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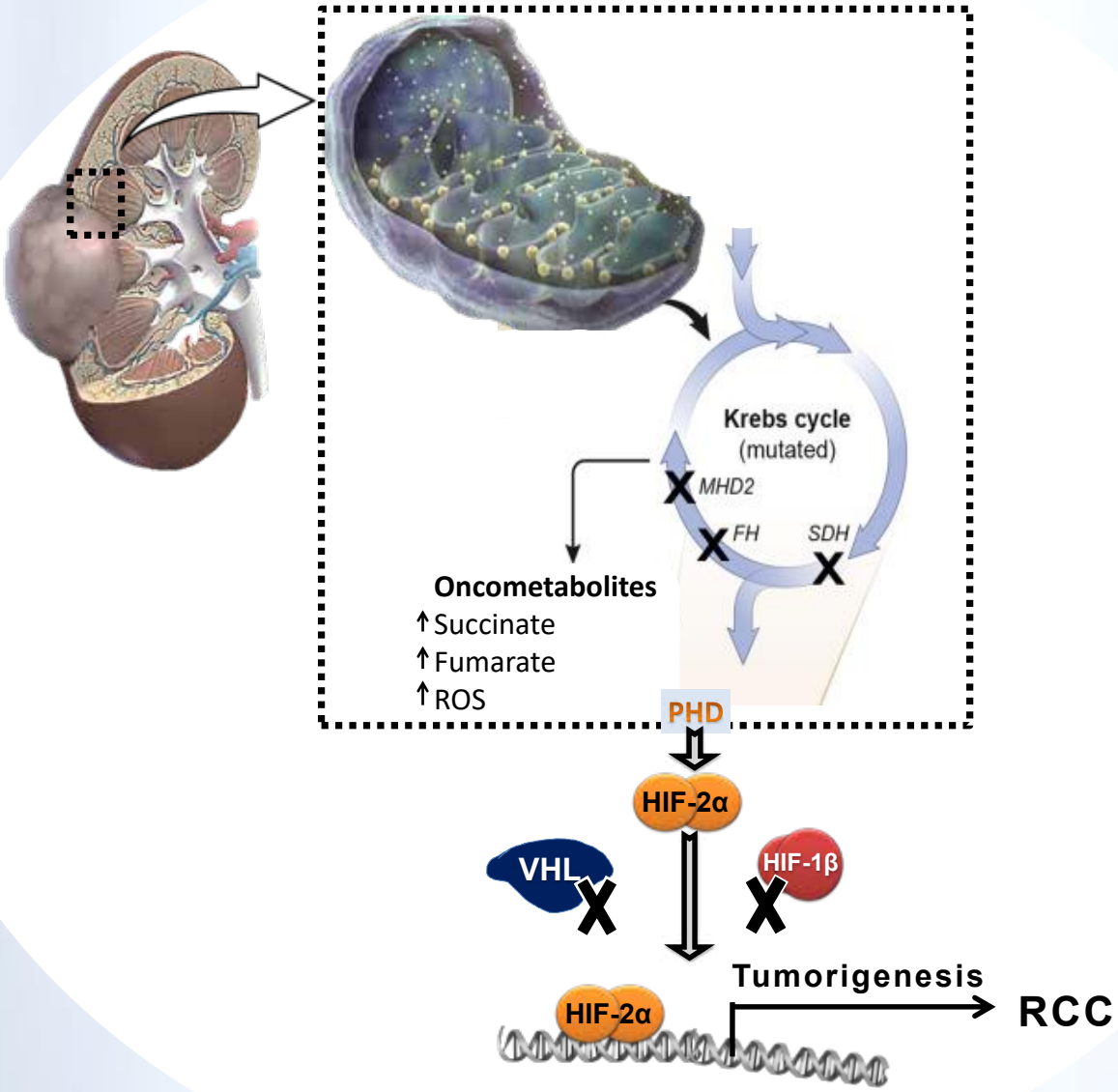
Kidney Cancer JOURNAL

Official Journal of Kidney Cancer Association

Kidney-Cancer-Journal.com

Vol 21
Number 4
2023



An Educational Service for Medical Oncologists, Hematologist-Oncologists, and Urologists

Artist rendering; for illustration purposes only.

In RCC, <u>all</u> T3 tumors are characterized by their invasiveness.[1]
These tumors extend into structures within or adjacent to the kidney system, including the renal fat, the renal vein, the vena cava, or the pelvicalyceal system.[1,a]

Patients with more invasive tumors are at a higher risk of their cancer returning.[2]
Identify patients in your practice who have T3 tumors so you can take appropriate action following nephrectomy.

How will you manage your next patient with an invasive T3 tumor?

*T3 tumors do not extend beyond Gerota's fascia or into the ipsilateral adrenal gland.[1]
RCC = renal cell carcinoma.

References: 1. Edge SB, Greene FL, Byrd DR, et al, eds. Kidney. In: *AJCC Cancer Staging Manual*. 8th ed. Springer International Publishing; 2017:739–748. **2.** Sundaram M, Song Y, Rogerio JW, et al. Clinical and economic burdens of recurrence following nephrectomy for intermediate high- or high-risk renal cell carcinoma: a retrospective analysis of Surveillance, Epidemiology, and End Results-Medicare data. *J Manag Care Spec Pharm*. 2022;28(10):1149–1160. doi:10.18553/jmcp.2022.22133.

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ABOUT THE COVER
A graphic illustration of mechanistic development of fumarate hydratase-mutated Renal Cell Carcinoma driven by accumulation of oncometabolites such as fumarates and succinates.

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Kidney Cancer Journal (ISSN 1933-0863) is published quarterly by BMG (BioMedz Global).
Kidney Cancer Magazine is a federally Registered Trademark of BMG.

A USA Based Publication

A Renaissance in Renal Research: A New Editor's Perspective

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https://doi.org/10.52733/KCJ21n4-e

Dear colleagues,

Welcome colleagues, to this new chapter in the fight against kidney cancer. This field, once shrouded in darkness, is now illuminated by the brilliant light of scientific progress. We stand on the precipice of a new era, where the once-daunting landscape of kidney cancer is being reshaped by transformative discoveries at a blistering pace, and this journal stands at the very epicenter of this revolution.

Fresh off the heels of International Kidney Cancer Symposium (IKCS) 2023 in Nashville, I'm buzzing with excitement about the incredible advancements in kidney cancer research. Here's a quick rundown of the highlights that left me most impressed:

1. **Precision Medicine Takes Center Stage**: The promise of personalized treatment for kidney cancer was truly on display. Presentations on genetic and molecular profiling which aimed at developing tailored therapies to individual patient characteristics were at the forefront. The excitement surrounding clinical trials utilizing next-generation sequencing and AI-powered diagnostics was palpable. Research unveiled promising results from clinical trials exploring drugs targeting specific mutations, like MET, BHDH, and TKI resistance. PARP inhibitors and tyrosine kinase inhibitors are showing impressive efficacy in specific subtypes, and research into novel targets like HIF-2α and FGF receptors offers tantalizing possibilities. This paves the way for more personalized, effective treatment approaches. Non-invasive monitoring and early detection using liquid biopsies for tumor dynamics and biomarker analysis garnered much attention.

2. **Immunotherapy's Evolving Landscape**: Another dominant theme of IKCS 2023 was the continued reign of immunotherapy. Exciting data showcased the efficacy of novel combinations, including ICI-based regimens with TKI inhibitors and PARP inhibitors. Early-stage trials investigating neoadjuvant and adjuvant immunotherapy also sparked optimism, offering a glimpse into a potential future where prevention takes the helm. CAR-T therapy, though in its nascent stages, offers a glimmer of hope for even the most recalcitrant tumors. However, the challenge of resistance and optimizing patient selection for ICI therapy remains a critical area of focus. The discussions about overcoming resistance and optimizing immunotherapy regimens for patients who don't respond to standard treatments were particularly insightful. However, navigating the complex interplay between ICIs, tumor heterogeneity, and resistance mechanisms remains a significant challenge. Can we refine patient selection and predict response with greater accuracy? Can we overcome resistance and unleash the full potential of this powerful tool?

3. **Early Detection on the Horizon**: The quest for earlier diagnosis received a much-needed boost with presentations on promising new biomarkers and

Figure 1. At the general session of IKCS2023.

imaging techniques. liquid biopsies, circulating tumor DNA analysis, and advanced MRI protocols are raising hopes for catching kidney cancer at its earliest, most treatable stage. Studies explored AI-powered tools for predicting disease progression and tailoring treatment based on individual risk profiles. This personalized approach can optimize care and avoid unnecessary interventions.

4. **Beyond the Tumor - A Holistic Focus**: The conference wasn't just about the science; it also addressed the human side of the equation. Sessions addressed the significant impact of treatment-related side effects on patients' quality of life. Discussions on survivorship, psychosocial support, and navigating the healthcare system resonated deeply with patients and caregivers alike. The emphasis on holistic care and patient empowerment was truly commendable.

5. **A Catalyst for Collaboration**: Perhaps the most significant outcome of IKCS 2023 was the renewed sense of community and collaboration. Researchers from diverse disciplines, institutions, and countries came together to share knowledge, forge partnerships, and accelerate the pace of progress against kidney cancer. This collaborative spirit gives me immense optimism for the future of the field.

6. **Emerging Challenges**: Overcoming treatment resistance and adapting therapies to individual tumor profiles remain significant challenges. The high cost of novel therapies raises concerns about equitable access and affordability for all patients. Addressing these disparities requires innovative healthcare models and collaborative efforts. Managing long-term side effects and optimizing quality of life after treatment are crucial for overall patient well-being. Research into supportive care and survivorship programs needs to be prioritized. The rapid pace of advancements raises ethical concerns regarding informed consent, data privacy, and clinical trial design. Navigating these ethical complexities is essential to ensure responsible and patient-centered research.

There were countless other presentations, workshops, and discussions that deserve mention. But hopefully, this gives you a flavor of the excitement and momentum that characterized the 2023 IKCS. As we move forward, I'm confident that the insights gleaned from IKCS will translate into tangible improvements in the prevention, diagnosis, and treatment of kidney cancer. Similarly, I eagerly anticipate the GU ASCO 2024 conference in San Francisco. With its 20th anniversary theme, "20 Years of Advancing Science and Transforming Patient Care," As the editor of the Kidney Cancer Journal, I'm committed to keeping our readers informed of the latest developments in the field. I look forward to sharing my perspective on the key takeaways from GU ASCO 2024 and its implications for the future of kidney cancer research and treatment.

Figure2. A patient delivers a talk at a special session at the IKCS2023.

In recent years, we've witnessed a paradigm shift in our understanding of kidney cancer and therapeutic approaches. Gone are the days of a one-size-fits-all approach. The rise of personalized medicine, powered by genomic sequencing and targeted therapies, has begun to unravel the intricate tapestry of tumor genetics, paving the way for targeted therapies that once belonged to the realm of science fiction. Besides, at the forefront of this movement are immunotherapies, once a glimmer of hope, have become a mainstay. Yet, despite these remarkable advances, significant challenges remain. Many patients still lag behind, yearning for treatments that not only extend life but also preserve quality of life. optimizing combinations, mitigating resistance, and harnessing the immune system's full potential are puzzles calling for collaborative exploration.

This is where our journal takes center stage. As your editor, I pledge to champion research that pushes the boundaries of knowledge, accelerates clinical translation, and empowers clinicians with the tools to conquer this insidious disease. We will prioritize cutting-edge research that delves into the molecular nuances of kidney cancer, uncovers novel therapeutic targets, and optimizes existing treatment strategies. Our pages will not only be a repository of scientific facts but also a forum for engaging discourse and insightful commentary. We will feature provocative editorials that dissect the latest findings, raise critical questions, and chart the course for future investigations. We will cultivate an environment that fosters collaborative spirit, welcoming diverse perspectives and forging bridges between disciplines – from basic science to clinical oncology, from surgeons to patient advocates.

Welcome, once again, to the vanguard of renal research. This journal serves as a platform for disseminating the latest discoveries and fostering open dialogue within the kidney cancer community. We encourage you to submit your research, engage in critical discussions, and contribute to the collective effort to conquer this complex disease. Remember, the fight against kidney cancer is a collective journey. Let us continue to learn, collaborate, and advocate for a brighter future for all patients.

KCJ ORIGINAL RESEARCH

OPEN ACCESS

Molecular and Immune Landscape of Fumarate Hydratase-mutated Renal Cell Carcinoma

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doi.org/10.52733/KCJ21n4-or1

ABSTRACT

Fumarate hydratase-deficient renal cell carcinomas are an aggressive form of kidney cancer that often results in poor prognosis and high fatality rates. The implications of somatic mutations are not well described, and standard treatment has not been established for this renal cell carcinoma subtype. Further molecular characterization of fumarate hydratase-deficient renal cell carcinomas could potentially help to identify biomarkers that can be exploited with future targeted therapies. 2199 renal cell carcinomas were analyzed by DNA sequencing (592-gene panel) and whole- transcriptome sequencing and 40 tumors were identified with pathogenic FH mutations. Co-occurrence of mutation with other cancer-related genes were assessed along with immune profiles and immunotherapy biomarkers. Fumarate hydratase-deficient renal cell carcinomas had a lower prevalence of co-mutation with common renal cell carcinoma driver mutations such as VHL and chromatin remodeling genes when compared to wild type renal cell carcinoma. Conversely, prevalence of several cancer-related genes (MAX, BRCA1, PMS2, BRAF, NF2, and AKT1) was higher in fumarate hydratase-deficient renal cell carcinomas. Immunotherapy biomarkers (mismatch repair deficiency and tumor mutational burden) were detected at low frequency in mutant and wild type renal cell carcinomas, while PD-L1 expression occurred at higher frequency in fumarate hydratase-deficient renal cell carcinomas. Fumarate hydratase-mutated kidney tumors may have a different mutational and immune landscape than wild type tumors. The absence of VHL mutations in a significant number of fumarate hydratase-deficient renal cell carcinomas suggest that FH mutations may drive tumorigenesis using distinct angiogenic pathways. Our study highlights potential therapeutic implications that will require further study.

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INTRODUCTION

Fumarate hydratase (FH) is a key component of the Krebs cycle, and loss of FH function leads to multiple disorders, including aggressive forms of cancer. Heterozygous germline mutations leading to FH deficiency are associated with hereditary predisposition to multiple tumors.[1,2] Fumarate can act as an oncometabolite by inhibiting multiple α-ketoglutarate (α-KG)-dependent dioxygenases, which in turn stabilizes hypoxia inducible factor 1 subunit alpha (HIF1α), creating a state of pseudohypoxia that leads to angiogenesis and tumor growth.[3-5] Thus, functional FH is often referred to as a tumor suppressor. FH-deficient renal cell carcinoma (RCC) is an aggressive form of renal cancer that was first described as part of hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome.[1,6] Although it was initially regarded as papillary type II RCC, the term FH-deficient RCC is now preferred as it can present in other histological subtypes of RCC. Germline mutations in the FH gene impart a high risk for developing tumors at an early age,[6-8] and HLRCC patients who develop RCC have significantly shor-

ter survival when diagnosed with advanced stage compared to early stage.[9] To improve early detection rates and survival, regular screening for RCC in HLRCC individuals is recommended.[10,11] FH-deficient RCC can also develop by sporadic loss-of-function mutation in the FH gene; however, there is no consensus on the implications of FH alterations in RCC outside of the HLRCC syndrome.[12,13]

FH-deficient tumors often result in poor prognosis and high fatality rates, while standard treatment in the advanced disease stage setting has not been established for this aggressive RCC subtype.[9] While immunotherapy combination strategies have improved outcomes for patients with clear cell RCC (ccRCC),[14] they have not been heavily tested in variant histologies. It is also unclear how the mutational landscape in FH-deficient patients augments sensitivity to immunotherapy or other targeted therapies. Therefore, further characterization of FH-deficient RCC with comprehensive molecular profiling could potentially help to identify biomarkers that can be exploited with future targeted therapies. The goal of this study is to enhance our knowledge of the molecular landscape of FH-deficient renal tumors (hereafter referred to as *FH-mut tumors*) in relation to wild type tumors (WT) lacking FH alterations. From DNA and RNA analysis, co-occurrence of mutation with other cancer-related genes were assessed along with immune profiles and immunotherapy biomarkers.

MATERIALS AND METHODS

Sample collection from participants

A total of 2199 RCCs underwent comprehensive tumor profiling at Caris Life Sciences (Phoenix, AZ, USA). This study was conducted in accordance with guidelines of the Declaration of Helsinki, Belmont Report, and U.S. Common Rule. In keeping with 45 CFR 46.101 (b), this study was performed utilizing retrospective, deidentified clinical data from patients with renal cancer. Therefore, this study was considered Institutional Review Board exempt and no patient consent was necessary from the subjects.

Next-Generation Sequencing (NGS)

NGS was performed on genomic DNA isolated from formalin-fixed paraffin-embedded (FFPE) tumor samples using the NextSeq or NovaSeq platform (Illumina, Inc., San Diego, CA, USA). For NextSeq, a custom-designed SureSelect XT assay was used to enrich 592 whole-gene targets (Agilent Technologies, Santa Clara, CA). All variants were detected with >99% confidence based on allele frequency and amplicon coverage, with an average sequencing depth of coverage of >500x and an analytic sensitivity of 5%. For NovaSeq, a hybrid pull-down panel of baits designed to enrich for more than 700 clinically relevant genes at high coverage (>500x) and high read-depth was used, along with another panel designed to enrich for an additional >20,000 genes at lower depth (>250x). Genetic variants identified were interpreted by board-certified molecular geneticists and categorized as pathogenic, likely pathogenic, or variant of unknown significance, according to ACMG standards. All variants were detected with greater than 99% confidence based on allele frequency and amplicon coverage, with an average sequencing depth of coverage of greater than 500 and an analytic sensitivity of 5%.

For RNA sequencing (RNA-Seq), biotinylated RNA baits were hybridized to the synthesized and purified cDNA targets and the bait-target complexes were amplified in a post capture PCR reaction. The resultant libraries were quantified, normalized, and the pooled libraries were denatured, diluted, and sequenced; the reference genome used was GRCh37/hg19 and analytical validation of this test demonstrated ≥97% positive percent agreement (PPA), ≥99% negative percent agreement (NPA) and ≥99% overall percent agreement (OPA) with a validated comparator method. Transcripts per million (TPM) values were generated using the Salmon expression pipeline for transcription counting.

Multiple test platforms were used to determine the microsatellite instability (MSI) or mismatch repair (MMR) status of the tumors, including fragment analysis (FA), IHC, and NGS. For IHC the following antibodies were used: M1 antibody for MLH1 (Roche Diagnostics, Belmont, CA, USA), G219-1129 antibody for MSH2 (Roche Diagnostics, Belmont, CA, USA), 44 antibody for MSH6 (Thermo Fisher Scientific, Carlsbad, CA, USA), and EPR3947 antibody for PMS2 (Abcam, Waltham, MA, USA). For NGS, 7,000 target microsatellite loci were examined and compared to the reference genome hg19). The tumor was determined MSI-high (MSI-H) by FA if two or more mononucleotide out of the five markers included in the assay were abnormal; the tumor was considered mismatch repair deficient (dMMR) by IHC if complete absence of protein expression of any of the four proteins was observed; the tumor was considered MSI-H by NGS by a threshold of 46 or more altered loci per tumor. MSI or MMR status of the tumor was determined in the order of IHC, FA, and NGS.

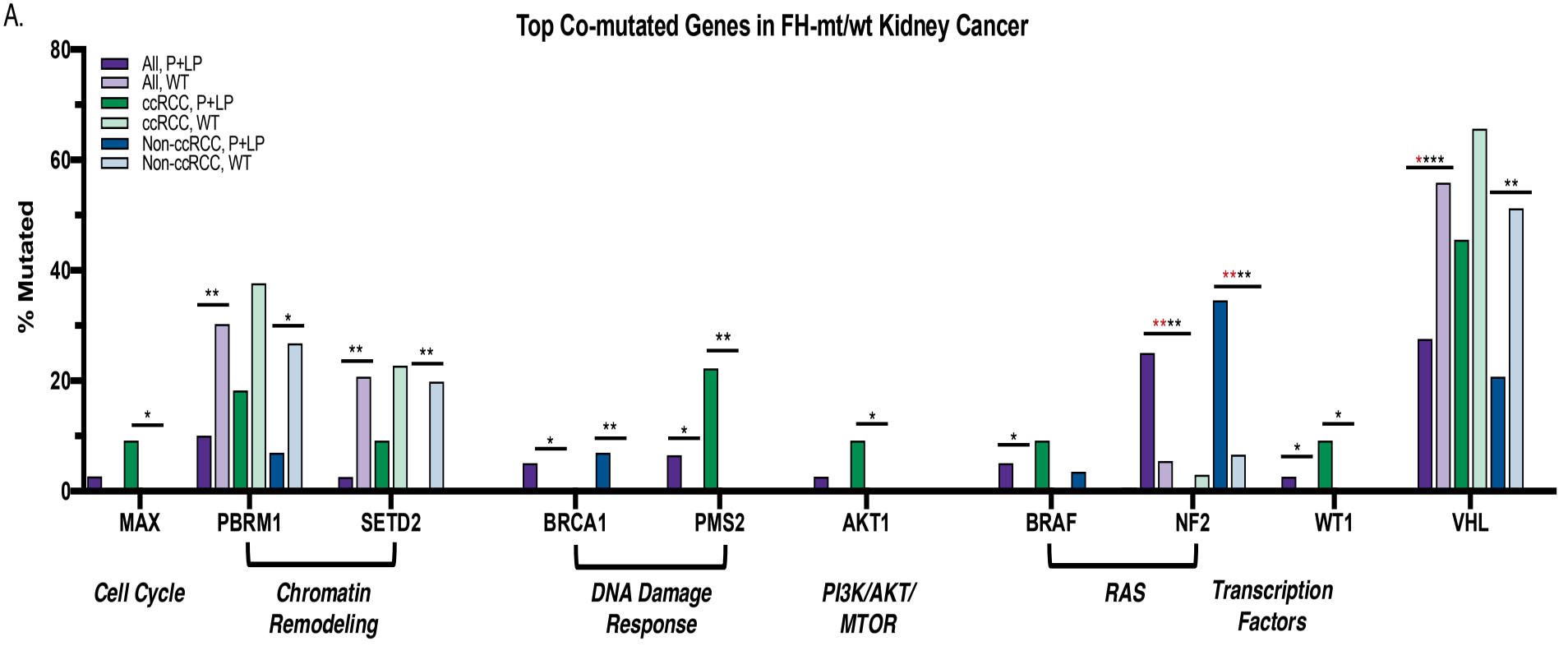
TMB was measured by counting all non-synonymous mutations found per tumor that had not been previously described as germline alterations in dbSNP151, Genome Aggregation Database (gnomAD) databases or benign variants identified by Caris geneticists. A cutoff point of >=10 mutations per MB was used based on the KEYNOTE-158 pembrolizumab trial.[15,16]

Immune cell fractions were calculated from deconvolution of bulk RNA-Seq data using the QuantiSeq computational pipeline.[17] Interferon-gamma score (IFN score) was calculated based on weighted sum of TPM values of 18 genes as previously described.[18]

Immunohistochemistry (IHC)

IHC was performed on full FFPE sections of glass slides using automated staining techniques, per the manufacturer's instructions, and were optimized and validated per CLIA/CAO and ISO requirements. The staining was scored for intensity (0 = no staining; 1+ = weak staining; 2+ = moderate staining; 3+ = strong staining) and staining percentage (0–100). Results were categorized as positive or negative by defined thresholds specific to each marker based on published clinical literature that associates biomarker status with patient responses to

A.



B.

Pathway	Biomarker	All Kidney Cancer					ccRCC					Non-ccRCC				
		P/LP, Pos (%)	WT, Pos (%)	fold change (%)	p-value	q-value	P/LP, Pos (%)	WT, Pos (%)	fold change (%)	p-value	q-value	P/LP, Pos (%)	WT, Pos (%)	fold change (%)	p-value	q-value
Cell Cycle	NGS-MAX	1 (2.63)	3 (0.14)	18.79	0.070	1	1 (9.09)	2 (0.3)	30.30	0.048	1	0 (0)	1 (0.07)	0 < 0.07	1	1
Chromatin Remodeling	NGS-PBRM1	4 (10)	642 (30.2)	0.33	0.006	0.277	2 (18.2)	256 (37.6)	0.48	0.225	1	2 (6.9)	386 (26.7)	0.26	0.016	0.652
	NGS-SETD2	1 (2.5)	436 (20.7)	0.12	0.005	0.270	1 (9.09)	153 (22.7)	0.40	0.471	1	0 (0)	283 (19.8)	0 < 19.8	0.008	0.353
DNA Damage Response	NGS-BRCA1	2 (5)	8 (0.375)	13.33	0.014	0.498	0 (0)	3 (0.44)	0 < 0.44	1	1	2 (6.9)	5 (0.34)	20.29	0.007	0.353
	NGS-PMS2	2 (6.45)	6 (0.411)	15.69	0.011	0.456	2 (22.2)	2 (0.41)	54.15	0.002	0.140	0 (0)	4 (0.41)	0 < 0.41	1	1
PI3K/AKT/MTOR	NGS-AKT1	1 (2.56)	3 (0.14)	18.29	0.070	1	1 (9.09)	1 (0.15)	60.60	0.032	1	0 (0)	2 (0.14)	0 < 0.14	1	1
RAS	NGS-BRAF	2 (5)	9 (0.42)	11.90	0.016	0.532	1 (9.09)	1 (0.15)	60.60	0.031	1	1 (3.45)	8 (0.55)	6.27	0.163	1
	NGS-NF2	10 (25)	115 (5.4)	4.63	5.41E-05	0.008	0 (0)	20 (2.94)	0 < 2.94	1	1	10 (34.5)	95 (6.55)	5.27	1.36E-05	0.002
Transcription Factors	NGS-WT1	1 (2.56)	1 (0.047)	54.47	0.036	1	1 (9.09)	0 (0)	9.09 > 0	0.016	0.866	0 (0)	1 (0.07)	0 < 0.07	1	1
Other	NGS-VHL	11 (27.5)	1194 (55.8)	0.49	3.63E-04	0.036	5 (45.5)	450 (65.6)	0.69	0.204	1	6 (20.7)	744 (51.2)	0.40	1.15E-03	0.107

FIGURE 1 | Genomic Features of FH-mt/wt Renal Cell Carcinoma. (**A**) Bar graphs showing the top significantly/trending co-mutated genes in FH-mt/wt Renal Cancer for all histologies and for ccRCC and non-ccRCC histologies. (**B**) Table showing number of tumors positive for the mutation, mutation frequency, frequency difference between mt/wt tumors and the statistical significance of each comparison across each histology grouping. Black asterisks indicate p-values, red asterisk indicate q-value. *p/q<0.05, **p/q<0.01, ***p/q<0.001, ****p/q<0.0001.

Patient Characteristics	All Kidney Cancer				
	P+LP	VUS	WT	sum	P-value
N	40	16	2143	2199	
Age, Median (Range)	53.5 (25-84)	65.5 (27-79)	63 (2-90)		<0.001
Gender, N (%)					1
Male	28 (70)	10 (62.5)	1514 (70.6)		
Female	12 (30)	6 (37.5)	629 (29.4)		
Site, N (%)					0.24
Primary	21 (52.5)	2 (12.5)	921 (43)		
Metastatic	19 (47.5)	14 (87.5)	1207 (56.3)		
Unclear	0 (0)	0 (0)	15 (0.7)		
Patient Characteristics	**Clear Cell Renal Cell Carcinoma (ccRCC)**				
N	11	7	686	704	
Age, Median (Range)	47 (26-67)	64 (41-79)	63 (26-90)		0.002
Gender, N (%)					0.647
Male	6 (54.5)	5 (71.4)	489 (71.3)		
Female	5 (45.5)	2 (28.6)	197 (28.7)		
Site, N (%)					0.502
Primary	7 (63.6)	1 (14.3)	363 (52.9)		
Metastatic	4 (36.4)	6 (85.7)	316 (46.1)		
Unclear	0 (0)	0 (0)	7 (1.02)		
Patient Characteristics	**Non-ccRCC**				
N	29	9	1457	1495	
Age, Median (Range)	54 (25-84)	67 (27-78)	64 (2-90)		<0.001
Gender, N (%)					0.519
Male	22 (75.9)	5 (55.6)	1025 (70.4)		
Female	7 (24.1)	4 (44.4)	432 (29.6)		
Site, N (%)					0.285
Primary	14 (48.3)	1 (11.1)	558 (38.3)		
Metastatic	15 (51.7)	8 (88.9)	891 (61.2)		
Unclear	0 (0)	0 (0)	8 (0.55)		

TABLE 1: Patient demographics and frequency of FH mutations in all kidney cancers, in clear cell renal cell carcinomas, and in non-clear cell renal cell carcinomas. P+LP = pathogenic and likely pathogenic variants. VUS = variants of unknown significance. Gender, p-value =0.475. Site, p-value=0.049.

therapeutic agents. A board-certified pathologist evaluated all IHC results independently. The primary antibody used against PD-L1 was SP142 (Spring Biosciences, San Francisco, CA, USA). The staining was regarded as positive if its intensity on the membrane of the tumor cells was 2+ (on a semiquantitative scale of 0–3: 0 for no staining, 1+ for weak staining, 2+ for moderate staining, or 3+ for strong staining) and the percentage of positively stained cells was >5%.

Statistical Analysis

The molecular features of tumors carrying pathogenic or likely pathogenic (P/LP) and WT FH tumors were compared. Categorical data was assessed using a chi-square or Fisher Exact test, where appropriate. Immune cell abundance in the tumor micro-environment were estimated using the method described above[17] and significance was tested using a nonparametric Wilcoxon rank-sum test. Gene expression for immune checkpoint genes was normalized to the median gene expression in the control group and fold change was calculated; significance was tested using nonparametric Wilcoxon rank-sum test. P-values were adjusted for multiple hypothesis testing by Bonferroni or Benjamini-Hochberg. All statistical analyses were two sided at a significance level set to 0.05.

Availability of data and materials

The deidentified sequencing data are owned by Caris Life Sciences. The datasets generated during and analyzed during the current study are available from the authors upon reasonable request and with permission of Caris Life Sciences.

RESULTS

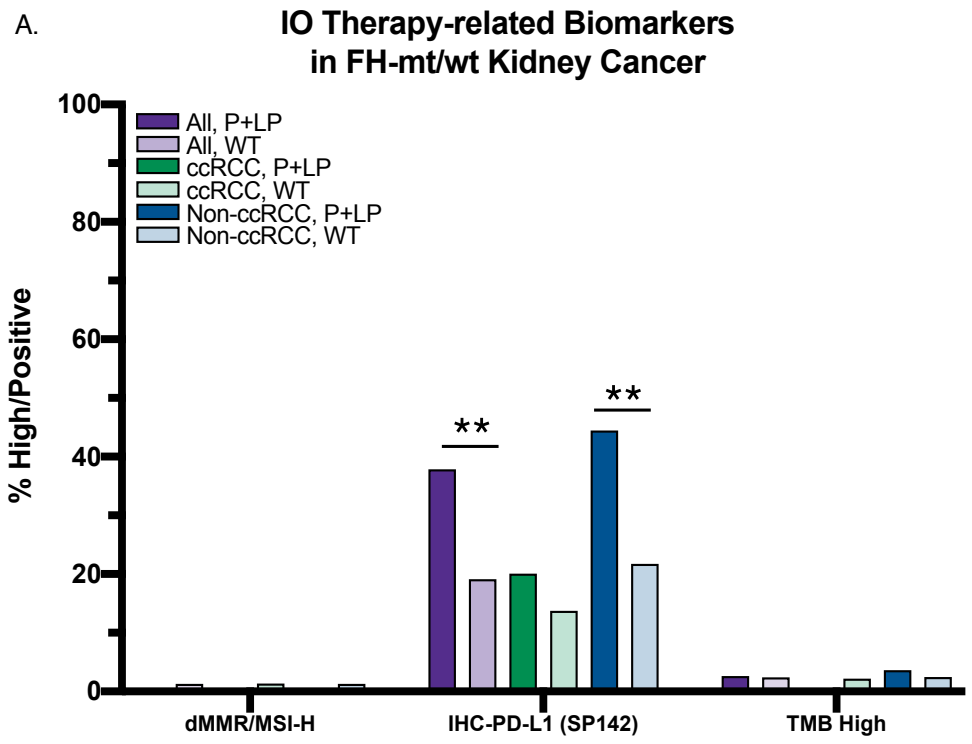
Basic Cohort Description

A total of 2199 RCCs were included in this analysis, with ages ranging from two to 90 years old, and a median age of 63. In this cohort, 29.4% were females and 70.6% were males. Nine hundred forty-four (42.9%) samples were from a primary tumor, and 1240 (56.4%) samples were from a metastatic or distant site (Table 1). Among all tumors, 2143 (97.4%) of the tumors did not harbor a FH mutation (wildtype, WT), 40 (1.82%) tumors had a pathogenic mutation or likely pathogenic mutation (P+LP-mt), and 16 (0.73%) tumors had a variant of unknown significance (VUS-mt) (Table 1). There was no significant difference in gender distribution among the various FH-mutant groups (P+LP-mt vs VUS-mt vs WT: 30% vs 37.5% vs 29.4% for female and 70% vs 62.5% vs 70.6% for male). However, more P+LP-mt tumors were from the renal primary site compared to VUS-mt or WT tumors (52.5% vs 12.5% vs 43%) (Table 1). We sorted the data to differentiate two main histological subtypes of renal cancer: tumors clearly noted as clear cell histology (ccRCC) and those with unclear or other histological subtypes (non-ccRCC). Among the 704 ccRCC tumors included in this analysis, 11 (1.56%) were P+LP-mt. Among 1495 non-ccRCC tumors, 29 (1.94%) were P+LP-mt tumors.

Mutational landscape of FH-mutated Renal Cell Carcinoma

When examining the co-occurrence of cancer-related mutations in our cohort (Figure 1), a lower prevalence of FH co-mutation was observed with VHL in P+LP-mt tumors compared to WT tumors overall (27.5% vs 55.8%, p-value=3.63E-04). The lower frequency of VHL co-mutation was observed in both ccRCC to non-ccRCC, but the difference between P+LP-mt and WT tumors was more significant in the latter (p-value=1.15 E-03). A similar pattern was observed with chromatin remodeling genes, with lower prevalence of co-mutation with PBRM1 and SETD2 in P+LP-mt tumors (10% vs 30.2%, p-value=0.006; and 2.5% vs 20.7%, p-value=0.005, respectively). Again,

A.



B.

Biomarker	All Kidney Cancer P/LP, Pos (%)	WT, Pos (%)	fold change (%)	p-value	q- value
dMMR/MSI-H	0 (0)	27 (1.27)	0 < 1.27	1	1
IHC-PD-L1 (SP142)	14 (37.8)	389 (19.1)	1.98	0.004	0.270
TMB High	1 (2.56)	48 (2.34)	1.09	0.608	1

ccRCC P/LP, Pos (%)	WT, Pos (%)	fold change (%)	p-value	q- value
0 (0)	9 (1.33)	0 < 1.33	1	1
2 (20)	88 (13.7)	1.46	0.635	1
0 (0)	14 (2.13)	0 < 2.13	1	1

Non-ccRCC P/LP, Pos (%)	WT, Pos (%)	fold change (%)	p-value	q-value
0 (0)	18 (1.25)	0 < 1.25	1	1
12 (44.4)	301 (21.7)	2.05	0.005	0.330
1 (3.57)	34 (2.44)	1.46	0.506	1

FIGURE 2: Immunotherapy-related Biomarkers in FH-mt/wt Renal Cell Carcinoma. (**A**) Bar graphs showing the frequency of dMMR/MSI-H status, PD-L1 positivity and TMB high frequency in FH-mt/wt Kidney Cancer for all histologies and for ccRCC and non-ccRCC histologies. (**B**) Table showing number of tumors positive/high, positive/high frequency, frequency difference between mt/wt tumors and the statistical significance of each comparison across each histology grouping. Black asterisks indicate p-values, red asterisks indicate q-value. *p/q<0.05, **p/q<0.01, ***p/q<0.001, ****p/q<0.0001.

this difference was observed in both ccRCC and non-CCRCC, but more significantly in the latter. (p-value=0.016 for PBRM1; p-value=0.008 for SETD2).

Conversely, co-mutation prevalence in P+LP-mt tumors was higher in several cancer-related genes. With the cell cycle gene, MAX, co-mutations were detected at a higher rate in P+LP-mt tumors compared to WT tumors (2.63% vs 0.14%, p-value=0.07) and observed only in the ccRCC histology subtype (p-value=0.048). BRCA1 co-mutations were higher in P+LP-mt tumors (5% vs 0.38, p-value=0.014) only in the non-ccRCC histology subtype. Alternately, PMS2 co-mutations were higher in P+LP-mt tumors (6.45% vs 0.41%, p-value=0.11) only in the ccRCC histology subtype. Among genes in the RAS pathway, higher BRAF co-mutations in P+LP-mt tumors (5% vs 0.42%, p-value=0.016) were observed in both histology subtypes, yet more significantly in ccRCC (p-value=0.031). NF2 co-mutations were higher in P+LP-mt tumors compared to WT (25% vs 5.4%, p-value=5.41E-05) only in non-ccRCC. Other prevalent co-mutations that increased in P+LP-mt tumors were detected in AKT1 (2.56% vs 0.14%, p-value=0.07) and WT1 (2.56% vs 0.05%, p-value=0.036), both of which were only observed in ccRCC (p-value=0.032 for AKT1; p-value=0.016 for WT1) (Figure 2). Distribution of mutations among ccRCC and non-ccRCC, and primary vs metastatic tumors is further illustrated in Supplemental Figure 1.

Mismatch repair deficiency, or MSI-high status, was found at low frequency (1.27%) in WT tumors, and not observed in P+LP-mt tumors (Figure 2). TMB-high status was also very low in both P+LP-mt tumors and WT tumors with no significant difference between the groups (2.56% vs 2.34%, respectively. p-value=0.608). On the other hand, PD-L1 expression was detected at a higher frequency of P+LP-mt tumors compared to WT tumors (37.8% vs 19.1%, p-value=0.004). This pattern was observed in both ccRCC and non-ccRCC, although only significant in the latter (p-value=0.005).

Immune landscape of FH-mutated Renal Cancer

Immune infiltration analysis indicated P+LP-mt tumors had less NK cell and M2 macrophage infiltration compared to WT tumors (Figure 3). This pattern was observed in both ccRCC and non-ccRCC, though significant only in non-ccRCC. Most other immune cell types demonstrated slightly lower infiltration in P+LP-mt tumors,

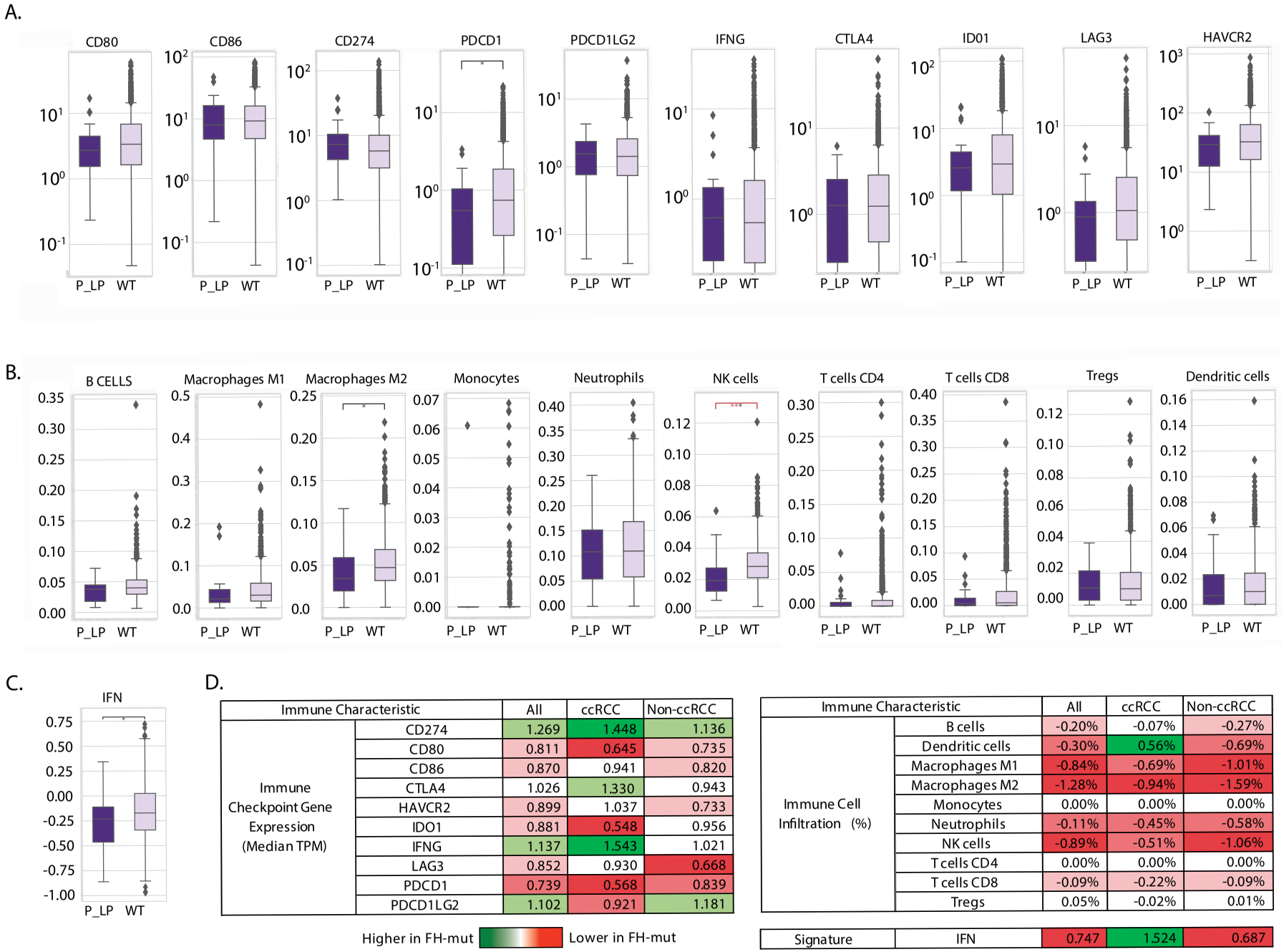


FIGURE 3 | Immune Tumor Microenvironment of FH-mt/wt Renal Cell Carcinoma. **(A)** Expression of immune checkpoint genes in FH-mt/wt tumors. (**B**) Immune cell infiltrates estimated by Quantiseq in FH-mt/wt tumors. (**C**) IFN score in FH-mt/wt Renal Cancer. (**D**) Table showing immune tumor microenvironment changes in all tumors, ccRCC, and non-ccRCC (values represent P+LP FH-mutant tumors relative to WT). Bold/italicization indicates p<0.05. Black asterisks indicate p-values, red asterisks indicate q-value. *p/q<0.05, **p/q<0.01, ***p/q<0.001, ****p/q<0.0001.

with the exception of dendritic cells which were higher in ccRCC and lower in non-ccRCC. Most differences in expression levels of immune checkpoint genes were not statistically significant, except for lower expression of LAG3 and PDCD1 in P+LP-mt tumors relative to WT tumors. P+LP-mt tumors exhibited higher expression of CD274 in both histology subtypes. Although not statistically significant, expression of CTLA4 and IFNG were highest in ccRCC tumors (Figure 3A, 3D). The IFN signature was higher in ccRCC, but significantly lower only in non-ccRCC (Figure 3C, 3D).

DISCUSSION

Numerous reports have described distinct prognostic indicators and therapeutic options for specific RCC subtypes,[19-22] yet most of the available literature and clinical trials have not been conducted in the context of genomic mutations, including FH status. Although the relatively small numbers of FH-mut tumors within each histology subgroup limits the conclusions that can be drawn, some of the results point to possible trends that may warrant further investigation. Examination of co-mutated genes revealed that some mutations which are commonly found in RCC (VHL, PBRM1, SETD2) often do not occur concurrently in FH-mut tumors. This suggests that loss of FH may be an important driver of tumorigenesis in RCC independently of classic RCC drivers. The presence or absence of such co-mutations may also affect the efficacy of targeted therapies that have recently been developed for RCC naively of FH status. For example, PBRM1 deficiency has been associated with clinical benefit from ICI therapy,[23] and recently transcriptome-based molecular profiles integrated with PBRM1 status and angiogenesis signatures have been developed to further facilitate clinical guidance.[23-25] With advances in the use of molecular subtypes for predictive value, FH status and associated mutations may therefore be considered in the cases where common RCC driver mutations are absent.

We observed VHL mutations occurring most frequently in ccRCC, which agrees with reports citing the prevalence of VHL mutations in ccRCC. In our study, VHL mutations were decreased in all FH-mut tumors with the most significant decrease in non-ccRCC (Figure 1). Neoangiogenesis linked to the von-Hippel Lindau (VHL) gene has been commonly implicated as the main pathway of tumorigenesis in renal cancers.[26] As VHL inactivation leads to HIF activation, subsequent tumorigenesis may occur in a similar fashion to what has subsequently been attributed to FH deficiency. Reduced FH expression in ccRCC was demonstrated via HIF stabilization to increase VEGF production.[27] Thus, HIF inhibitors and other drugs targeting metabolic pathways have become the basis of emerging targeted therapies against RCC and may also be applicable to FH-deficient tumors.[28,29]

Antiangiogenic tyrosine kinase inhibitors (TKI) of the VEGF pathway led to improved outcomes in several studies involving metastatic RCCs.[30-33] Further improvements have also been demonstrated when TKIs were combined with immunotherapies.[34] The similar angiogenic effects that FH mutations and VHL mutations have indicates that FH-mut tumors may also respond well to TKIs; however, the distinctions between these RCCs may warrant independent clinical trials to validate this as a therapeutic option. Clinical trials with FH-deficient tumors in HLRCC (AVATAR trial, NCT01130519) have shown promising results inhibiting angiogenesis by targeting the VEGF and EGFR pathways, which led to NCCN recommendation of this regimen in the treatment of HLRCC patients.[35,36] One smaller study compared erlotinib/bevacizumab combinations to immunotherapy/TKI combinations in FH-deficient RCC, reporting more favorable clinical outcomes in the latter.[37] Further molecular comparisons between responders and non-responders may help to identify biomarkers that influence response to this treatment.

The most common co-mutation between FH-mut and WT tumors was in the NF2 gene (Figure 1), which prevents tumor growth through inhibition of different pathways including the RAS, PI3K/AKT, and HIPPO pathways.[38,39] Concurrent mutations between FH and NF2 have also been previously reported in RCC.[12,37,40] Previous studies have demonstrated that targeting YAP1 resulted in reduced tumor growth in NF2-mutated RCCs, suggesting that a significant subset of the FH-mut population may also benefit from targeting the Hippo pathway.[41-43]

Concurrent mutations were also observed between FH and DNA damage repair gene, BRCA1 (Figure 1). BRCA1 mutations are an indication for the use of Poly (ADP-ribose) polymerase (PARP) inhibitors in some tumor types. PARP inhibitors alone or in combination with other agents are also undergoing evaluation in VHL-deficient RCCs based on the DNA repair detect status and/or potential sensitivity of this genomic status to immunotherapies.[44-46] However, one phase II study determined the combination of PARP inhibitors and PD-L1 inhibitors to be ineffective in VHL-mutated RCC.[47] Accumulation of fumarate has also been reported to suppress the homologous recombination (HR) repair pathway,[48] which would not be detected by DNA sequencing, but suggests the sensitivity of FH-mut tumors to DNA damaging agents. Co-mutations between FH and AKT1 were higher specifically in ccRCC. AKT signaling and the mTOR signaling pathway have also been linked to DNA damage response,[49] suggesting that targeting these pathways may be useful for a subset of the population. Combinations of mTOR inhibitors and angiogenesis inhibitors have demonstrated robust activity in RCC patients.[50] Other studies have used gene expression signatures to reveal prognostic value of angiogenesis signatures and T-cell-inflamed GEP signatures for use of VEGF and mTOR inhibitors in RCCs.[51]

RCCs have often been described as highly immunogenic, and numerous studies have demonstrated the efficacy of immunotherapies. In our study the analysis of immune checkpoint gene expression did not reveal significant differences between FH-mut and WT tumors. LAG3 exhibited the most significant difference in immune gene expression, which was

observed specifically in non-ccRCC (Figure 3). Recent studies suggested that targeting LAG-3 might provide a promising partner in combinatorial immunotherapies in RCC,[52] although our data may suggest differences between histology subtypes in this context. The analysis of immune cell infiltration also did not reveal significant changes between FH-mut and WT tumors for most immune cells, with the exception of lower infiltration of NK cells and M2 macrophages in the non-RCC population (Figure 3).

The IFN-γ response-related signature (IFN score) has been developed as a predictive biomarker for immunotherapy.[53,54] When a similar IFN-γ response-related signature was described as a prognostic indicator in ccRCCs, a high-risk group exhibited low sensitivity to several drugs, not including immunotherapies.[55] In our study, the IFN-γ response-related signature was significantly reduced in FH-mut tumors in the non-ccRCC group, whereas the IFN score was higher in ccRCC (Figure 3). Although the development of biomarkers for stratification of patients in immunotherapy selection is ongoing in RCC, these results suggest that variability in histological subtypes might be considered in future studies.

In our study, there were no significant differences observed between FH-mut and WT tumors for prevalence of TMB and MSI-H status (Figure 2). A previous study also reported low TMB and stable MSI status in both somatic and germline FH-mut RCCs.[12] However, RCCs have been reported to have positive responses to immunotherapies and combination therapies with TKIs. A study of 336 ccRCC patients reported that higher TMB was correlated with lower immune cell infiltration and poor survival outcomes.[56] Thus, contrary to what has been observed in some other cancer types, findings from numerous studies suggest that higher mutation rates in RCC are associated with immunologically cold tumor microenvironments. In contrast to TMB and MSI biomarkers, measurement of PD-L1 expression by IHC revealed higher expression of PD-L1 in FH-mut tumors, which was more pronounced in non-ccRCC (Figure 2). Several studies have described PD-L1 as a prognostic indicator of poor survival rates in immunotherapy-naive RCCs.[57-59] Other studies have demonstrated the efficacy of ICI therapy for RCC, and the CheckMate 214 trial led to FDA approval of ICI combination therapy in 2018.[60,61] However, most of these studies do not describe the genomic context to identify biomarkers that could differentiate responders from non-responders. In other tumor types, biomarkers developed to stratify patients for immunotherapy selection have included PD-L1 expression, TMB, MSI, and TME. However, the characteristics of RCCs have thus far precluded them from effective use of predictive ICI biomarkers. Follow-up studies from the CheckMate 214 trial reported that biomarkers previously associated with ICI benefit were not predictive in RCC.[62]

A few studies with small cohorts have analyzed drug response from FH-deficient RCCs with varying results. One study with 18 patients reported that patients with FH-deficient RCC who received immunotherapy had better clinical outcomes than patients who received antiangiogenic therapy alone.[40] Conversely, another study with 24 patients reported that FH-deficient RCCs responded better to various antiangiogenics compared to immunotherapies or mTOR inhibitors.[63] Therefore, further studies are needed to investigate the benefits of immunotherapies in FH-deficient renal cancers with the use of other potentially predictive biomarkers.

Although a significant number of RCC patients respond to immunotherapy, a significant portion of this population also exhibits resistance, or develops resistance within several months. There is increasing interest in utilizing TKIs in combination with ICIs as a first- or second-line treatment, as well as understanding mechanisms of resistance.[37,64,65] In addition to promoting angiogenesis and tumor migration, activation of HIF and increased VEGF also influence changes in the tumor microenvironment, including the release of immunosuppressive factors such as PD-L1.[34] Alternately, reports have described that antiangiogenic molecules can overcome immunosuppressive networks and thereby influence sensitivity of tumors to immunotherapies.[66] Analyzing the molecular features of FH-deficient RCCs in the context of drug response will be beneficial for better understanding the clinical and therapeutic implications of such a dynamic system.

Study Limitations

The primary limitation of this study is the small cohort size. Although it is the largest cohort of FH-deficient RCC tumors that has been described by comprehensive molecular profiling, a total sample size of 40 FH-mut samples limits the comparative analyses that could be performed. Although there is considerable heterogeneity among RCCs, small cohort size also limits conclusions about prevalence in histological subtypes, molecular subtypes, or comparisons between primary and metastatic tumors. Furthermore, this study does not include other variables which may impact the molecular landscape of the sequenced samples, including demographic information, or clinical information about staging or treatment regimens. The lack of clinical outcomes data associated with the cohort also limits the clinical implications that can be drawn from the observed molecular characteristics. RNA-Seq data from FFPE samples also has inherent limitations which should be considered with immune profiling methods used in this study. Despite the rare incidence of FH-mut RCCs, the accurate diagnosis of FH status is important due to their aggressive nature. The accumulation of succinate dehydrogenase in FH-deficient tumors provides a highly immunoreactive target in recently improved IHC-based screening methods that could provide clinical utility for many renal cancers.[67,68]

In conclusion, comprehensive genomic profiling of FH-deficient RCCs yielded results in this study that were generally consistent with prior reports of genetic

characteristics of FH-deficient RCCs, while analysis of a large sample size enabled observation of some interesting trends. FH-deficient RCCs exhibit molecular characteristics that may distinguish them from WT-RCCs. Common RCC driver mutations of renal cell carcinoma (RCC) are reduced in FH-mutated RCC, while some other co-mutations are increased that may point to new therapeutic options. Overall, these findings point to several possible trends in FH-deficient RCC that could be validated in a larger clinical study, while comprehensive molecular analysis may provide the potential for identifying novel therapeutic approaches in FH-deficient RCC.

SUPPLEMENTAL INFORMATION

Access supplemental information online. https://kidney-cancer-journal.com/KCJ21n4-or1.php

AUTHORS DISCLOSURES:

SW, AH, AG, AH, and CN are employees of Caris Life Sciences. BN reports a consulting or advisory role for Exelixis. PCB reports a consulting or advisory role for Bayer, BMS, Caris Life Sciences, Clovis Oncology, Dendreon, Eisai, EMD Serono, and Pfizer; PCB reports research funding from Blue Earth Diagnostics. CJR reports a consulting or advisory role for Advanced Accelerator Applications, Bayer, Clovis Oncology, Dendreon, Myovant Sciences, and Roivant; CJR reports receiving honoraria from Bayer and Janssen Oncology; CJR reports research funding from Clovis Oncology and Genzyme. RRM reports a consulting or advisory role for Astellas Medivation, AstraZeneca, Bayer, Bristol-Myers Squibb, Calithera Biosciences, Caris Life Sciences, Dendreon, Exelixis, Janssen, Merck, Myovant Sciences, Novartis, Pfizer, Sanofi, Sorrento Therapeutics, Tempus, and Vividion Therapeutics; RRM reports research funding from Bayer, Pfizer, and Tempus. EIH reports a consulting or advisory role for Agensys, AstraZeneca, Bayer, Dendreon, and Sanofi; EIH reports receiving honoraria from AstraZeneca, Bayer, Dendreon, Sanofi, and Seattle Genetics. EIH reports funding for travel and/or the speaker's bureau from Sanofi, Agensys, and Bayer; EIH reports research funding from Agensys, AIQ Solutions, Astellas Pharma, AstraZeneca, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Calibr, Caris Life Sciences, Celgene, Celldex, Champions Oncology, Corcept Therapeutics, Curemeta, Daiichi Sankyo Inc., Dendreon, eFFECTOR Therapeutics, Eisai, Esanik, Five Prime Therapeutics, Fortis, Genentech/Roche, GlaxoSmithKline, Ignyta, Infinity Pharmaceuticals, Inovio Pharmaceuticals, Janssen Research & Development, Medivation, Merck, Merck Sharp & Dohme, Millennium, Mirati Therapeutics, Modra Pharmaceuticals, Novartis, Oncolys BioPharma, Pellficure, Peloton Therapeutics, Pharmacyclics, Plexxikon, Seattle Genetics, Synta, Tokai Pharmaceuticals, Zenith Epigenetics, and Zenith Epigenetics. All other authors have declared no conflicts of interest.

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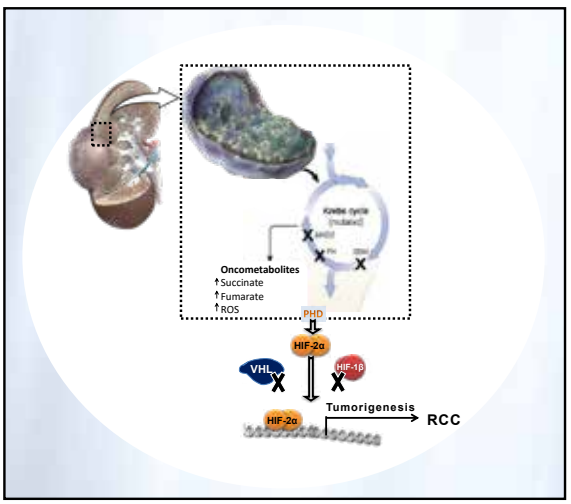
Commentary for the KCJ article "*Molecular and Immune Landscape of Fumarate Hydratase-Mutated Renal Cell Carcinoma*"

Nirmish Singla, MD, MSCS, FACS

https://doi.org/10.52733/KCJ21n4-commentary

Fumarate hydratase (FH)-deficient renal cell carcinomas (RCC) are a rare yet aggressive type of kidney cancer. Both their rarity and aggressiveness make them particularly challenging to study. The authors of this study (*refer pages 115-124, this Q4 issue*) are to be commended for providing perhaps the largest genomic and transcriptomic characterization of FH-deficient RCC to date. As the investigators acknowledge, there are undoubtedly several limitations to their findings, including the limited clinicopathologic information and outcomes data in their cohort, absence of data concerning therapeutic exposures prior to sample acquisition, and heterogeneity in the tumor sites for the samples analyzed.

Nevertheless, they offer useful molecular insights into a rare disease that may help inform future work. Co-occurrence of NF2 mutations in FH-deficient RCC has been described previously and further corroborated in a considerable subset of the present cohort, suggesting that inhibitors of the Hippo pathway may carry therapeutic potential in some of these patients. Elucidating the immune microenvironment for these tumors may provide a further basis for combined therapeutic strategies.



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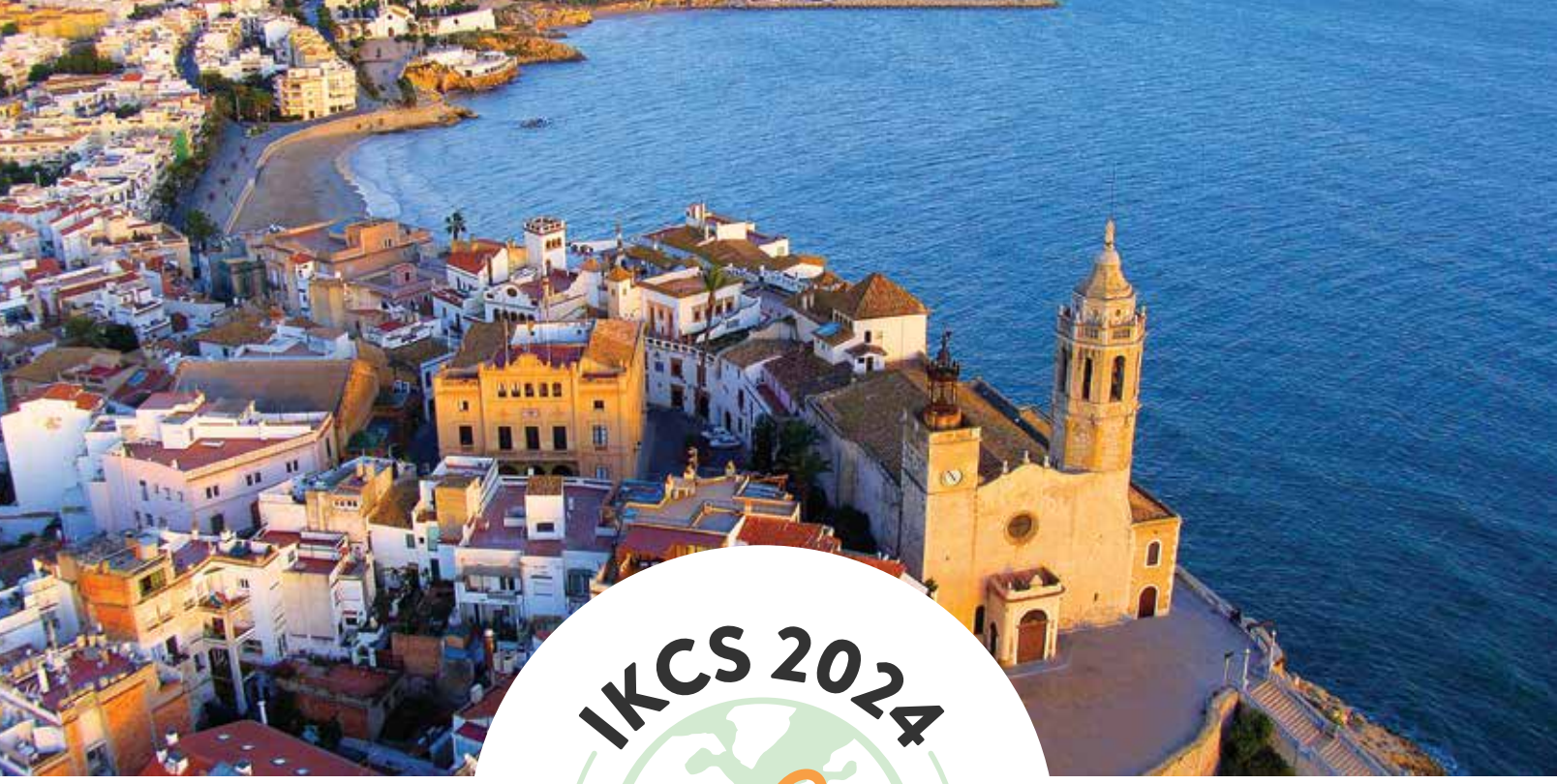

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These recommended abstracts from ASCO 2023 Annual Meeting have been selected by Thomas E Hutson, DO, PharmD, *Editor-in- Chief* of the *Kidney Cancer Journal.* The chosen abstracts provided here highlight some of the most important trends in ongoing trials and reflect the foremost research and strategies from latest clinical trials that impact the current standard of care in renal cancer.

https://doi.org/10.52733/IKCS23abs

ABSTRACT LBA 1: Zanzalintinib (XL092) in clear cell renal cell carcinoma (ccRCC): Results from STELLAR-001. *Pal S et al.*

BACKGROUND: Zanzalintinib (XL092) is a novel, multi-targeted TKI that targets VEGFR, MET, and TAM kinases. Here we present initial results of single-agent zanzalintinib in the ccRCC expansion cohort, including outcomes by prior exposure to cabozantinib.

METHODS: Adult patients with advanced ccRCC and ECOG ≤1 were eligible following radiographic progression on ≥1 prior systemic therapy for inoperable, locally advanced or metastatic disease. Patients received zanzalintinib at a starting dose of 100 mg once daily. ORR by investigator per RECIST 1.1 and safety were evaluated.

RESULTS: A total of 32 patients were enrolled in the ccRCC expansion cohort. Median follow-up was 7.0 months (range: 4.4–12.5). Median age was 64 (range 39–79) years, and 72% were male; 81% had IMDC intermediate-risk disease, and 6% had poor risk. Patients had received a median of 2 (range 1–3) lines of prior therapy. Fourteen (44%) patients had never received cabozantinib (cabo-naïve), and 17 (53%) received prior cabozantinib (cabo-exposed); cabozantinib exposure was unknown for 1 patient. In the cabo-exposed and cabo-naïve subgroups, 10/17 (59%) and 5/14 (36%) patients had ECOG 1, respectively, and 10/17 (59%) and 2/14 (14%) had ≥3 prior lines of therapy. At data cutoff, 18 (56%) patients remain on study treatment. With a best response of 10 PRs and 18 SDs, the ORR was 31% and disease control rate (DCR) was 88%. In cabo-naïve and cabo-exposed patients, ORR was 43% and 24%, respectively; DCR was 86% and 94%. Two cabo-naïve patients who had unconfirmed PRs at data cutoff were subsequently confirmed to have PR (updated ORR 38% in the overall population and 57% in the cabo-naïve population).

CONCLUSIONS: Single-agent zanzalintinib showed promising preliminary antitumor activity and manageable toxicity in patients with previously treated advanced ccRCC. Antitumor activity was observed in both cabo-naïve and cabo-exposed patient populations, with most patients in both subgroups achieving disease control.

ABSTRACT2: Pembrolizumab Development of models of Neurofibromatosis 2 (NF2) loss in kidney cancer of Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC). *Ohtake S et al.*

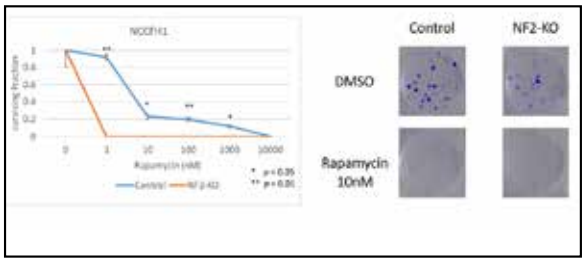
BACKGROUND: Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC) is characterized by cutaneous leiomyomas, uterine leiomyomas, and renal cell carcinoma, caused by a germline mutation in the Fumarate Hydratase (FH) gene. HLRCC patients have aggressive disease with poor outcomes due to limited treatment options. Neurofibromatosis 2 (NF2) is an autosomal dominant disease mainly characterized by high risk of schwannomas. NF2 mutations are identified in 15-20% of HLRCC kidney cancer. As there has been extensive research on Neurofibromatosis-related cancers, we created models of the NF-2 deficient HLRCC kidney cancer to assess the biologic effects and therapeutic sensitives to agents that have been investigated in this disease.

METHODS: Three isogenic NF2-KO cell lines were generated from NF-2 wild-type HLRCC patients derived cell lines (NCCFH1, UOK262, and UOK268), using CRISPR. Protein abundance was analyzed using Western Blot. Gene expression changes were evaluated using the Nanostring nCounter Tumor Signaling 360 gene expression panel and analyzed by ROSALIND^{TM}. Cell proliferation, soft agar, scratch wound-healing, and transwell invasion assays were performed. Clonogenic survival assays were performed in NF2-KO HLRCC cell lines treated with Rapamycin, GSK2256098, and TAK228.

RESULTS: Loss of function of NF2 increased kidney cancer cell proliferation, migration, invasion, and colony formation. Gene expression profiling revealed increased activation of mammalian targets of rapamycin (mTOR) signaling, Glucose Metabolism, HIF1 Signaling. NF2 deficient NCCFH1 and UOK262 models displayed increased sensitivity to rapamycin.

CONCLUSIONS: Our current data indicated that FH deficient cell lines with NF2 loss of function may have

more aggressive potential, and further suggest that mTOR complex-1 (mTORC-1) therapy could play a role into treatment algorithms of NF-2 deficient HLRCC kidney cancers. In vivo experiments are planned to further characterize the models and test therapeutic approaches.



ABSTRACT 3 Germline susceptibility to renal cell carcinoma and implications for genetic screening.

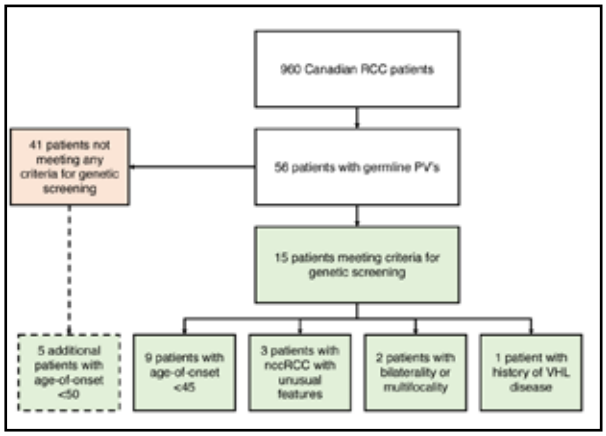
Glennon KI et al.

BACKGROUND: There are large, unexplained variations in the incidence of renal cell carcinoma (RCC) across the globe. Germline genetic variation contributes strongly to individual differences in susceptibility to cancer; however, genetic risk factors for RCC are poorly understood. Likewise, little is known about differences between the genetic basis of ccRCC and other RCCs (nccRCC).

METHODS: We investigated genetic susceptibility to RCC within the Canadian population through targeted sequencing of 19 RCC-related and 27 cancer-predisposition genes in a cohort of 960 patients, and compared potential risk-genes to those identified in other populations. We identified pathogenic variants (PVs) and conducted gene-based association tests between patients with RCC and non-cancer controls to identify risk-genes for RCC.

RESULTS: We identified 39 germline PVs in 56 Canadian RCC patients. Compared to cancer-free controls, PVs in CHEK2, and ATM were significantly enriched in patients with ccRCC, whereas PVs in FH were enriched in patients with nccRCC. We observed an association between PVs in BRCA1/BRCA2 and ATM with the presence of metastasis. Gene-burden comparisons to other populations showed an enrichment for TP53 in RCC patients from Japan, while RCC patients from Canada, UK, and USA showed an enrichment for CHEK2 and ATM. RCC patients from the USA were enriched for germline PVs in FH and BAP1. We evaluated the performance of current genetic screening criteria for RCC. We reveal that current criteria for referral to genetic screening for hereditary RCC fail to include the majority (73%) of patients harboring rare germline PVs in risk genes for RCC.

CONCLUSIONS: This serves as the first investigation into RCC susceptibility within the Canadian population. These findings also provide insight into differences in global RCC-susceptibility, and that investigation of germline risk-genes in additional populations are needed to fully understand the heterogeneous susceptibility to RCC.



ABSTRACT 4 - LITESPARK-013: Randomized Phase 2 Study of Two Doses of Belzutifan in Patients With Advanced Clear Cell Renal Cell Carcinoma (ccRCC).

Ghatalia P et al.

BACKGROUND: In the phase 1 LITESPARK-001 study, the maximum tolerated dose of belzutifan was not reached for doses up to 240 mg/day, and the recommended phase 2 dose (RP2D) regimen was 120 mg once daily. The randomized phase 2 LITESPARK-013 study (NCT04489771) was conducted to examine whether a higher belzutifan dose could improve efficacy while maintaining an acceptable safety profile.

METHODS: Patients with advanced ccRCC, measurable disease per RECIST v1.1, ≤3 prior systemic regimens for advanced ccRCC, and disease progression during or after anti–PD-1/L1 therapy were randomly assigned 1:1 to receive oral belzutifan 120 mg once daily or 200 mg once daily. Patients were stratified by IMDC risk (0 vs 1/2 vs 3-6) and number of prior TKI therapies (0 vs 1 vs 2/3). The primary end point was ORR per RECIST v1.1 by blinded independent central review (BICR). Secondary end points were DOR and PFS per RECIST v1.1 by BICR, OS, safety, and PK.

RESULTS: Overall, 154 patients were randomly assigned to the 120-mg (n=76) or 200-mg group (n=78). Median follow-up was 20.1 months (range, 14.8-28.4). Efficacy outcomes were similar between groups (Table). Seventy patients (92.1%) in the 120-mg group and 72 (92.3%) in

the 200-mg group experienced a treatment-related adverse event (TRAE). Percentages of treatment-related anemia (81.6% with 120 mg; 83.3% with 200 mg) and hypoxia (23.7% with 120 mg; 26.9% with 200 mg) were similar between groups.

CONCLUSIONS: The efficacy of belzutifan was similar between patients who received the 120-mg RP2D and those who received a 200-mg dose. The safety of both doses was consistent with the known safety profile of belzutifan. These results support 120 mg orally once daily as the preferred dosage for belzutifan.

Table. Efficacy of belzutifan at 2 different dose levels

End point	120-mg (n=76)	200-mg (n=78)
ORR, %	23.7 (18 PR)	23.1 (4 CR; 14 PR)
	Difference: −0.5 (95% CI, −14.0 to 12.9)[a]	
DOR, median (range), months	Not reached (2.6+ to 16.1+)	16.1 (2.1+ to 23.5+)
PFS, median, months	7.3	9.1
	HR, 0.94 (95% CI, 0.63-1.40)	
OS, median, months	No reached	Not reached
	HR, 1.11 (95% CI, 0.65-1.90)	

[a]Using the Miettinen-Nurminen method stratified by IMDC risk.

+ indicates ongoing response.

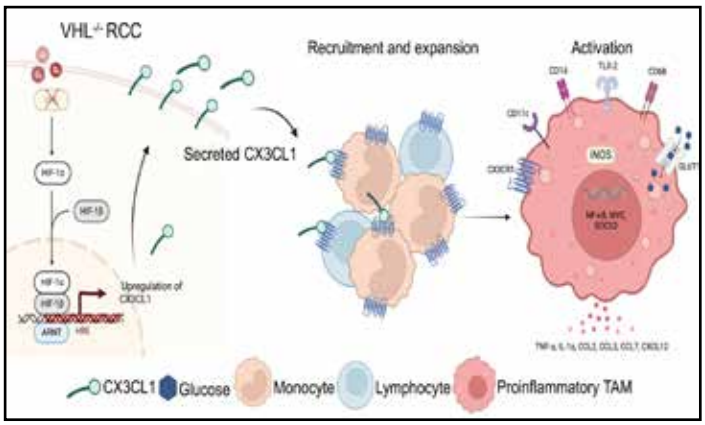
ABSTRACT 22: VHL loss reprograms the immune landscape to promote an inflammatory myeloid microenvironment in renal tumorigenesis. Wolf M et al.

BACKGROUND: Clear cell renal cell carcinoma (ccRCC) is an aggressive disease characterized by dysregulated hypoxia signaling, metabolic defects, and a complex tumor microenvironment (TME) highly enriched in lymphoid and myeloid immune cells. Loss of the oxygen sensing gene, von Hippel Lindau (VHL), is a critical early event in ccRCC pathogenesis and promotes stabilization of hypoxia inducible factors (HIF) that upregulate pro-growth signaling pathways, including angiogenesis and aerobic glycolysis. However, whether VHL loss in cancer cells impacts the composition, metabolism, or function of immune cells in the TME remains unclear.

METHODS: To answer this question, we used immunocompetent murine models of kidney cancer, in which we manipulated the VHL axis in vitro, to explore the impacts on immune cell repertoire and function in vivo.

RESULTS: We found that VHL KO tumors were less proliferative and more infiltrated by immune cells. Tumor-associated macrophages (TAM) from VHL deficient tumors demonstrated enhanced proinflammatory transcriptional signatures and increased in vivo glucose consumption. VHL loss did not confer increased in vivo glucose uptake in cancer cells or lymphocytes, and did not result in detectable changes in metabolites in the interstitial fluid. Enhanced secretion of the chemokine, CX3CL1, was observed in VHL KO cancer cells and its cognate receptor, Cx3cr1, was significantly elevated on myeloid cells residing in the TME of VHL deficient tumors. Human ccRCC tumors exhibit high expression of CX3CL1 and CX3CR1 as well as enhanced myeloid metabolism and proinflammatory properties.

CONCLUSIONS: Here, we identify the importance of cancer cell-specific genetic features to drive environmental reprograming and shape the tumor immune landscape that may be a putative therapeutic target in the treatment of ccRCC.



ABSTRACT 5 Comparing the postoperative glomerular filtration rate prediction accuracy of a fully-automated AI-generated and a validated clinical model in patients with renal masses. *Abdallah, N et al.*

BACKGROUND: The American Urologic Association recommends estimating the postoperative glomerular filtration rate (postopGFR) in patients with renal mass to prioritize partial (PN) over radical nephrectomy (RN) when it is< 45 mL/min/1.73m2. Validated models based on clinical equations or renal volumes from hand/semi-automated segmentations are accurate but have seen limited

adoption. We hypothesize that fully-automated artificial intelligence (AI)-GFR prediction based on preoperative (preop) computed tomography (CT) scan can predict postopGFR as accurately as a validated clinical model.

METHODS: Three hundred patients undergoing PN or RN for renal tumor from the 2021 Kidney and Kidney Tumor Segmentation Challenge (KiTS21) were analyzed, excluding seven having bilateral tumors. Split-renal function (SRF) was determined in a fully automated way from preopCT and our previously developed deep learning segmentation model. The AI model predicted postopGFR as 1.24×preopGFR×contralateral SRF for RN, and 89% of preopGFR for PN. We compared the AI performance to a validated clinical model predicting postopGFR as 35+preopGFR(x0.65)-18 (if RN)-age(x0.25)+3 (if tumor>7 cm)-2 (if diabetes), using correlation coefficients (R). We compared the models' prediction ability of postopGFR< 45 using logistic regression and AUCs.

RESULTS: In 293 patients, median age was 60 years (IQR 51-68), 40.6% were females, and 62.1% had PN (TABLE1). Median tumor size was 4.2 cm (2.6-6.1), and 91.8% were malignant. When comparing the predictions to the measured postopGFR, correlation coefficients were 0.75 and 0.77 for AI and clinical models, respectively. For predicting postopGFR< 45 ml/min/1.73m2, the AI and clinical models performed similarly (AUC 0.89 and 0.9, respectively).

CONCLUSIONS: We introduced a fully automated prediction of postopGFR based on CT imaging and baseline GFR with comparable predictive accuracy to validated clinical models. These AI-generated predictions can be implemented for decision-making without clinical details, clinician time, or measurements needed.

Characteristic (N=293)	
Age, years- median (IQR)	60 (51-68)
Female- n (%)	119 (40.6%)
Body mass index, Kg/m²- median (IQR)	29.7 (26.1-35.5)
Diabetes- n (%)	58 (19.8%)
Partial nephrectomy- n (%)	182 (62.1%)
Size- median (IQR)	4.2 (2.6-6.1)
R.E.N.A.L. nephrometry score- median (IQR)	8 (7-9)
Malignant tumor- n (%)	269 (91.8%)
Tumor necrosis- n (%)	64 (21.8%)
High-grade- n (%)	92 (31.4%)
High-stage- n (%)	75 (25.6%)

ABSTRACT 7: CABOSUN II: A Phase 2, Open-Label, Multi-Center Randomized Study of Cabozantinib (CABO) vs. Sunitinib (SUN) for Non-Clear Cell Renal Cell Carcinoma (NCCRCC) *Martin H Voss et al.*

BACKGROUND: NCCRCC are diverse, rare diseases with limited data to guide treatment. CABO is highly effective in clear cell RCC, but it is unknown whether it is superior to SUN for metastatic NCCRCC.

METHODS: In this phase II study (NCT03541902), patients (pts) were randomized 1:1 to CABO 60mg daily or SUN 50mg daily (4 weeks on, 2 weeks off). SUN dose modification was allowed for toxicity. Sixty pts with metastatic NCCRCC were planned to detect CABO as better than SUN (1-sided). Stratification was by papillary RCC (PRCC) vs. non-PRCC (NPRCC), IMDC risk group, and prior TKI. The primary outcome was progression-free survival (PFS) [RECIST v1.1] compared between arms (log-rank test). Secondary outcomes were objective response rate (ORR), overall survival (OS), and adverse event (AE) rates (2-sided).

METHODS: Eligible 32 pts were randomized to CABO (N=15) or SUN (N=17) between 9/2018 and 6/2021. The trial stopped early due to a change in standard therapy for PRCC. Median ages were 57 and 61 years for CABO and SUN. Pts were primarily white (84%), male (72%), and with good/intermediate risk (88%). NPRCC were chromophobe (N=6; 5 received SUN), unclassified (N=5), and MiT family translocation (N=3; all received CABO). With median follow-up 33.3 months, median PFS for CABO vs. SUN was 8.2 vs. 13.8 months (p=0.96). There were no statistically significant differences in ORR or OS between arms. AEs were in line with previous studies.

CONCLUSIONS: CABO was not superior to SUN in this study. Despite stratification by PRCC/NPRCC, differences in NPRCC subtypes between arms may have impacted the results. Most pts with chromophobe histology (often indolent) received SUN while all pts with MiT family translocation (relatively aggressive) received CABO. Permitted SUN dose modifications may have influenced outcomes. While CABO was superior to SUN for PRCC in the PAPMET study, optimal treatments for rare, NPRCC remain a pressing need.

Table: Clinical Outcomes by Treatment Arm

		CABO (N=15)	SUN (N=17)	TOTAL (N=32)	P-value
PFS	Events	11	9	20	0.96
	Median (mos) [95% CI]	8.2 [4.3-NR]	13.8 [11-NR]	11.0 [7.6-14.9]	
OS	Events	9	7	16	0.67
	Median [95% CI]	28.0 [17-NR]	34.9 [28.6-NR]	28.7 [28.0-NR]	
ORR	N (%), [95% CI]				
	Partial Response	2 (13.3), [1.7-40.5]	1 (5.9), [0.2-28.7]	3 (9.4)	0.59
	Stable Disease	8 (57.1)	9 (52.9)	17 (54.8)	
	Progressive Disease	4 (28.6)	6 (35.3)	10 (32.3)	
	Not Evaluable/Missing	1 (6.7)	1 (5.9)	2 (6.3)	

NR=Not reached

ABSTRACT 19 Active surveillance versus microwave

ablation: comparing renal and oncologic outcomes for ct1a small renal masses *Vasiliadis T et al.*

METHODS: A cohort of 111 AS and 112 MWA patients were eligible. Tumor diameters were 2.2 versus 2.8 cm (p< 0.001) for AS and MWA, respectively. For AS, masses grew 1.2 (IQR 0-3.8) mm/year with sixteen (14.4%) progressing to treatment after 21.3 months (8.8-39.1). Eleven progressed for growth concerns (≥3 cm or ≥5 mm/year), 3 for patient preference, 1 for liver-transplant eligibility, and 1 unspecified. For MWA patients, 5 (4.5%) had recurrences after 22.3 (13.0-24.9) months. There was no difference in metastasis between treatment modalities. There was 1 cancer-related death in the MWA cohort. Surgical complications were significantly higher (p=0.002) in MWA (15%) versus AS patients who later required treatment (2.7%). Changes in RF measured by CKD stage progression and 30% eGFR decline at 6 months and 1 year were not different between cohorts. RF was worse at 6 months for MWA patients but improved by 1 year.

CONCLUSIONS: Active surveillance for RCC has been shown to be effective for selected SRM patients. MWA is emerging as a safe and effective treatment of SRM. While both modalities have no difference in CKD progression, metastasis, or overall death, patients on AS with tumors < 3 cm are at lower risk for procedural complications than MWA.

Variable	AS (n=111)	MWA (n=112)	p-value
Age at SRM Diagnosis, year	65 (54–73)	66 (58.8–72)	0.37
Sex			0.85
Female	43	42	
Male	68	70	
Charlson Comorbidity Index	5 (4–7)	4 (3–6)	0.005
Initial Nephrometry Score	6 (5–8)	7 (6–8)	0.11
Initial Mass Diameter, cm	2.2 (1.6–2.8)	2.8 (2.1–3.2)	<0.001
Length of follow-up, months	18.9 (9.9–47.9)	25.8 (12.6–49.1)	0.70
RENAL FUNCTION			
At Baseline			
Serum creatinine, mg/dL	1 (0.8–1.2)	1 (0.8–1.2)	0.83
eGFR, mL/min	70.5 (58–89.8)	74 (55.3–91)	0.75
At 6 months			
CKD stage progression, % of patients (patients progressed/total)	17.9 (12/67)	23.2 (22/95)	0.42
30% eGFR decline, % of patients (patients progressed/total)	4.5 (3/67)	15.9 (10/94)	0.16
At 1 year			
CKD stage progression, % of patients	24.7 (18/73)	30 (18/60)	0.57
30% eGFR decline, % of patients	9.6 (7/73)	11.7 (7/60)	0.70
ONCOLOGIC			
Metastasis	1 (0.9%)	3 (2.7%)	0.35
Time to Metastasis, months	5.0	28.0 (16.6–30.5)	–
RCC Specific Death	0 (0%)	1 (0.8%)	0.44
Time to RCC Death, months	-	35.9	-
Overall Death	7 (6.4%)	5 (4.5%)	0.44
Time to Death, months	31.6 (30.0–50.4)	32.6 (26.9–35.9)	0.56
COMPLICATIONS			
Complications	3 (2.7%)	17 (15.2%)	0.002
Clavien-Dindo Score	2 (1–3b)	3a (3a–3b)	

SRM-small renal mass; GFR- glomerular filtration rate; CKD- chronic kidney disease; RCC- renal cell carcinoma; MWA- microwave ablation; AS- active surveillance; Data are presented as median (IQR), n (%) as appropriate, or as labeled

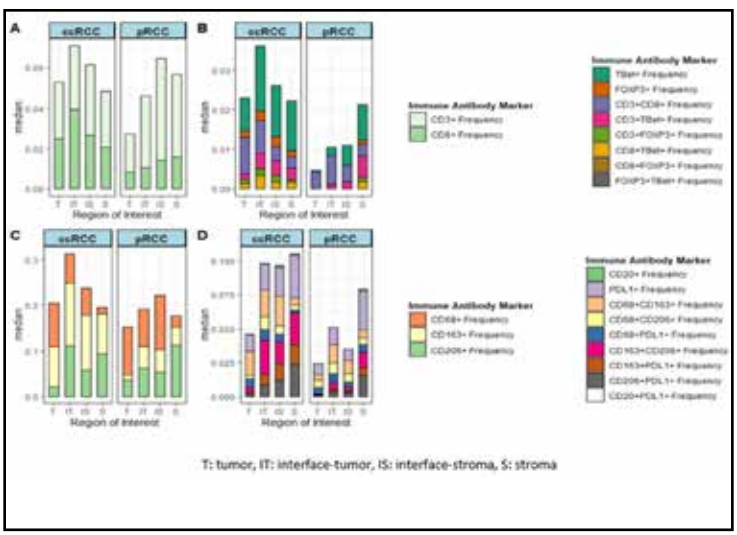
ABSTRACT 15 Spatial analysis of the tumor immune cell microenvironment in papillary renal cell carcinoma *Hayes H et al.*

BACKGROUND: Spatial analysis of the tumor immune microenvironment (TIME) has yet to be explored in papillary renal cell carcinoma (pRCC). We utilized multiplex immunofluorescence (mIF) and spatial transcriptomics using spatial molecular imaging (SMI) to evaluate TIME properties in pRCC and contrasted these results with clear cell RCC (ccRCC).

METHODS: Tumor specimens were obtained from localized RCC tumors. mIF was performed on regions of interest (ROIs) selected from matched compartments from tumor, stroma, and tumoral/stromal subsets of the interface. Two antibody panels were used for markers against T cells and B cells/macrophages. Marker abundance and clustering differences between pRCC and ccRCC were evaluated across ROIs. The SMI platform used for validation utilized probes against 959 transcripts. Cells were phenotyped using InSituType with the Kidney Cell Atlas reference. Cell clustering was quantified by univariate and bivariate Ripley's K using the spatialTIME package in R.

RESULTS: mIF was performed on 1178 ROIs from 16 pRCC tumors and 70 ccRCC tumors. Compared to ccRCC, pRCC immune cell abundance was statistically lower amongst many T cell types and M2-like macrophages (Figure). M1-like macrophages were the only cell line seen at higher levels in interface compartments only. Increased macrophage clustering was observed in pRCC, including doubly positive M2-like macrophages in interface compartments (p=0.001 and 0.007). Higher abundance of CD8+ and FOXP3+ T cells in pRCC was associated with worse clinical stages, but no trend was seen with marker clustering. Four ROIs from 2 pRCC patients underwent SMI validation. On SMI of the tumor compartment, T cells were significantly clustered with other T cells, B cells, and M1 macrophages.

CONCLUSIONS: Compared to ccRCC, pRCC has fewer T cells and macrophages but more macrophage clustering. Using spatial transcriptomics, we found significant clustering between T cells, macrophages, and B cells in pRCC.



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KCJ ORIGINAL REVIEW

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Novel Therapies Take Center Stage- IKCS NA 2023 Highlights

Neil J Shah, MD

Memorial Sloan-Kettering Cancer Center, New York NY

doi.org/10.52733/KCJ21n4-s3

ABSTRACT

The International Kidney Cancer Symposium (IKCS) in 2023 emerged as a pivotal event, uniting top experts in kidney cancer. Showcasing groundbreaking research, the symposium provided practical insights into the latest developments in diagnosis and treatment. With a strong focus on patient-centered care, IKCS 2023 served as a crucial platform for staying updated on the evolving landscape of kidney cancer research, fostering collaboration and knowledge exchange among professionals.

KEYWORDS

The International Kidney Cancer Symposium (IKCS), Kidney cancer, personalized medicine, novel therapies, improved diagnostics, patient-centered care, healthcare disparities

 # CORRESPONDENCE

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The IKCS 2023 meeting held in Nashville TN, provided a glimpse into the future of kidney cancer treatment, with exciting developments in personalized medicine, novel therapies, and improved diagnostics in the renal cancer splace. Here are some key takeaways from the meeting.

Oral Abstract Session: This session was moderated by Dr. Daniel Geynisman, featuring panelists Dr. Sumanta (Monty) Pal, Dr. Shinji Ohtake, Kate Glennon, and Dr. Pooja Ghatalia. Dr. Pal presented data from the STELLE-001 study, focusing on the evaluation of the safety and efficacy of the novel tyrosine kinase inhibitor Zanzalintinib (Zanza). Zanza inhibits VEGF, MET, and TAM kinases, similar to cabozantinib, but with a unique short half-life that may improve drug tolerability.

The study included a single-agent dose escalation cohort and a ccRCC (clear cell renal cell carcinoma) specific dose expansion cohort. The recommended dose for Zanza was 100mg. The overall response rate (ORR) for previously treated ccRCC patients (up to 3 lines) was 38%, including a 57% response rate for Cabozantinib-naïve patients. The median follow-up for the study was 8.3 months, with a median duration of response of 7.4 months. All patients experienced some grade of adverse events (AEs), with 65% developing grade 3 AEs. Zanza was generally well-tolerated, and no CTCAE grade 4 or 5 AEs were observed.

Dr. Ohtake presented significant findings on NF2-mutated Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC), shedding light on its molecular underpinnings. His research elucidated that NF2 loss triggers alterations in oxidative metabolism, leading to the accumulation of the oncometabolite fumarate, which, in turn, contributes to the emergence of a particularly aggressive variant of renal cell carcinoma (RCC)

in HLRCC patients. Notably, NF2 mutations were identified in approximately 14% of cases with fumarate hydratase (FH) deficiency in RCC. In pre-clinical studies, the team observed that treating FH-deficient, NF2-mutated tumor cells with rapamycin significantly curtailed their growth. These early findings suggest promising therapeutic potential for mTOR-targeted medications in addressing the challenges posed by NF2-mutated HLRCC.

Ms. Glennon presented research on germline susceptibility to renal cell carcinoma (RCC) in Canada, emphasizing global variations. The study identified CHEK2 and MITF germline mutations as the most frequent, with an overall 6% prevalence of pathogenic germline mutations among RCC patients. Interestingly, these results aligned with data reported by Yngvadottier et al. in a European patient population, where CHEK2, MITF, and ATM were prevalent mutations. However, Ms. Glennon's findings contrasted sharply with the Japanese patient population, as Sekine et al. identified TP53 as the most common germline mutation in their research. These insights underscore the importance of considering regional differences in germline susceptibility patterns when studying RCC.

Dr. Ghatalia presented compelling data from the LITESPARK-013 study, a phase 2 randomized trial designed to evaluate the efficacy of two different doses of belzutifan (200mg and 120mg daily) in previously treated clear cell renal cell carcinoma (ccRCC) patients, with up to 3 lines of prior treatment.

The study provided a comprehensive comparison of the two belzutifan doses. Notably, there were no significant differences observed in key efficacy parameters between the 200mg (n=78) and 100mg (n=76) daily doses. The overall response rate (ORR) for the 200mg dose was 23.1%, closely mirroring the 23.7% observed with the 100mg dose. Progression-free survival (PFS) stood at 9.1 months for the 200mg cohort and 7.3 months for the 100mg cohort. Additionally, the duration of response was consistent between both groups, with each recording a median duration of response of 3.6 months. In terms of safety, overall treatment-related adverse events were similar in both dose cohorts. However, it is noteworthy that Grade 3 anemia was more prevalent in patients receiving the higher 200mg dose.

Keynote Lecture: Creating AI-Driven Learning Health Systems to Advance Discovery and Care: Now, it's Personal(ized)! Dr. Peter Embi shared his personal journey and discussed the potential of AI in hospital care for kidney cancer. He highlighted how AI and Informatics can advance discovery and care, presenting emerging examples. Dr. Embi emphasized the importance of monitoring AI applications through "algorithmovigilance."

Belzutifan and RCC: The story of Belzutifan unfolded in a session moderated by Dr. Jodi Maranchie, tracing its journey from basic science research labs to FDA approval. The panel, consisting of experts such as Dr. Bruce A. Posner, Dr. Eric Jonasch, Dr. Jaleh Fallah from the FDA, and industry partners Dr. Naseem Zojwalla and Dr. Rodolpho Perini, offered a comprehensive discussion on the various challenges encountered at each stage of Belzutifan's development.

Dr. Fallah took the audience through a detailed review of the LITESPARK-004 study, shedding light on the scientific intricacies and regulatory considerations that shaped the development of Belzutifan. The session provided valuable insights not only into the scientific journey of this novel therapy but also the collaborative efforts and regulatory considerations that played a pivotal role in achieving FDA approval.

Imaging and Molecular Diagnostics biomarkers: Dr. Brian Shuch delivered a presentation on novel imaging biomarkers for renal cell carcinoma (RCC), focusing on CA-IX Imaging with Geruntiximab and sharing insights from the ZIRCON study. The study, involving 300 patients with T1a and T1b renal tumors (tumors less than 7 cm), demonstrated promising results with a sensitivity of 85.5% and specificity of 87%, along with a robust positive predictive value of 93%. Dr. Shuch highlighted the evolving role of this imaging biomarker, particularly for patients with metastatic disease, suggesting it could open new therapeutic avenues for RCC.

Dr. Alna Tan discussed the application of circulating tumor DNA (ctDNA) in renal cell carcinoma. Addressing various ctDNA assays, Dr. Tan explored the evolving role of ctDNA in tailoring adjuvant treatments and novel approaches for immune checkpoint inhibitor (IO) and tyrosine kinase inhibitor (TKI) treatment deintensification for metastatic RCC patients.

Dr. Ivan Pedrosa delved into the role of artificial intelligence (AI) in guiding RCC imaging. He provided insights into ongoing work and emphasized the importance of multicenter collaborative efforts in harnessing AI for more accurate and efficient imaging in the diagnosis and management of renal cell carcinoma. This comprehensive overview showcases the advancements in imaging biomarkers, liquid biopsy

applications, and AI integration in the field of RCC research and clinical practice.

Novel Immunotherapy and Cellular Therapies: Dr. Qing Zhang outlined the potential of targeting specific markers such as TIM-3, LAG3, TBK1, ERV, and anti-VISTA for the development of immunotherapies in renal cancers. His key message emphasized the future of RCC treatment lying in immunotherapies and combination therapies. This underscores the growing importance of personalized and targeted approaches in the evolving landscape of renal cell carcinoma treatment.

Dr. Michael Hurwitz discussed the promising results and challenges in CAR-T cell-based clinical trials for RCC. While acknowledging the potential of CAR-T therapies becoming standard care, he also highlighted the substantial work ahead to address complexities and optimize their effectiveness in the context of renal cell carcinoma.

Dr. Vivek Narayan presented insights into novel immunotherapy development in RCC by adapting the cancer-immunity cycle. He discussed the ARCHITECT trial involving Botensilimab, a next-gen Fc-enhanced anti-CTLA4 agent, and highlighted ongoing clinical developments targeting MEDI5752, LAG-3, TIM3, CD39-CD73-A2AR, and TIGIT. Dr. Narayan's talk emphasized the importance of a comprehensive understanding of the cancer-immunity cycle for advancing immune therapies in renal cell carcinoma. These presentations collectively underscore the potential and challenges of immunotherapies in shaping the future of RCC treatment.

Papillary Renal Cell Carcinoma: In a session on papillary renal cell carcinoma (pRCC) expertly moderated by Dr. Maria Carlo, Dr. Randy Weis delved into the intricate landscape of pRCC, shedding light on both its progress and the challenges encountered in understanding this renal cell carcinoma subtype. Dr. Weis particularly emphasized the involvement of unique pathways, such as MET, that drive pRCC, contributing to its distinct tumor microenvironment.

Dr. Benjamin Maughan contributed valuable insights by providing clinical updates on metastatic pRCC. He acknowledged the emerging role of combination treatments, notably mentioning Cabozantinib plus Nivolumab and Lenvatinib plus Pembrolizumab. Dr. Maughan highlighted ongoing developments, including the PAPMET2 trial, underscoring the importance of conducting randomized trials to rigorously evaluate the efficacy of combination therapies in the context of metastatic pRCC.

Dr. Bradley McGregor shared significant lessons learned from the CaNI trial, which explored a triple therapy approach involving Cabozantinib plus Ipilimumab plus Nivolumab for variant RCC histologies. His emphasis on treatment-related adverse events associated with this triplet therapy, both for clear cell RCC (ccRCC) and non-clear cell RCC (nccRCC), provided crucial insights.

FIGURE 1. At the general session of IKCS2023.

Additionally, Dr. McGregor noted that the Cabo/Nivo/Ipi combination is still in the developmental stage for RCC, signaling ongoing efforts to refine and optimize therapeutic strategies for this complex cancer subtype.

Variant RCC Histologies: Moderated by Dr. Kiran Virdee, a session on variant kidney cancer histologies featured insights from panelists Dr. Yasser Ged, Dr. Sara E. Wobker, Dr. Mohammed Alghamdi, and Dr. Sounak Gupta. Dr. Ged discussed translocation RCC, reviewing recent phase II trial data for Cabozantinib plus Nivolumab and Lenvatinib plus Pembrolizumab, emphasizing their efficacy for non-clear cell renal cell carcinoma. Dr. Wobker focused on unclassified RCC subtypes, highlighting the evolving categorization of kidney cancer and the utility of molecular analysis. Dr. Alghamdi and Dr. Gupta presented the pros and cons of molecular testing for non-clear cell RCC. The session provided valuable insights into the evolving genomic landscape and recent treatments for non-clear cell RCC.

Locally advanced renal cell carcinoma (RCC) with inferior vena cava (IVC) thrombus and large tumors with Solitary Kidney: This session was moderated by Dr. Phillip M. Pierozario, focused on insightful debates about locally advanced RCC with IVC thrombus and large RCC tumors with solitary kidneys. Panelists included Dr. Andres F. Correa, Dr. Sandy Srinivas, and Dr. Shivani Sud. The session commenced with a touching patient's kidney cancer journey, followed by a case discussion on managing IVC thrombosis, atrial tumor thrombus, and large renal primaries in solitary kidneys. Panelists emphasized the significance of advanced imaging, particularly MRI, for detecting tumor thrombus. They also highlighted a multi-modal approach, such as preoperative SABR + surgery for IVC tumor thrombus and upfront systemic treatment followed by delayed surgery.

Academy of Kidney Cancer Investigators (AKCI): Dr. Brian Rini, the dean of the AKCI, began the session with an overview of the AKCI academy. Following the introduction, there was a presentation on the 4th kidney cancer research awardees. Dr. Chen Yao presented her proposed research on stem-like CD8 T cells in renal cell carcinoma (RCC), suggesting that the quantity, metabolic fitness, and tumor microenvironment of these cells might influence the efficacy of immune checkpoint inhibitor (ICI) therapy for RCC. This work highlights the importance of understanding the role of specific immune cell subsets in the context of RCC and their potential impact on treatment outcomes. Dr. Anirban Kundu discussed Sema5B as a novel hypoxia-inducible factor (HIF)-target oncoprotein in RCC, proposing it as a potential therapeutic target for RCC therapies. This insight into a novel molecular target contributes to the ongoing efforts to identify precise and effective therapeutic strategies for RCC. Dr. Maxine Sun presented data on the impact of clonal hematopoiesis on the outcomes of kidney cancer. She explained that clonal hematopoiesis is associated with a 40% higher risk of mortality, primarily driven by coronary artery disease and ischemic stroke. Preliminary data from the UK Biobank suggests that carriers of mosaic chromosomal alterations (MCA) have a higher risk of death from cardiovascular and cancer-related causes. Dr. Sun proposed further investigation of these findings in RCC patients, emphasizing the potential importance of clonal hematopoiesis as a prognostic factor in kidney cancer and cardiovascular disease associated mortality.

SUMMARY

IKCS 2023 proved an exciting hub for oncologists, showcasing progress in immuno-oncology and targeted therapy combinations for both common and rare kidney cancers. The conference fostered valuable interdisciplinary dialogue between medical oncologists, scientists, and surgeons, emphasizing the importance of teamwork in advancing research and improving patient outcomes. The conference highlighted the potential of personalized treatment strategies guided by genomic profiling and biomarker identification. For advanced cases, promising clinical trials emerged, with a continued emphasis on combination therapies. However, challenges remain in managing rare RCC subtypes, prompting collaborative efforts to develop effective solutions. IKCS also recognized the critical role of patient advocacy and support, ensuring patient perspectives remain at the heart of clinical research and treatment decisions. Overall, the conference served as a valuable platform for oncologists to stay updated, network, and collaborate, paving the way for a brighter future in kidney cancer treatment.

https://doi.org/10.52733/KCJ21n3-jc

Phase I/Ib, open-label, multicenter, dose-escalation study of the anti-TGF-β monoclonal antibody, NIS793, in combination with spartalizumab in adult patients with advanced tumors.

Bauer TM et al, J Immunother Cancer. 2023 Nov 29;11(11):e007353. doi: 10.1136/jitc-2023-007353. PMID: 38030303.

RESULTS: Sixty patients were treated in dose escalation, 11 with NIS793 monotherapy and 49 with NIS793 plus spartalizumab, and 60 patients were treated in dose expansion (MSS-CRC: n=40; NSCLC: n=20). No dose-limiting toxicities were observed. The RDE was established as NIS793 30 mg/kg (2100 mg) and spartalizumab 300 mg Q3W. Overall 54 (49.5%) patients experienced ≥1 treatment-related adverse event, most commonly rash (n=16; 13.3%), pruritus (n=10; 8.3%), and fatigue (n=9; 7.5%). Three partial responses were reported: one in renal cell carcinoma (NIS793 30 mg/kg Q2W plus spartalizumab 400 mg Q4W), and two in the MSS-CRC expansion cohort. Biomarker data showed evidence of target engagement through increased TGF-β/NIS793 complexes and depleted active TGF-β in peripheral blood. Gene expression analyses in tumor biopsies demonstrated decreased TGF-β target genes and signatures and increased immune signatures.

CONCLUSIONS: In patients with advanced solid tumors, proof of mechanism of NIS793 is supported by evidence of target engagement and TGF-β pathway inhibition.

Mesenchymal-Epithelial Transition Kinase Inhibitor Therapy in Patients with Advanced Papillary Renal-Cell Carcinoma: A Systematic Review and Meta-Analysis

Moraes FCA, et al. *Int J Mol Sci. 2023 Dec 18;24(24):17582. doi: 10.3390/ijms242417582. PMID: 38139411.*

ABSTRACT: Papillary subtypes of renal-cell carcinoma (pRCC) represent 10-15% of the cases and commonly have MET alterations. This systematic review and single-arm meta-analysis evaluated MET inhibitor therapy (METi) efficacy and safety in adults with confirmed advanced pRCC. The search strategy included PubMed, Web-of-science, Cochrane, and Scopus. We used the DerSimonian/Laird random effect model for all analyses; p-value < 5% was considered significant, and heterogeneity was assessed with I2. Three clinical trials and six cohort studies were included with 504 patients; 31% were MET-driven. Our pooled analysis demonstrated an objective response rate (ORR) in MET-driven, MET-independent, and overall patients of: 36% (95%CI: 10-62), 0% (95%CI: 0-3), and 21% (95%CI: 1-41), respectively. One-year disease control and progression-free survival rates were, respectively, 70% (95%CI: 52-88) and 15% (95%CI: 10-20). Twelve- and twenty-four-month survival rates were, respectively, 43% (95%CI: 23-64) and 10% (95%CI: 0-30). The prevalence of adverse events of any grade and grades 3-5 were 96% (95%CI: 91-100) and 44% (95%CI: 37-50), respectively. We suggest METi has anti-tumor activity and is tolerable in patients with advanced pRCC.

Cabozantinib in the Routine Management of Renal Cell Carcinoma: A Systematic Literature Review of Real-World Evidence.

Gross-Goupil M, et al. *Clin Genitourin Cancer. 2023 Nov 8:S1558-7673(23)00237-9. doi: 10.1016/j.clgc.2023.11.001.*

ABSTRACT: Real-world cabozantinib use has increased since its approval to treat patients with advanced renal cell carcinoma (RCC) in 2016. We reviewed cabozantinib use in real-world clinical practice and compared outcomes with pivotal cabozantinib randomized control trials (RCTs). This PRISMA-standard systematic literature review evaluated real-world effectiveness and tolerability of cabozantinib in patients with RCC (PROSPERO registration: CRD42021245854). Systematic MEDLINE, Embase, and Cochrane database searches were conducted on November 2, 2022. Eligible publications included ≥ 20 patients with RCC receiving cabozantinib. After double-screening for eligibility, standardized data were abstracted, qualitatively summarized, and assessed for risk of bias using the Newcastle-Ottawa Scale. Of 353 screened publications, 41 were included, representing approximately 11,000 real-world patients. Most publications reported cabozantinib monotherapy cohort studies (40/41) of retrospective (39/41) and multicenter (32/41) design; most included patients from North America and/or Europe (30/41). Baseline characteristics were demographically similar between real-world and pivotal RCT populations, but real-world populations showed greater variation in prevalence of prior nephrectomy, multiple-site/brain metastasis, and non-clear cell RCC histology. Cabozantinib activity was reported across real-world treatment lines and tumor types. Overall survival, progression-free survival, and objective response rate values from pivotal RCTs were within the ranges reported for equivalent outcomes across real-world studies. Common real-world grade ≥ 3 adverse events were consistent with those in pivotal RCTs (fatigue, palmar-plantar erythrodysesthesia syndrome, diarrhea, hypertension), but less frequent. No new tolerability concerns were identified. Real-world RCC survival outcomes for cabozantinib monotherapy were broadly consistent with pivotal RCTs, despite greater heterogeneity in real-world populations.

Phase I LITESPARK-001 study of belzutifan for advanced solid tumors: Extended 41-month follow-up in the clear cell renal cell carcinoma cohort.

Jonasch E, et al. Eur J Cancer. 2024 Jan;196:113434. doi: 10.1016/j.ejca.2023.113434. Epub 2023 Nov 15. PMID: 38008031.

RESULTS: Median follow-up was 41.2 months (range, 38.2-47.7). Patients received a median of 3 (range, 1-9) prior

systemic therapies. Of 55 patients, 14 (25 %) achieved an objective response. Median DOR was not reached (range, 3.1 + to 38.0 + months). Adverse events (AEs) attributed to study treatment by investigator assessment were reported in 53 patients (96 %). 22 patients (40 %) had grade 3 treatment-related AEs; the most common were anemia (n = 13; 24 %) and hypoxia (n = 7; 13 %). No grade 4 or 5 treatment-related AEs occurred.
CONCLUSION: After a median follow-up of 41.2 months, belzutifan monotherapy demonstrated durable antitumor activity in patients with advanced ccRCC and acceptable safety

phase I study of the combination of atezolizumab, tiragolumab, and stereotactic body radiation therapy in patients with metastatic multiorgan cancer. Roussot N, et al.

BMC Cancer. 2023 Nov 9;23(1):1080. doi: 10.1186/s12885-023-11534-6. PMID: 37946136.

METHODS: This phase I study (ClinicalTrials.gov NCT05259319) will assess the efficacy and safety of the combination of atezolizumab with tiragolumab and stereotactic body radiation therapy in patients with histologically proven metastatic non-small cell lung cancer, renal cell cancer, bladder cancer, and head and neck cancer previously treated. First part: 2 different schedules of SBRT in association with a fixed dose of atezolizumab and tiragolumab will be investigated only with metastatic non-small cell lung cancer patients (cohort 1). The expansion cohorts phase will be a multicentric, open-label study at the recommended scheme of administration and enroll additional patients with metastatic bladder cancer, renal cell cancer, and head and neck cancer (cohort 2, 3 and 4). Patients will be treated until disease progression, unacceptable toxicity, intercurrent conditions that preclude continuation of treatment, or patient refusal in the absence of progression or intolerance. The primary endpoint of the first phase is the safety of the combination in a sequential or concomitant scheme and to determine the expansion cohorts phase recommended scheme of administration. The primary endpoint of phase II is to evaluate the efficacy of tiragolumab + atezolizumab + SBRT in terms of 6-month PFS (Progression-Free Survival). Ancillary analyses will be performed with peripheral and intratumoral immune biomarker assessments.

Impact of Prior Cytoreductive Nephrectomy on Efficacy in Patients with Synchronous Metastatic Renal Cell Carcinoma Treated with Avelumab plus Axitinib or Sunitinib: Post Hoc Analysis from the JAVELIN Renal 101 Phase 3 Trial.

Grimm MO, et al. *Eur Urol. 2024 Jan;85(1):8-12. doi: 10.1016/j.eururo.2023.09.016. Epub 2023 Oct 16. PMID: 37852850.*

ABSTRACT: Data on the effects of prior cytoreductive nephrectomy (CN) in patients with renal cell carcinoma (RCC) with synchronous metastases (M1 disease) before immune checkpoint inhibitor (ICI) treatment are limited. In this post hoc analysis of treatment-naive patients with advanced RCC from the phase 3 JAVELIN Renal 101 trial, we assessed efficacy outcomes in the avelumab + axitinib and sunitinib arms in patients who were initially diagnosed with M1 disease (n = 412) grouped by prior CN (yes vs no). Progression-free survival (PFS) and overall survival (OS) were analyzed using multivariable Cox regression, and objective response rates (ORRs) were analyzed using logistic regression. After adjusting for imbalances in baseline variables, the hazard ratio (HR) for PFS in the prior CN versus no prior CN subgroup was 0.79 (95% confidence interval [CI] 0.53-1.16) in the avelumab + axitinib arm, and 1.15 (95% CI 0.77-1.70) in the sunitinib arm. The corresponding HRs for OS were 0.59 (95% CI 0.38-0.93) and 0.86 (95% CI, 0.55-1.34), and the odds ratios for ORR were 2.67 (95% CI 1.32-5.41) and 2.02 (95% CI 0.82-4.94), respectively. Prospective studies of the potential benefits of CN and its appropriate timing in patients receiving first-line treatment with ICI-containing combinations are warranted. PATIENT SUMMARY: This study looked at patients with kidney cancer whose disease had already spread outside the kidneys when it was first detected. We found that patients whose kidney had been removed before starting treatment with avelumab + axitinib had better outcomes than those whose kidney had not been removed. For patients treated with sunitinib, the results were more similar between the groups with and without prior kidney removal. However, statistical tests did not find any significant differences. The JAVELIN Renal 101 trial is registered on ClinicalTrials.gov as NCT02684006.

TITAN-RCC study group. Tailored immunotherapy approach with nivolumab with or without nivolumab plus ipilimumab as immunotherapeutic boost in patients with metastatic renal cell carcinoma (TITAN-RCC): a multicentre, single-arm, phase 2 trial.

Grimm MO, et al; Lancet Oncol. 2023 Nov;24(11):1252-1265. doi: 10.1016/S1470-2045(23)00449-7. Epub 2023 Oct 13. PMID: 37844597.

RESULTS: A total of 15,989 elderly KC patients undergoing surgery were included. All patients were randomly divided into training set (N = 11,193, 70%) and validation set (N = 4796, 30%). The nomogram produced C-indexes of 0.771 (95% CI 0.751-0.791) and 0.792 (95% CI 0.763-0.821) in the training and validation sets, respectively, indicating that the nomogram has excellent predictive accuracy. The ROC, AUC, and calibration curves also showed the same excellent results. In addition, DCA and time-dependent ROC showed that the nomogram outperformed the TNM staging system with better net clinical benefits and predictive efficacy.
CONCLUSIONS: Independent influencing factors for postoperative OS in elderly KC patients were sex, age, histological type, tumor size, grade, surgery, marriage, radiotherapy, and T-, N-, and M-stage. The web-based nomogram and risk stratification system could assist surgeons and patients in clinical decision-making.

https://doi.org/10.52733/KCJ21n3-mi

The FDA Approves Belzutifan for advanced Renal Cell Carcinoma

The FDA has approved belzutifan (Welireg) for the treatment of patients with advanced renal cell carcinoma (RCC) who have progressed following treatment with a PD-1 or PD-L1 inhibitor and a VEGF-TKI, announced Merck, the developer of the drug, in a news release. The approval is based on the findings from the phase 3 LITESPARK-005 trial (NCT04195750), in which belzutifan demonstrated superior progression-free survival (PFS) vs everolimus in patients with advanced RCC whose tumors had progressed following treatment.

Specifically, the risk of disease progression or death was reduced by 25% with belzutifan. The objective response rate (ORR) among patients who received belzutifan was 22% , compared with 4% among patients who received everolimus. Median PFS among patients in the belzutifan cohort was 5.6 months (95% CI, 3.9-7.0) versus 5.6 months (95% CI, 4.8-5.8) for everolimus. In total, 82 patients (22%) in the belzutifan arm demonstrated a response, with a complete response (CR) rate of 3% (n = 10) and a partial response (PR) rate of 19% (n = 72). Among the 82 patients with a response in the belzutifan arm, 25 patients (30%) achieved a duration of response of at least 12 months. ORR among patients in the everolimus arm was 4%, with no patients achieving a CR and a PR rate of 4% (n = 13). "Despite recent progress in the treatment of advanced RCC, there is yet to be an option specifically approved for patients whose disease progresses following a PD-1 or PD-L1 inhibitor and a TKI therapy," Toni K. Choueiri, MD, LITESPARK-005 study chair, director of the Lank Center for Genitourinary Oncology at Dana-Farber Cancer Institute.

Dr. Nizar Tannir received Humanitarian Award from the Kidney Cancer Association

During the Humanitarian Award session at The 2023 International Kidney Cancer Symposium: North America, Dr. Nizar M. Tannir was presented with the Nicholas J. Vogelzang Humanitarian Award in honor of his outstanding service and compassion for his patients, his mentorship of colleagues, and his contributions to the KCA and the wider kidney cancer community. "*I am humbled to have been selected as the recipient of the 2023 Nicholas J. Vogelzang Humanitarian Award*," said Dr. Tannir, a Professor in the Department of Genitourinary Medical Oncology at The University of Texas MD

Anderson Cancer Center in Houston, Texas. "*During my 22 years in academic oncology, Nick and I shared patients, collaborated on multiple clinical trials, and participated in numerous conferences and advisory board meetings. I always admired Nick for his fierce advocacy for his patients, his wisdom and broad knowledge in oncology, his sponsorship of his fellows and faculty, and above all for his humanity. Nick truly epitomized our noble profession. To receive an award carrying his name is a great honor.*" Said Dr. Tannir. The Nicholas J. Vogelzang Humanitarian Award was named in honor of the KCA's late co-founder and board member Dr. Nicholas J. Vogelzang, a world-renowned genitourinary oncologist specializing in rare cancer types. "*Dr. Tannir is unwaveringly caring and compassionate with his patients as well as his colleagues – his concern for the well-being of others seems to be limitless*," said Dr. Bradley C. Leibovich, a urologic oncologist at the Mayo Clinic in Rochester, Minnesota, and Chair of the KCA's Board of Directors.

Dr. Alexander Kutikov receives Andrew C. Novick Award

Dr. Alexander Kutikov, MD, FACS, Chair of the Department of Urology and the Roberta R. Scheller Chair in Urologic Oncology at Fox Chase Cancer Center, received the Andrew C. Novick Award. The award recognizes highly respected healthcare professionals who have made significant contributions in urology and medical oncology for the treatment of kidney cancer. He delivered an award lecture at the session. "*Receiving this award is particularly poignant*

for me, as I was trained by Fox Chase's President and CEO, Dr. Robert Uzzo, for whom Dr. Novick was a critical mentor. *Dr. Novick's legacy has certainly influenced my outlook and dedication to the field*," said Kutikov. Uzzo, who is also the Executive Director of the Fox Chase-Temple Urologic Institute, was honored with the award in 2016.

Genetic variants help uncover potential new treatment pathway in kidney cancer

The Kidney Cancer Association is planning to launch its groundbreaking new podcast series called "Kidney Cancer Unfiltered". Hosted by Annamaria Scaccia, a member of the Kidney Cancer Association's Patient & Caregiver Advisory Committee, this seven-episode podcast aims to shed light on the personal journeys, challenges, and emotions that people navigating kidney cancer face. "Kidney Cancer Unfiltered" isn't just another podcast; it's a collection of raw, intimate conversations—fireside chats—between individuals touched by kidney cancer, from patients and caregivers to family members and healthcare professionals. Each episode delves deep into various aspects of the kidney cancer experience.. With topics including managing emotions, having cancer at a young age, and how to navigate intimacy, "Kidney Cancer Unfiltered" is about creating a community where every listener feels understood, supported, and empowered. "Kidney Cancer Unfiltered" will be available soon across all major podcast platforms.

REFERENCE: *https://www.kidneycancer.org/stories/podcast-coming-soon/*

Dr. Kimryn Rathmell was appointed as the Director of NCI.

Dr. Kimryn Rathmell, M.D., Ph.D., has been appointed as the 17th director of the NCI, part of the NIH. A renowned kidney cancer expert and influential leader in cancer research and patient care, Dr. Rathmell was selected by President Biden to succeed Monica M. Bertagnolli, M.D., who left NCI to become the NIH director on November 9, 2023.

"I want to officially welcome Dr. Rathmell to the NCI on her first day as director," said Department of Health and Human Services Secretary Xavier Becerra. "Dr. Rathmell begins her new role at an important time. The President and First Lady reignited the Biden Cancer Moonshot℠ to dramatically accelerate progress in the fight against cancer—and NCI is helping to lead the charge. Dr. Rathmell comes to NCI from Vanderbilt University Medical Center in Nashville, Tennessee, where she served as the Hugh Jackson Morgan Chair in Medicine, chair of the Department of Medicine, and physician-in-chief. Before joining Vanderbilt University, she served on the faculty of the University of North Carolina at Chapel Hill.

REFERENCE: 1) https://www.nih.gov/news-events/news-releases/w-kimryn-rathmell-md-phd-begins-work-17th-director-national-cancer-institute

Telix has submitted a BLA for its Zircaix

Telix Pharmaceuticals has submitted a BLA application to the FDA for its investigational PET imaging agent, Zircaix (TLX250-CDx). Zircaix is a radioactive imaging agent intended for the PET/CT imaging of ccRCC. It is designed to visualise tumours by binding to CAIX, which is over-expressed in ccRCC.

The submission is based on positive results from the Phase III ZIRCON study. The prospective, open-label, multi-centre study enrolled 300 subjects and concluded last year, meeting all the primary and secondary endpoints. Telix aims to initiate programmes for patient access outside clinical trials. Earlier this month, Telix dosed the first subject in an early access European programme for Zircaix, in Nijmegen, the Netherlands.

"The ZIRCON study demonstrated the superior sensitivity and specificity of this advanced diagnostic imaging agent, which, if approved, will be the first and only agent available to target carbonic anhydrase IX, a highly relevant target in kidney cancer, said, Brian Shuch, MD, Director of the Kidney Cancer Program and the Alvin & Carrie Meinhardt Endowed Chair in Kidney Cancer Research at UCLA Institute of Urologic Oncology.

2023 roundup: The most important kidney cancer research stories of the year

Each of these stories is an incredible example of the progress we've made in kidney cancer research from 2023, based on their impact and significance.

1. Belzutifan shines in LITESPARK-005 trial: This HIF-2α inhibitor significantly delayed disease progression in patients with advanced kidney cancer who had progressed on previous treatments, offering new hope for this challenging subgroup.

2. Pembrolizumab/lenvatinib combo shows promise: This combination therapy demonstrated superior benefit in the frontline setting for non-clear cell renal cell carcinoma (nccRCC), potentially offering a new option for this subtype.

3. PADRES trial and neoadjuvant axitinib: The results of this phase 3 KEYNOTE-564 trial showed that adjuvant pembrolizumab improved OS compared with placebo in patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions, informing future treatment decisions.

4. Stereotactic ablative radiation for oligometastatic RCC: This treatment modality proved effective in controlling tumors in patients with limited metastatic disease, offering a minimally invasive option for select cases.

5. FDA grants Fast Track Designation to CAR T-cell therapy for kidney cancer. In August 2023, the FDA granted a Fast Track Designation to the chimeric antigen receptor (CAR) T-cell therapy IVS-3001 for the treatment of patients with renal cell carcinoma. The decision was based on a first-in-human, single-arm, open-label, phase 1/2 trial (NCT05672459) of the CAR T-cell therapy in patients with previously treated, locally advanced, or metastatic solid tumors that are HLA-G–positive.

6. The CLEAR study data has revealed the potential benefits of lenvatinib/pembrolizumab combination in aRCC

The CLEAR study presented at the ASCO 2023 annual meeting has established the lenvatinib plus pembrolizumab as a new standard of care for first-line treatment of advanced RCC. Also, it offered a more effective and potentially more durable treatment option for patients. The data reinforced the value of combination immunotherapy in RCC and also provided a strong foundation for further research into combination strategies in RCC and other cancers.

7. ZIRCON study of TLX250-CDx confirms imaging agent's potential in renal cell carcinoma. Findings from the phase 3 ZIRCON study (NCT03849118) confirmed high specificity and sensitivity of the non-invasive TLX250 CDx PET/CT imaging agent for detection of clear cell renal cell carcinoma in patients with indeterminate renal masses. Overall, TLX250 CDx PET/CT demonstrated a sensitivity of 85.5% and a specificity of 87.0% in this patient population.

8. Phase 3 COSMIC-313 data for cabozantinib triplet in kidney cancer published made a breakthrough in PFS. The COSMIC-313 trial, is the first study to investigate adding a TKI to the established combination of dual CPI for RCC, and is a major step forward in the treatment of advanced RCC. It provides strong evidence for the potential of a triple therapy (adding cabozantinib to nivolumab plus ipilimumab) approach and offers hope for improved outcomes for patients with this aggressive disease.

9. Researchers identify biomarkers predictive of response to Immunotherapy in patients with kidney cancer. Investigators at the Johns Hopkins Kimmel Cancer Center in Baltimore, Maryland shown that biomarkers derived from hematoxylin and eosin-stained (H&E) were able to predict the response to anti-PD-1 therapy in patients with mcRCC.

10. Zanzalintinib shows early promise in advanced RCC: This novel tyrosine kinase inhibitor's encouraging preliminary results pave the way for further investigation in advanced treatment stages.

KCJ Author Guidelines

Scope of Manuscripts

Kidney Cancer Journal considers the following types of manuscripts for publication:

- Reviews that summarize and synthesize peer-reviewed literature to date on relevant topics in a scholarly fashion and format.
- Original contributions based on original, basic, clinical, translational, epidemiological, or prevention studies relating to kidney cancer that are well documented, novel, and significant.
- Letters to the Editor on timely and relevant subjects pertaining to the diagnosis and treatment of renal cell carcinoma.
- Clinical case studies.

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Length: Full-length manuscripts should not exceed 4000 words, including references. Please limit the reference list to 50 citations. Manuscripts should be accompanied by figures and/or tables. Generally 4-5 figures and 2-3 tables are preferred for each manuscript. Please include a brief description to accompany these items, as well as a legend for all abbreviations. Manuscripts should not contain an abstract but an introduction is recommended.
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References

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