 disease was the strongest predictor of progression (OR 4.87, p=0.003); longer pre-surgical therapy duration was modestly protective (OR 0.95/month, p=0.034). Complete pathologic response independently associated with lower progression odds (OR 0.1, p<0.041) and improved PFS (p=0.023).

Conclusions: Baseline metastatic burden and complete pathologic response are key determinants of progression after neoadjuvant therapy and nephrectomy for RCC — supporting pathologic response as a candidate surrogate endpoint, pending validation in larger prospective cohorts.


Table – Multivariable Logistic Regression – Predictors of Progression After Surgery

| Covariate | Odds Ratio | 95% CI | p-value |
|---|---|---|---|
| Age at diagnosis (per year) | 1.03 | 0.98–1.07 | 0.223 |
| Female sex (vs. male) | 0.40 | 0.14–1.18 | 0.097 |
| Clinical T stage (ordinal, T1→T4) | 1.36 | 0.74–2.48 | 0.319 |
| Clinical N1 (vs. N0) | 1.55 | 0.60–3.96 | 0.363 |
| **Clinical M1 (vs. M0)** | **4.87** | 1.72–13.82 | **0.003** |
| **Duration of pre-surgical therapy (per month)** | **0.95** | 0.90–1.00 | **0.034** |
| TKI-containing regimen (vs. ICI-only) | 1.06 | 0.44–2.52 | 0.901 |
| Tumor necrosis present | 0.88 | 0.29–2.67 | 0.815 |
| **Pathologic complete response** | **0.10** | **0.01-0.91** | **0.041** |

P5 – Surgery & Localized Interventions

LATE-BREAKING DATA SUBMISSION ABSTRACT

# CT-guided Cryoablation for Biopsy-proven T1a Renal Cell Carcinoma: Long-term Oncological Outcomes from the Prospective Multinational EuRECA Registry

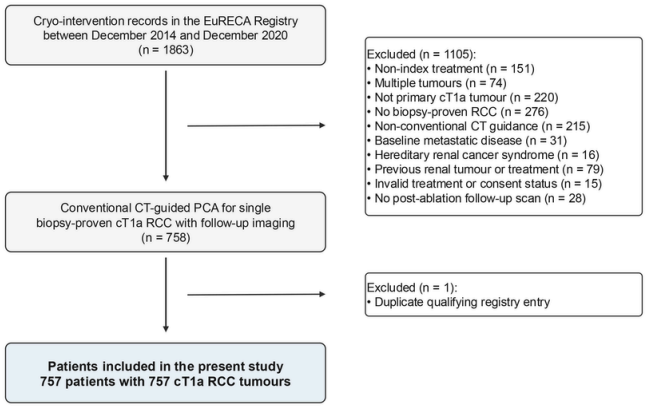
Background and Objective: Prospective long-term data on percutaneous cryoablation of biopsy-proven cT1a renal cell carcinoma (RCC) using surgical-comparable endpoints remain limited. We report long-term oncological outcomes after CT-guided percutaneous cryoablation from the European Registry for Renal Cryoablation (EuRECA).

Methods: This prospective multinational registry study included adults with biopsy-proven cT1a RCC who underwent CT-guided percutaneous cryoablation (Dec 2014–Dec 2020). Primary endpoint: local recurrence-free survival (LRFS) after primary technique efficacy. Secondary outcomes: residual unablated tumour, metastasis-free survival (MFS), cancer-specific survival (CSS), overall survival (OS), and 30-day complications. Kaplan–Meier estimates were used.

Results: Among 757 patients (median follow-up 5.0 yr [IQR 3.3–5.8]), residual unablated tumour occurred in 16 (2.1%); primary technique efficacy was 97.9%. Among 741 patients with primary technique efficacy, 28 developed local recurrence (5-yr LRFS 96.1%, 95% CI 94.2–97.5). Metastatic progression occurred in 17 (2.2%; 5-yr MFS 97.6%, 95% CI 96.1–98.6). RCC-specific death occurred in 4 (0.5%; 5-yr CSS 99.2%, 95% CI 97.8–99.7); 5-yr OS was 86.1% (95% CI 83.1–88.6). Median hospital stay was 1 day; major complications (Clavien-Dindo ⩾IIIa) occurred in 1.6%. Secondary technique efficacy after repeat cryoablation was 87.5%.

Conclusions: In this large, prospective, multinational registry, CT-guided percutaneous cryoablation provided durable oncological control and low treatment burden in patients with biopsy-proven cT1a RCC who were less suitable for surgery. These mature 5-yr, surgical-comparable outcomes support cryoablation as a guideline-consistent nephron-sparing option and provide a contemporary benchmark for shared decision-making and patient counselling.

**Figure 1.** Flow diagram




CT = computed tomography; EuRECA = European Registry for Renal Cryoablation; PCA = percutaneous cryoablation; RCC = renal cell carcinoma.

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Q1 – Health Equity & Global Oncology

REGULAR ABSTRACT

# Diagnostic and surveillance imaging burden in patients undergoing evaluation for a renal mass: real-world analysis of US claims data


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Background: Evaluation of a renal mass typically requires multiple imaging studies (CT, MRI, ultrasound, PET, Sestamibi/nuclear scans) before a management decision is reached. This multi-modality scan approach is poorly quantified in the real world and becomes a burden on patients, payors, and healthcare systems in terms of cost, time, and radiation exposure. Recently, 89Zr-girentuximab PET (targeting CAIX, expressed on >95% of ccRCC) demonstrated high diagnostic accuracy for clear cell renal cell carcinoma (Shuch 2024 Lancet Oncol) and has been proposed as a most cost-effective diagnostic strategy in renal mass evaluation (Kanabur 2026 J Urol). To quantify the potential for 89Zr-girentuximab to reduce repeated imaging burdens on patients and payors, we used US claims data to quantify the number and timing of scans before a definitive renal procedure.

Methods: The IQVIA Longitudinal Access and Adjudicated Data (LAAD) US claims database of 400 million de-identified patients included adults ⩾18y with ⩾1 urologist visit, ⩾24 months of medical history, and ⩾2 renal mass diagnosis codes (⩾1 before and ⩾1 after first renal index procedure) between October 2017-February 2023. Index procedures included kidney biopsy, ablation, complete or partial nephrectomy, destruction,
extraction, excision, kidney resection, or extirpation of matter from kidney. Patients were classified using the last diagnosis code before the index procedure and most recent code after. Imaging burden, biopsy utilization, and time from first scan to index procedure were evaluated during the 24 months preceding the index procedure. Because indeterminate renal masses represent the greatest diagnostic challenge and potential opportunity for improved risk stratification, analyses focused on patients reclassified from indeterminate to benign or malignant.

Results: 89,119 patients met criteria (median age 67y; 62% male; 74.8% of index procedures performed by a urologist). During the 24 months before index procedure, patients underwent a mean 3.3 scans (median 2); 77.6% had ⩾1 pre-procedure scan. Lesions were reclassified from indeterminate to benign or malignant in nearly 24,000 patients. Mean time from first scan to procedure was 6.0 months (median 2.6). Among these patients, scan burden was similar, with a mean 2.8 scans in indeterminate-to-benign patients and 2.6 scans in indeterminate-to-malignant patients (median 2 scans in both cohorts); mean time from first scan to index procedure was 5.8 and 5.3 months, respectively. Pre-procedure CT imaging was common (62.3–64.6%). Kidney biopsy occurred in 31.6% of indeterminate-to-malignant patients compared with 2.7% of indeterminate-to-benign patients (Table 1).

Conclusions: 89Zr-girentuximab PET may offer a cost-effective approach to renal mass risk stratification with the potential to reduce substantial diagnostic burden, prolonged evaluation timelines, and unnecessary procedures. In the large real-world claims analysis, patients undergoing renal mass experienced multiple imaging studies and a mean six-month interval from first imaging to definitive management. Patients experience additional burden through delayed diagnosis, radiation exposure, procedure-related risks, organ loss, and anxiety. The burden extends to payors and healthcare systems through costs of serial imaging, repeated or unnecessary procedures, and potential biopsy- or surgery-related adverse events and hospitalizations. These claims data highlight a real-world opportunity for a more definitive diagnostic study like 89Zr-girentuximab PET to support faster and more accurate diagnosis, reduce redundant imaging and unnecessary biopsy or surgery, lower healthcare costs, and better support patients throughout diagnostic evaluation.



Disclosure: LAAD data acquisition funded by Telix Pharmaceuticals.


Table 1. Pre-procedure imaging burden, time from first scan to index procedure, and biopsy in patients with renal lesion reclassification from US claims data.

| | Indeterminate to Benign | Malignant to Benign | Indeterminate to Malignant | Benign to Malignant |
|---|---|---|---|---|
| Total patients | 1,842 | 1,370 | 22,135 | 2,517 |
| Patients with any pre-procedure scan (% total) | 1,396 (75.8) | 1,103 (80.5) | 16,272 (73.5) | 1,817 (72.2) |
| Total number of scans before index procedure | | | | |
| Average | 2.79 | 3.21 | 2.62 | 2.68 |
| Median | 2 | 2 | 2 | 2 |
| Abdominal/Pelvis CT scan before index procedure | | | | |
| Average | 1.36 | 1.48 | 1.28 | 1.30 |
| Median | 1 | 1 | 1 | 1 |
| Pts with ≥1 CT (% total) | 1,190 (64.6) | 905 (66.1) | 13,562 (62.3) | 1,526 (60.6) |
| Sestamibi scans before index procedure | | | | |
| Average | 0.05 | 0.06 | 0.06 | 0.06 |
| Median | 0 | 0 | 0 | 0 |
| Pts with ≥1 sestamibi (% total) | 79 (4.3) | 73 (5.3) | 1162 (5.2) | 132 (5.2) |
| Time from first any scan to index procedure (months) | | | | |
| Average | 5.76 | 6.15 | 5.26 | 5.79 |
| Median | 2.55 | 2.87 | 2.10 | 2.32 |
| Patients with kidney biopsy before index procedure (% total) | 50 (2.7) | 77 (5.6) | 700 (31.6) | 152 (6.0) |

R1 – Imaging

REGULAR ABSTRACT

# Exploiting the Krebs Defect: [18F]FDG PET/CT for Extent of Disease Evaluation in Fumarate Hydratase-Deficient Renal Cell Carcinoma

The value of [18F]FDG PET/CT imaging in the management of fumarate hydratase (FH)-deficient renal cell carcinoma (RCC), a rare and aggressive type of kidney cancer, is not established. We describe the findings on [18F]FDG PET/CT obtained for extent of disease evaluation and treatment planning. Methods: From an institutional database (2015-2026), we identified FH-deficient RCC patients who underwent [18F]FDG PET/CT scans as part of clinical care. When available, baseline [18F]FDG PET/CT was used; otherwise, the earliest available follow up scan performed for concern of recurrence or progression was included. For all scans, sites of abnormal [18F]FDG uptake were assessed, SUVmax of the most avid was quantified, and tumor-to-normal tissue ratios (TNR) were calculated. Results: 20 patients were identified: 18 with germline FH-deficiency associated with hereditary leiomyomatosis and renal cell cancer (HLRCC), and 2 with sporadic FH-deficient RCC. Eight patients underwent baseline PET/CT for initial staging, while 12 underwent PET/CT during follow-up. On PET, 17/20 patients had clearly [18F]FDG avid disease. The three patients without [18F]FDG avid lesions also lacked evidence of disease on anatomical imaging or follow up PET/CT. Of the 8 patients with baseline PET/CT, 5 had intact renal primary tumors and all 5 (100%) were [18F]FDG avid (median SUVmax 18.8, range: 13.6-19.6; median TNR blood 14.0, range: 6.5-17.1). 10/17 had [18F]FDG avid nodal metastatic disease (median SUVmax 24.9, range: 6.2-51.7). Extranodal disease was observed in 14 patients, most commonly in the bones (n = 9; median SUVmax 9.8, range: 4.3-26.2), liver (n = 5; median SUVmax 9.1, range: 4.1-10.3) and soft tissues (n = 5; median SUVmax 6.6, range: 4.8-17.4). Conclusion: FH-deficient RCC is an intensely [18F]FDG avid malignancy, which may facilitate assessment of disease extent in affected patients.

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