Kidney Cancer JOURNAL

Official Journal of
Kidney Cancer Association

The 24th Annual Meeting of

The International Kidney Cancer Symposium

North America

KidneyCancerJ
KidneyCancerJ

KidneyCancerJournal
KidneyCancerJournal

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

CABOMETYX® (cabozantinib) tablets + OPDIVO® (nivolumab)

EXPLORE A **BALANCE OF DATA**

ACCESS THE CHECKMATE-9ER CLINICAL TRIAL RESULTS
bit.ly/view9ER

CABOMETYXhcp.com

25 Years of Progress: Key Takeaways from the 2024 IKCS

Thomas E Hutson, DO, PharmD

Texas Tech University Health Science Center,
School of Medicine
Lubbock, Texas 79415

https://doi.org/10.52733/KCJ22n4-e

Dear colleagues,

The recent 2024 International Kidney Cancer Symposium (IKCS) marked its 25th anniversary, a significant milestone in its journey of fostering collaboration and innovation in the fight against kidney cancer. The symposium showcased a wealth of groundbreaking research and clinical advancements, offering fresh perspectives on the evolving landscape of kidney cancer. From novel therapeutic approaches to improved prognostic markers, the event highlighted the relentless pursuit of better outcomes for patients with this challenging disease.

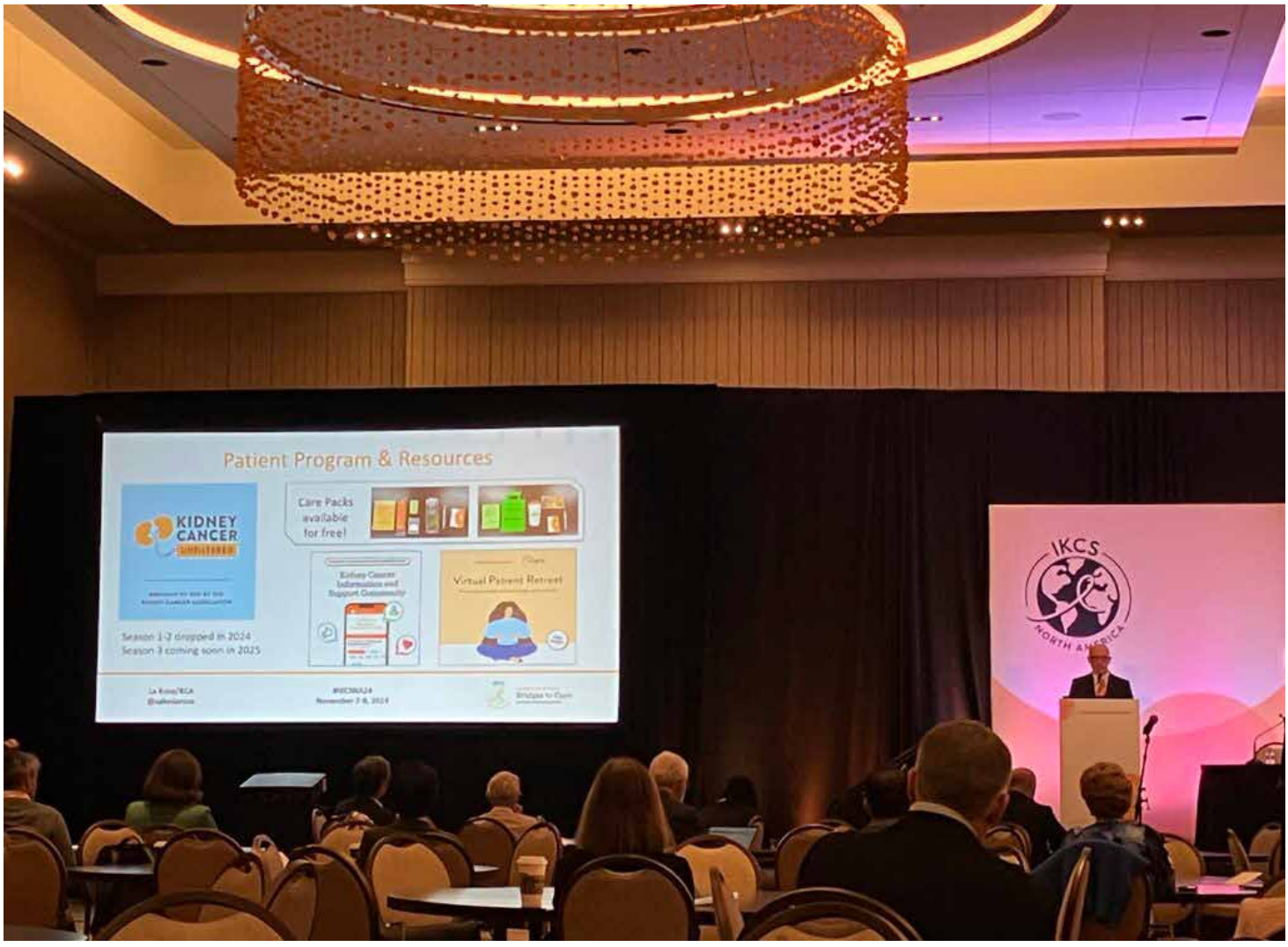
Key topics at the symposium included immunotherapy, targeted therapies, clinical trials, personalized medicine, and patient advocacy. The event featured educational sessions, networking opportunities, and discussions on improving patient outcomes. IKCS aims to foster collaboration, raise awareness, and advance the standard of kidney cancer care globally.

One notable theme that emerged from the symposium was the increasing emphasis on precision medicine. Researchers presented data on the development of biomarkers to identify patients who are most likely to benefit from specific therapies, allowing for more targeted and personalized treatment strategies. Additionally, the symposium featured discussions on the role of immunotherapy in various stages of kidney cancer, with

promising results demonstrating the potential to enhance treatment efficacy and improve patient survival.

Following are some of the key findings presented at the meeting.

Updated safety and efficacy from the phase I TRAVERSE multicenter study (*Abstract F2*) shown that a single infusion of ALLO-316 was well-tolerated, with manageable side effects, particularly after implementing a new approach to mitigate the risk of immune effector cell hemophagocytic lymphohistiocytosis-like syndrome. A quarter of patients with a high CD70 TPS responded to ALLO-316, and this increased to 40% with lymphodepletion. Moreover, three out of six patients treated with a higher dose also responded. A sequential treatment approach of immunotherapy (IO) followed by a tyrosine kinase inhibitor (TKI) demonstrated superior efficacy compared to a perioperative IO regimen (*Abstract F7*). The IO/TKI sequence yielded a higher objective response rate (32.1% vs. 22.2%) and increased the rate of inferior vena cava (IVC) thrombus downstaging (45.5% vs. 37.5%). Furthermore, progression-free survival (PFS) was positively correlated with the extent of post-treatment tumor necrosis, which was more pronounced in patients treated with IO/TKI. Patients receiving perioperative IO/TKI tended to exhibit greater reductions in primary tumor



size and increased tumor necrosis.

A landmark 8-year analysis of the CheckMate 214 trial (*Abstract F3*) reaffirms the clinical significance of nivolumab/ipilimumab in first-line advanced RCC. The combination therapy continues to offer deep, durable responses and a significant survival advantage over sunitinib, establishing it as the standard of care. The non-randomized, phase II study (*Abstract L2*) aimed to investigate the potential benefit of surgery in carefully selected patients with metastatic renal cell carcinoma (RCC). The findings suggest that surgery may delay disease progression and improve overall survival in this patient population.. A population-based study (*Abstract P1*) demonstrated a substantial increase in the risk of locoregional recurrence (more than four-fold) and metastatic recurrence (almost two-fold) among patients who opted for local ablation rather than partial nephrectomy. Despite these differences, the overall recurrence rate remained low for both surgical and nonsurgical treatment approaches. These results underscore the significance of shared decision-making, where patients can weigh the potential risks and benefits of various treatment options to make informed choices. The CLEAR trial result (*Abstract F8*) indicated that Pts in the L+P arm trended to show later progression across tumors. At overall disease progression, the tumor burden of target lesions was lower with L+P vs S. Pts in the L+P arm stayed on 2L axitinib or cabozantinib longer than pts in the S arm. These results continue to support L+P as a standard-of-care 1L therapy in pts with aRCC.

Beyond the symposium, the global kidney cancer research community continues to make significant strides. Recent studies have explored the impact of emerging technologies, such as artificial intelligence and machine learning, on early detection, diagnosis, and treatment planning. These advancements hold the promise of revolutionizing the way kidney cancer is managed and ultimately improving patient outcomes. As the field of kidney cancer research evolves, it is imperative to foster collaboration between researchers, clinicians, and patients. By sharing knowledge and resources, we can accelerate the development of innovative therapies and improve the quality of life for individuals affected by this disease. The 2024 IKCS served as a powerful platform for this exchange, and we eagerly anticipate the continued momentum in the years to come.

Wishing you a year 2025 filled with innovative ideas, groundbreaking projects, and industry-leading results!

IKCS 2024: Moving Kidney Cancer Care Forward: Insights from the 25th Anniversary Symposium

Yousef Zakharia, M.D.

Kidney Cancer Program
Mayo Clinic Comprehensive Cancer Center, Mayo Clinic AZ

doi.org/10.52733/IKCS24Summary

ABSTRACT

The 25th Anniversary International Kidney Cancer Symposium (IKCS 2024) in Louisville, Kentucky, brought together leading experts to discuss the latest advancements in kidney cancer research and treatment. Key highlights included presentations on novel therapeutic approaches, including emerging immunotherapies and targeted therapies. The symposium also emphasized the importance of multidisciplinary care, patient-centered outcomes, and the role of supportive care in improving the overall patient experience. This meeting summary provides a comprehensive overview of the key findings and discussions presented at IKCS 2024.

 # CORRESPONDENCE
Dr. Yousef Zakharia, MD
Mayo Clinic Comprehensive Cancer Center,
Mayo Clinic AZ.
Email: ZAKHARIA.YOUSEF@mayo.edu

INTRODUCTION

We had another successful International Kidney Cancer Symposium (IKCS North America) conference in Louisville, Kentucky, from November 7-9, 2024, and this year was a special one, marking the 25th anniversary for IKCS. This meeting has become a very important one for providers dealing with kidney cancer from different aspects and subspecialties, and it is all centered around our patients who battle this disease. The meeting was well attended, and more importantly, many patients and patient advocates were there to share their experiences and contribute to advancing the field.

DAY 1

Session 1: What do we do when a kidney mass is not easily operable?

The 1st day of the conference started with a panel discussion of inoperable kidney cancer, a topic that remains an area of debate among urologists, oncologists, and radiation oncologists. Dr. Steven Lee Chang, urologist oncologist at Brigham and Women's Hospital, discussed approaches for kidney masses with inferior vena cava involvement. Dr. Chang reviewed the epidemiology of localized RCC, including Locally Advanced Disease (≥T3 or pN+) encountered in about 20% of cases, with IVC thrombus extension occurring in approximately 4-10% of cases, and

extension to the right atrium in about 1% of cases, with a 5-year disease-free survival following surgery of 46-69%. Dr. Chang also reviewed predictors of good and poor outcomes of surgical intervention, illustrating that good outcomes are achieved with a multidisciplinary team approach, specifically in high-surgical-volume hospitals, and poor outcomes are associated with poor health (sarcopenia), IVC wall invasion, and unusual thrombus extension (Budd-Chiari Syndrome).

Dr. Raquibul Hannan of UTSW discussed the role of Stereotactic Radiation Therapy (SBRT) for Locally Advanced and Unresectable Primary RCC. Dr. Hannan concluded that SBRT is non-invasive and has high efficacy with an excellent safety profile for primary RCC. Specifically, for inoperable cases, SBRT can offer effective palliation (pain, bleeding, and other symptoms) and often consolidation and/or local control. Active areas of investigation include the role of stereotactic radiation for IVC tumor-thrombus in the neo/adjuvant setting, and the role of SBRT with immunotherapy, which is currently being addressed in the CYTOSHRINK (NCT04090710) and SAMURAI (NCT05327686) trials.

Surveillance, neoadjuvant/palliative treatment was the title of the presentation by Dr. Leonard J. Appleman, MD, PhD, at the University of Pittsburgh. This presentation discussed the role of systemic therapy for locally advanced RCC to allow resection with negative margins, and in patients with a solitary functioning kidney or low GFR with tumors not amenable to partial nephrectomy, to allow converting radical nephrectomy to partial nephrectomy. Dr. Appleman reviewed the current literature of the neoadjuvant approach in kidney cancer, highlighting the use of different TKIs prior to cytoreductive nephrectomy. While all current TKI clinical trials are limited by small sample size, the trend of downstaging and tumor shrinkage was evident. Relevant trials included combinations of TKIs and immunotherapy showing a similar trend. The question about the role of IO-based systemic therapy prior to cytoreductive nephrectomy in advanced renal cancer is actively being addressed in the PROBE clinical trial, which might help shed light on the use of systemic therapy in localized kidney cancer when surgical intervention is controversial.

An excellent panel discussion around the

management of inoperable renal masses prompted much discussion about the best way to approach these scenarios. The multidisciplinary approach in this setting, including expertise from urologist oncologists, radiation oncologists, and medical oncologists, remains the current preferred approach for better outcomes.

Session 2: Expanding Supportive Care Options to Improve the Patient Experience and Outcomes Before, During, and After Therapy

This session started with the patient perspective by patient advocate Sid Sadler, who discussed the importance of social media while battling cancer, pointing out that social media can harbor harmful misinformation. Sid also highlighted the importance of patient advocacy and getting involved in kidney cancer societies like the KCA.

Dr. Viraj Master, a urologist oncologist at Emory University, presented the role of Integrative Oncology in kidney cancer. Dr. Master highlighted that Americans spend between $30 billion and an estimated $60 billion out-of-pocket on complementary health approaches. Some of these therapies don't work, but patients are still taking them, and some complementary therapies may interfere with conventional therapy. He also discussed the role of acupuncture, massage therapy, and others recommended by the ASCO Guidelines for pain management in oncology.

Mindfulness, Wellness-Based, Nutritional Interventions, and *Practices for Symptom and Toxicity Management* were presented by Anna Bausum, ND, Integrative Oncology Specialist at Winship Cancer Institute. The focus of this talk was the importance of lifestyle changes as foundational support, including omega-3 fatty acids to prevent cachexia and reduce fatigue. The role of insulin sensitivity in renal cancers and how as little as 2-10 minutes of gentle movement after meals has been shown to support postprandial glucose levels were also discussed. Anna Bausum, ND, reviewed the benefits of anti-anxiety and stress reduction in cancer patients, especially during active treatment and around the time of surgery, and how that could reduce opioid use. Encouraging patients to adopt small changes in their lifestyle as integrative techniques are cost-effective and feasible to

implement.

Dr. Sarah Psutka from the University of Washington presented on the management of sleep, fatigue, and distress from the perspective of cognitive neurosurgeons. The presentation concluded that distress, fatigue, and disrupted sleep can significantly affect cognitive function during cancer treatment. Dr. Psutka highlighted how behavioral strategies, including compensation techniques, diaphragmatic breathing, regular physical activity, and sleep hygiene, can help manage symptoms of distress, fatigue, and sleep disturbances.

This session concluded with a presentation about exercise in medicine by Dr. Hanna Hunter from the Department of Rehabilitation Medicine at the University of Washington. Dr. Hunter emphasized that oncology providers should recommend aerobic and resistance exercise during active treatment to help mitigate side effects of cancer treatment.

Session 3: Divergent Histology in Kidney Cancer

A dedicated session about Divergent Histology in Kidney Cancer started with the presentation by Dr. Ying-Bei Chen about the WHO Definitions of Divergent Pathology and how it depends on combined definitions of histomorphology and molecular features. Dr. Chen reviewed the current histopathological features for non-clear cell RCC and emphasized that the diagnosis of high-grade RCC with papillary or poorly differentiated features is challenging and often relies on the exclusion of molecularly defined entities using specific ancillary tools.

Drs. Bradley McGregor and Ben Maughan reviewed the current standard of care treatments and the ongoing clinical trials prospectively in non-clear cell renal cell carcinoma. While the current standard of care (SOC) with combination therapies have high response rates in single-arm phase 2 trials, participation in a clinical trial remains the best recommended treatment for patients with non-clear cell RCC, as new ongoing trials are exploring novel targets and focusing on individual diseases with unique biologic drivers.

Session 4: Oral Abstract Session

The oral abstract session included many important clinical and translational presentations. Patterns of progression and subsequent therapy in the Clear Trial suggested that patients treated with lenvatinib and pembrolizumab stayed on 2L axitinib or cabozantinib treatment longer than patients in the sunitinib arm. Time to progression and tumor burden at progression were both in favor of the combination. A real-world competing risk analysis about the occurrence of local recurrences (LR) and distant metastases (DM) after ablation versus partial nephrectomy suggested that ablative treatment had a 4.3 times higher risk of LR and a 1.9 times higher risk of DM.

Another abstract utilizing blood-based multiomics profiling suggested an association between response to immune checkpoint inhibitors and a decrease in polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs) during treatment, with accumulation of regulatory phenotype T-cells among non-responders.

An abstract by the team at UCLA suggested 99mTc-Sestamibi SPECT/CT in differentiating between aggressive and indolent lesions, and this can non-invasively identify more indolent oncocytic lesions with 78%, 94% sensitivity, and specificity, respectively.

Data about safety and efficacy was presented from the Phase 1 TRAVERSE clinical trial using CD70 CAR T cell therapy in 39 patients with refractory clear cell RCC. Pancytopenia was a notable side effect in this trial, including grade (G) 3 neutropenia, anemia, and thrombocytopenia of 51%, 33%, and 26%, respectively. Severe infection occurred in 31% of cases and G3 neurotoxicity in 8% of cases. The majority of CD70+ tumors shrunk with this treatment, with confirmed ORR in 24% of these patients with high CD70 expression.

Keynote Lecture

The conference keynote lecture was delivered by Professor Celeste Simon. This presentation, titled

"*Targeting Metabolism: Beating Kidney Cancer at Its Own Game*," was thought-provoking. Professor Simon reviewed different metabolic pathways altered in ccRCC, including loss of the gluconeogenic enzyme, fructose 1-6-bisphosphatase, loss of urea cycle enzymes, and accumulation of neutral lipids. She pointed out the overexpression of Scavenger Receptor Class B Member 1 (SCARB1) in ccRCC and how targeting SCARB1 could slow tumor growth.

Following the keynote lecture, the Wood Rising Star Award was presented to David Braun, MD, PhD, from Yale University for his efforts studying mechanisms of response and resistance to immune therapy in RCC.

Session 6: Going Beyond RECIST

A dedicated session about *radiomics in kidney cancer and the role of artificial intelligence* tackled the limitations of the current radiology imaging modalities and the RECIST criteria used for renal cancer clinical trials. These methods fail to account for the common occurrence of necrosis, especially when patients are treated with tyrosine kinase inhibitors (TKIs). By blocking the tumor's blood supply, TKIs often cause the best response to appear as necrotic lesions that may not shrink in size, or even enlarge due to inflammation. According to the RECIST criteria used for evaluating treatment response in clinical trials, these lesions are often mistakenly classified as stable or progressive disease, even though they could indicate a strong response to treatment. In fact, resection of these lesions frequently shows pathological complete remission. Additionally, the typical FDG PET-CT scan, widely used in other cancers, lacks the sensitivity and specificity necessary for renal

cancer. There is a clear need for improved imaging modalities and criteria beyond RECIST to better manage clear cell RCC (ccRCC), both in clinical trials and in routine clinical practice. An exciting new development in RCC imaging is the 89Zr-DFO-girentuximab, a monoclonal antibody targeting carbonic anhydrase IX (CAIX), an enzyme that is highly expressed in ccRCC. In the phase 3 ZIRCON clinical trial, 300 patients with renal masses ≤7 cm (stage cT1) undergoing partial nephrectomy were enrolled. The co-primary objectives for sensitivity and specificity of this PET modality were 86% (80%, 90%) and 87% (79%, 92%), respectively, offering a non-invasive method to identify ccRCC. We are just beginning to scratch the surface of how artificial intelligence (AI) can be applied to detect kidney cancer, assess tumor volume, and evaluate treatment responses.

Session 7: Mentorship Awards with Brian Rini

A mentoring session was moderated by Dr. Brian Rini of the Academy of Kidney Cancer Investigators, a formal organization dedicated to providing research direction and career guidance for early-career investigators. This was followed by presentations from four mentees showcasing their ongoing research projects. An excellent poster walk was hosted by Drs. Arpita Desai and Priyanka Chablani.

DAY 2

Day 2 started with KCA updates by Chief Scientific Officer Salvatore La Rosa, PhD, who reviewed the available resources for patients and healthcare providers through the organization and highlighted the forums and tools to help experts advance kidney cancer research topics, activated multiple partnerships to expand grant offerings, and promote research collaborations. This session was followed by recognizing the IKCSNA24 Planning Committee.

Session 9: Tumor board - Management of the SRM

Scientific sessions started with a debate about triggers for intervention for patients on active surveillance. Dr. Maxine Tran from University College London argued that tumor size is an important factor when counseling patients diagnosed with a small renal mass (SRM), and that active surveillance is a safe management strategy in the majority of patients diagnosed with an SRM, while Dr. Brian Shuch of UCLA argued that tumor biology is the most important driver of outcome, and that management should not be driven by appearance, size, or growth as those do not tell the whole story.

Session 10: Patient centered outcomes in Kidney cancer research

This session started with Katie Coleman, patient advocate and founder of the Chromophobe and Oncocytic Tumor Alliance (COA). Katie reviewed her personal story with cancer and reminded the audience of the mental, social, and financial challenges that any cancer patient could go through. Katie highlighted that simple measures could make a difference in our patients' lives, like the flexibility around appointments or treatment schedules, to work around commute time and any work/home obligations. Dena Battle, President of KCCure, reviewed the impact of the disease on patients from diagnosis to outcome. This was addressed through surveys of patients asking different questions related to the frequency of clinic visits, emotions, and how much time patients spent thinking about their cancer, and how frequently cancer impacts their activities. The survey concluded that the cancer burden is excessive on the patient's daily activity, and new strategies, including future treatment developments, should aim to increase overall survival but decrease this burden. Next, a presentation by Professor David Cella about the financial toxicity and quality of life concluded that social determinants of health matter. They explain a lot of what we are responsible for when caring for patients.

SESSION 11: Beyond IO and TKI

Another session of oral abstracts was presented,

including clinical trials and translational work. One trial alternating pazopanib and bevacizumab in treatment-naïve metastatic ccRCC concluded that this modality is safe and could be viable options for those patients who are not eligible for immunotherapy, especially those with the IMDC favorable risk category. Another phase 1 trial combining sitravatinib with nivolumab and ipilimumab suggested that sitravatinib could not be safely combined with ipilimumab 1 mg/kg due to side effects; however, a dose reduction of ipilimumab to 0.7 mg/kg allowed safe sitravatinib escalation potentially at the cost of efficacy. The scientific presentation concluded with a session about newer treatment options beyond immunotherapy and tyrosine kinase inhibitors, followed by the "Woodfire session," the landmark of the meeting, presenting multiple challenging surgical and medical cases.

CONCLUSION:

The 2024 Kidney Cancer Association IKCS Meeting served as an excellent platform for networking and collaboration among researchers and providers while also sharing valuable insights and advancing the ongoing fight against kidney cancer. The meeting fostered a collaborative environment, inspiring further research and innovation in the field of kidney cancer. The insights gained from IKCS 2024 will undoubtedly contribute to improved patient outcomes and continued progress in the fight against this disease.

These recommended abstracts from 2024 IKCSNA Annual Meeting highlight some of the most important trends in ongoing trials chosen by Dr. Hutson 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/IKCS24abs

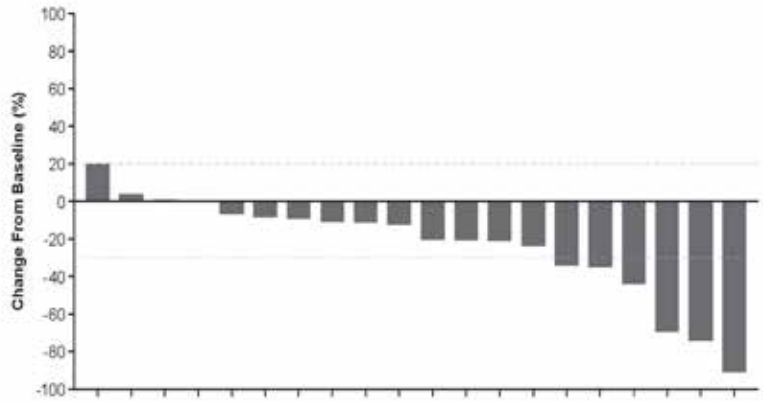
ABSTRACT F2: TRAVERSE: Updated safety and efficacy of ALLO-316 in advanced/metastatic clear cell renal cell carcinoma (ccRCC). *Srour SA et al.*

BACKGROUND: TPatients with relapsed/refractory metastatic RCC have poor clinical outcomes. ALLO-316 is an investigational, healthy donor-derived, HLA-unmatched, allogeneic CD70 CAR T cell product designed to recognize and kill both CD70+ tumors and CD70+ host T cells that drive allo-rejection. Initial data from TRAVERSE (NCT04696731), a first-in-human study of ALLO-316 in advanced/metastatic ccRCC, showed encouraging activity and manageable toxicities (Srour, Cancer Res 2023). Patients had CD70+ advanced/metastatic RCC that progressed on (or became intolerant to) ICI and VEGF–targeted therapy. Escalating doses of ALLO-316 (40 to 240×10^6 allogeneic CAR+ T cells) were administered intravenously after lymphodepletion (fludarabine and cyclophosphamide +/- ALLO-647, an anti-CD52 monoclonal antibody). The primary endpoint was dose-limiting toxicities ≤28 days after ALLO-316 infusion.

METHODS: By 05/28/2024, 32 patients were enrolled; 31 received ≥1 dose of lymphodepletion (median age, 62 years; male, 87%; median number of prior therapies, 3); and 29 received ALLO-316 (maximum administered dose, 240 × 10^6 allogeneic CAR+ T cells). For CD70+ tumors, 95% (19/20) had disease control, (≥1 follow-up visit with stable disease or partial/complete response); 80% (16/20) had tumor burden reduction (Figure 1); and 30% (6/20) had objective response (≥1 follow-up visit). The most common all-grade adverse events were fatigue (71%), nausea (61%), CRS (58%, low grade except one grade 3 [3%]), neutropenia (55%), leukopenia (45%), and anemia (45%). No ICANS or GvHD occurred. A subset of patients experienced immune effector cell-associated HLH-like syndrome (IEC-HS); these IEC-HS data and management with ruxolitinib will be presented. Updated data from phase 1a/1b will be presented.

CONCLUSIONS: Single-dose ALLO-316 demonstrated a manageable safety profile in relapsed/refractory advanced/metastatic ccRCC. Preliminary analyses in CD70+ tumors provided encouraging evidence of CAR activity, supporting further evaluation of ALLO-316 in CD70+ ccRCC and other CD70+ malignancies.

Figure 1. Tumor Reduction From Baseline in CD70+ Patients (N=20)



Modified intent-to-treat population of patients with CD70+ disease. Best reduction from baseline is defined as maximum percentage decrease (or minimum percent increase, if no decrease) in the sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) of target lesions at a given visit relative to baseline from baseline. The modified intent-to-treat analysis set includes all enrolled patients who received ALLO-316 and have any post-baseline tumor assessment or discontinued/died before first post-baseline response assessment.

ABSTRACT F3- Nivolumab plus ipilimumab vs sunitinib for first-line treatment of advanced renal cell carcinoma (aRCC): 8-year follow-up from the phase 3 CheckMate 214 trial. *Hans J. Hammers1 et al.*

BACKGROUND: Nivolumab plus ipilimumab (NIVO+IPI) provided substantial long-term survival and durable response benefits over sunitinib (SUN) in

patients with aRCC in CheckMate 214.

METHODS:

Patients with aRCC were randomized to NIVO 3 mg/kg + IPI 1 mg/kg Q3W×4 followed by NIVO (3 mg/kg or 240 mg Q2W, or 480 mg Q4W) or SUN 50 mg QD (4 weeks on, 2 weeks off). Efficacy endpoints: overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) in International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate/poor (IP; primary), any (intent-to-treat [ITT]; secondary), and favorable (FAV; exploratory) risk patients. PFS and ORR were assessed by an independent radiology review committee. RCC-specific survival post-hoc analyses in ITT patients censored all causes of death other than RCC.

RESULTS: With 8-year (99.1-month) median follow-up, the HR for OS with NIVO+IPI vs SUN was 0.72 (ITT), 0.69 (I/P), and 0.82 (FAV; Table). Median PFS was consistent with previous reports. ORR was higher with NIVO+IPI vs SUN in ITT (39% vs 33%) and IP (42% vs 27%) patients. In FAV patients, ORR was lower with NIVO+IPI vs SUN (30% vs 52%), yet complete response rates were higher and median duration of response was longer with NIVO+IPI regardless of IMDC risk group (Table). Median RCC-specific survival (95% CI) was 74 (63-91) months with NIVO+IPI vs 45 (38-53) months with SUN (HR, 0.69; 95% CI, 0.59-0.82). Treatment-related adverse events remained largely unchanged. No new drug-related deaths occurred since the previous database lock.

	ITT		IP		FAV	
Arm (n)	NIVO+IPI (N = 550)	SUN (N = 546)	NIVO+IPI (n = 425)	SUN (n = 422)	NIVO+IPI (n = 125)	SUN (n = 124)
OS HR (95% CI)	0.72 (0.62-0.83)		0.69 (0.59-0.81)		0.82 (0.60-1.13)	
mOS (95% CI), mo	53 (46-65)	38 (32-44)	47 (35-56)	26 (22-33)	78 (65-92)	67 (56-80)
PFS per IRRC, HR (95% CI)	0.88 (0.75-1.03)		0.73 (0.61-0.87)		1.76 (1.25-2.48)	
mPFS (95% CI), mo	12 (10-17)	12 (10-15)	12 (9-17)	9 (7-11)	12 (10-18)	29 (23-43)
ORR per IRRC, % (95% CI)	39 (35-44)	33 (29-37)	42 (38-47)	27 (23-32)	30 (22-38)	52 (43-61)
Complete responses, %	12	3	12	3	13	6
DOR per IRRC HR (95% CI)	0.52 (0.38-0.72)		0.48 (0.33-0.69)		0.70 (0.36-1.34)	
mDOR (95% CI), mo	76 (59-NE)	25 (20-33)	83 (54-NE)	20 (16-26)	61 (28-NE)	33 (25-51)

CONCLUSIONS:

Superior survival and durable response benefits were maintained with NIVO+IPI vs SUN after 8 years in the longest phase 3 follow-up of a first-line checkpoint inhibitor combination in aRCC. No new safety signals emerged.

ABSTRACT F7: Radiographic and pathological outcomes in patients (pts) with clear cell renal cell carcinoma (ccRCC) receiving perioperative immunotherapy (IO) combinations undergoing deferred nephrectomy

IssaW et al.

BACKGROUND: Immunotherapy (IO)-based combinations have improved outcomes for pts with metastatic RCC. However, optimal use of perioperative immunotherapy before nephrectomy remains understudied, needing data to inform practice..

METHODS: A retrospective analysis was performed at UTSW. Pts with advanced clear cell (cc)RCC were included if they received perioperative IO-based combinations: dual-IO (IO-IO) or tyrosine kinase inhibitor-IO (IO-TKI). Primary endpoint was objective response rate (ORR) per RECIST 1.1 between pts receiving IO-IO vs IO-TKI. Secondary endpoints included pathological downgrading, tumor necrosis, inferior vena cava (IVC) thrombus downstaging, immune related adverse events (irAEs), and time to progression. Chi-squared test or two-sample T-test was used to compare cohorts and Kaplan Meier was used to evaluate time to progression.

RESULTS: We identified 55 pts with ccRCC treated with IO combinations perioperatively, of whom 36 had metastatic disease and 19 had locally advanced disease. IO+TKI was administered to 51% of pts (n=28) and 49% (n=27) received IO+IO. Baseline characteristics were similar in both groups [IO-TKI vs IO-IO, age (median = 65.8 vs 61.6 yrs), sarcomatoid (18% vs 22%) and rhabdoid (18% vs 22%) features, and tumor size (median = 8.5 vs 8 cm)]. Median time on IO-TKI was 6 months vs 3 months for IO-IO. Median time to nephrectomy was 4.8 months for IO-TKI vs 5.8 months for IO-IO. IO-TKI treated pts experienced

greater primary tumor reduction (-2.6 vs -0.9 cm, p=0.2), higher ORR (32.1% vs 22.2%, p=0.5) and more tumor necrosis (median 30% vs 10%, p=0.06). IVC thrombus downstaging occurred in 5/11 (45%) for IO-TKI vs 3/8 (38%) in IO-IO. Fewer irAEs occurred in IO-TKI treated pts (29% vs 63%, p=0.01). Pts with >20% tumor necrosis in nephrectomy specimens had better prognosis than pts with ≤20% tumor necrosis (HR 0.24, p=0.017).

CONCLUSIONS: Greater primary tumor responses and more tumor necrosis was observed with perioperative IO-TKI than IO-IO in pts with ccRCC. Tumor necrosis post-IO may indicate better prognosis.

ABSTRACT F8. Lenvatinib plus pembrolizumab (L+P) vs sunitinib (S) in advanced renal cell carcinoma (aRCC): Patterns of progression and subsequent therapy in the CLEAR trial *Grünwald V. et al.*

BACKGROUND: In the primary CLEAR analysis of patients (pts) with aRCC, L+P significantly improved efficacy vs S. Results were confirmed at the final prespecified OS analysis. We report patterns of progression and subsequent therapy in CLEAR (NCT02811861).

METHODS: Treatment-naïve pts (n=1069) with aRCC were randomized to: L 20mg PO QD + P 200mg IV Q3W; or L 18mg + everolimus 5mg PO QD; or S 50mg PO QD (4 wks on/2 wks off). Stratification factors were region and MSKCC risk group. Time to progression (IIR, RECIST v1.1) was defined for each organ independently using lesions within each specific organ. Medians were estimated with Kaplan-Meier method; 95% CIs were estimated with generalized Brookmeyer and Crowley method. L+P vs S hazard ratios (HRs; stratified by region and MSKCC risk group) were based on Cox regression.

RESULTS: Time to progression HRs were: bone, 0.40; CNS, 0.47; kidney, 0.65; liver, 0.52; lung, 0.48; lymph nodes, 0.63 (Table). At overall disease progression, median sums of target lesion diameters were lower with L+P vs S (29.8mm vs 42.8mm; Table). In the L+P arm, 181 pts received subsequent anticancer regimens (axitinib, n=43; cabozantinib, n=101). In the S arm, 246 pts received subsequent regimens (axitinib, n=47; cabozantinib, n=107). Median times to discontinuation of axitinib or cabozantinib as first anticancer regimens are shown (Table).

CONCLUSIONS: Pts in the L+P arm trended to show later progression across tumors. At overall disease progression, the tumor burden of target lesions was lower with L+P vs S. Pts in the L+P arm stayed on 2L axitinib or cabozantinib longer than pts in the S arm. These results continue to support L+P as a standard-of-care 1L therapy in pts with aRCC.

	L+P (n=355)	S (n=357)
Pts with progressive disease and target lesions at baseline, n	176	195
Baseline sums of target lesion diameters (mm)		
Median (Q1, Q3)	56.7 (32.8, 117.0)	56.7 (38.2, 97.6)
Sums of target lesion diameters (mm) at progression		
Median (Q1, Q3)	29.8 (12.2, 66.1)	42.8 (24.6, 84.3)
Change in sums of target lesion diameters from baseline (%)		
Median (Q1, Q3)	−48.1 (−71.1, −26.3)	−17.4 (−40.3, 0.8)
L+P vs S time to progression HR (95% CI)		
Bone	0.40 (0.25-0.63)	
Central nervous system	0.47 (0.19-1.19)	
Kidney	0.65 (0.37-1.14)	
Liver	0.52 (0.32-0.84)	
Lung	0.48 (0.36-0.62)	
Lymph nodes	0.63 (0.46-0.85)	
Median time to discontinuation of first anticancer regimen		
Axitinib, n Months (95% CI)	20 23.7 (5.3-NE)	14 12.6 (6.8-NE)
Cabozantinib, n Months (95% CI)	70 13.2 (8.2-NE)	25 7.1 (4.1-20.0)

ABSTRACT F9: Phase 1 Study of Sitravatinib Combined with Nivolumab and Ipilimumab in Patients with Advanced Clear Cell Renal Cell Carcinoma: Clinical Outcomes and Translational Correlatives. *Pavlos Msaouel et al.*

BACKGROUND: Sitravatinib, an immunomodulatory tyrosine kinase inhibitor, has shown potential in enhancing the efficacy of immune checkpoint therapy (ICT). This phase 1 trial aimed to determine the optimal dosing regimen of sitravatinib in combination with nivolumab and ipilimumab in patients with advanced clear cell renal cell carcinoma (ccRCC) who had not received prior treatment.

METHODS: Twenty-two patients with advanced ccRCC were enrolled. The primary objective was to evaluate the safety and determine the appropriate dosing for the triplet therapy. Single-cell RNA sequencing was performed on longitudinal tumor biopsies from 12 patients to investigate mechanisms of treatment resistance.

RESULTS: Seven patients initially received sitravatinib 35 mg daily, nivolumab 3 mg/kg, and ipilimumab 1 mg/kg. Although DLT occurred in only 1/7 patients (grade 3 myositis / myasthenia gravis), immune-related adverse events requiring high-dose steroids occurred in 6/7 patients. The ipilimumab dose was subsequently reduced to 0.7 mg/kg, allowing for safe escalation of sitravatinib to 100 mg daily. Overall, the triplet therapy achieved an objective response rate of 45.5% and a disease control rate of 86.4%. Median progression-free survival was 14.5 months, with 72.7% of patients alive after a median follow-up of 15.7 months. Single-cell RNA-seq analysis revealed that treatment resistance within the tumor microenvironment was characterized by a shift from cytotoxic to exhausted T cell states and an increase in M2-like myeloid cells. Furthermore, we identified a tumor cell-specific transcriptomic signature linked to treatment resistance and poor outcomes. External validation of this signature in the TCGA ccRCC cohort showed significant association with worse survival.

CONCLUSIONS: The combination of sitravatinib, nivolumab, and ipilimumab in patients with advanced ccRCC demonstrated a promising safety profile and efficacy. The observed changes in gene expression and cellular states highlight potential biomarkers for resistance and may guide future strategies to enhance ICT effectiveness in ccRCC. ClinicalTrials.gov Identifier: NCT04518046

ABSTRACT G1: CANINE: Prospective Comparison of Contrast-Enhanced Computed Tomography Against 89-Zr-TLX250 PositroN Emission Tomography/Computed Tomography for the Imaging-Based DetectioN of REcurrent Clear Cell Renal Cell Carcinoma After Surgery. Brian M. Shuch et al.

BACKGROUND: Carbonic anhydrase 9 (CA9) is expressed on the majority of clear cell kidney cancer (ccRCC) and is a target for immunoPET/CT imaging. Recently the ZIRCON trial with 89-Zr-TLX250 (TLX250-CDx) demonstrated excellent performance in diagnosing ccRCC in tumors ≤7 cm. Two trials demonstrate the ability of TLX250-CDx to identify distant sites of disease. Therefore, we are conducting a prospective study evaluating its ability to stage high-risk, surgically resected ccRCC.

METHODS: CANINE (NCT06447103) is a single center study enrolling up to 90 patients with high-risk, resected ccRCC for post-op imaging 4-16 weeks. Key inclusion includes pathology features identical to KEYNOTE-564. Eligibility includes no prior post-op diagnostic imaging, eGFR ≥30, the ability to get iodinated contrast, and the absence of an active or high-risk, resected cancer. Eligible patients will have administration of TLX250-CDx and then have a PET/CT imaging 7±2 days after. The PET/CT includes a diagnostic-quality CT scan with IV contrast and includes the chest, abdomen, and pelvis. A research report will be generated with findings to the referring physician. Both the diagnostic and PET/CT finding will undergo blind independent central review (BICR) by three radiologists and nuclear medicine physicians, respectively. Standard of care follow-up can be performed locally with images sent to evaluate the standard of truth for performance metrics including biopsy results, growth on surveillance, or shrinkage/growth on treatment. Recurrence-free survival will be evaluated on follow-up.

RESULTS: ENDPOINTS 1˚-To compare the lesion detection rate between TLX250-CDx PET/CT compared to standard of care diagnostic contrast-enhanced CT alone at 4-16 weeks from surgical resection based on BICR. 2˚ endpoints include safety in post-operative setting, evaluation of positive predictive value (PPV), and the ability of initial PET/CT to improve risk- stratification based on staging results.4.92% vs 2.27%) were similar between two arms.

CONCLUSIONS: TLX250-CDx has shown the ability to detect ccRCC in primary kidney tumors, however early results show the potential for detection of distant disease. This study will determine if there is improved detection of distant sites compared to the

existing standard of care for high-risk patients for post-op decisions for surveillance, adjuvant therapy, or combination systemic therapy.

ABSTRACT K7: Comparative Real-World Outcomes of Nivolumab-Ipilimumab vs. Avelumab-Axitinib in First-Line Treatment of Metastatic Renal Cell Carcinoma. Ilya Tsimafeyeu et al.

BACKGROUND: Nivolumab in combination with Ipilimumab (Nivo-Ipi) and Avelumab in combination with Axitinib (Ave-Axi) have shown favorable safety profiles among first-line treatments for metastatic renal cell carcinoma (mRCC). However, limited real-world data exist on the comparative toxicity and efficacy of these combinations.

METHODS: This retrospective, observational cohort study included patients with clear-cell mRCC and intermediate/poor IMDC risk, treated with either Nivo-Ipi or Ave-Axi as first-line therapy from 2018 to 2023. The cohorts were balanced by IMDC risk and concomitant cardiovascular diseases. The primary objectives were to assess the rate of treatment-related adverse events (TRAEs) and progression-free survival (PFS)..

RESULTS: A total of 102 patients were included, with 51 receiving Nivo-Ipi and 51 receiving Ave-Axi. Patient characteristics were well-matched across the cohorts. For the full study population, the median age at mRCC diagnosis was 63.4 years (range 41–79), 76% were male, 61% had chronic cardiovascular diseases, 75% were nephrectomized, 59% had intermediate risk, and 42% had two or more metastatic sites. The Ave-Axi cohort tended to be younger (median age 61.0 vs. 64.9 years) and had a higher rate of bone metastases (25.5% vs. 15.7%) compared to the Nivo-Ipi cohort. There were no significant differences in all TRAEs (62.7% vs. 68.6%) or grade ≥3 TRAEs (11.7% vs. 17.6%) between the Nivo-Ipi and Ave-Axi cohorts, respectively. Patients treated with Ave-Axi had a significantly extended PFS (15.0 vs 9.7 months; $p < 0.001$) and a numerically higher ORR (37.5% vs 29.4%).

CONCLUSIONS: In this real-world study, Ave-Axi was associated with a significantly longer PFS and a numerically higher ORR compared to Nivo-Ipi, without a substantial difference in toxicity.

ABSTRACT M2: Characterization of the Safety Profile of Belzutifan in Patients With Renal Cell Carcinoma (RCC): A Pooled Analysis of 4 Clinical Trials. *Pooja Ghatalia1 et al.*

BACKGROUND:

The first-in-class HIF-2α inhibitor belzutifan is approved in the United States for certain patients with von Hippel-Lindau (VHL) disease and advanced RCC. We conducted a pooled analysis of the safety profile of belzutifan monotherapy and associated adverse event (AE) management strategies in patients with pretreated advanced clear-cell RCC in LITESPARK-001 (NCT02974738), LITESPARK-005 (NCT04195750), and LITESPARK-013 (NCT04489771) trials and patients with VHL disease-associated RCC in the LITESPARK-004 trial (NCT03401788).

METHODS: All patients who received ≥1 dose of belzutifan 120 mg orally QD across the 4 trials were included.

RESULTS: Overall, 576 patients were included (LITESPARK-001, n=58 [3 patients had non-RCC advanced solid tumors]; LITESPARK-005, n=381; LITESPARK-013, n=76; LITESPARK-004, n=61). Of 576 patients, 99.3% had ≥1 all-cause AE and 61.6% had ≥1 grade 3-5 AE. AEs led to dose modification (reduction/interruption/discontinuation) in 50.0% of patients; 6.4% discontinued treatment due to AEs. The most common AEs were anemia (84.2% [including decreased hemoglobin]; grade 3 or 4, 28.8%) and fatigue (42.7%; grade 3, 2.8%). Any-cause hypoxia occurred in 16.3%; 12.2% experienced a grade 3 or 4 hypoxia. Adverse drug reactions (ADRs; AEs considered associated with belzutifan) are summarized in the table. Among 485 patients with anemia or decreased hemoglobin, 22.9% were treated with erythropoiesis-stimulating agent (ESA) only, 17.5% with blood transfusions only, and 12.8% with ESA and

blood transfusions. Among 94 patients with hypoxia, 70.2% received supplemental oxygen therapy. Grade 3-5 treatment-related AEs occurred in 37.7% (grade 5, n=1 [multiple organ dysfunction syndrome]).

CONCLUSIONS: Belzutifan had a generally manageable safety profile in patients with advanced RCC; few patients discontinued treatment due to AEs. ADRs had a relatively early onset. To date, this is the largest pooled safety dataset for a HIF-2α inhibitor.

Table. Summary and time to first onset of adverse drug reactions

AE	Pooled population N = 576				
	Incidence, n (%)	Led to dose interruption, n (%)	Led to dose reduction, n (%)	Led to treatment discontinuation, n (%)	Median (range) time to first onset of AE (any grade), days
Anemia[a]	485 (84.2)	41 (7.1)	22 (3.8)	2 (0.3)	29 (1-834)
Hypoxia	94 (16.3)	31 (5.4)	36 (6.3)	8 (1.4)	31 (1-952)
Fatigue	246 (42.7)	15 (2.6)	10 (1.7)	1 (0.2)	42 (1-1017)
Nausea	139 (24.1)	14 (2.4)	2 (0.3)	1 (0.2)	43 (1-1346)
Dyspnea	123 (21.4)	10 (1.7)	3 (0.5)	1 (0.2)	57 (1-911)
Dizziness	103 (17.9)	9 (1.6)	0 (0)	1 (0.2)	49 (1-974)
Weight increased	44 (7.6)	0 (0)	0 (0)	0 (0)	111 (4-671)

[a]Includes patients with adverse events of anemia and decreased hemoglobin.

ABSTRACT D7: Clonal origin of belzutifan-resistant kidney tumors in VHL disease Pooja Ghatalia1 et al.

BACKGROUND: Von Hippel Lindau disease (VHL) is a genetic disorder caused by inactivation of VHL leading to multiple disease manifestations including clear cell renal cell carcinoma (ccRCC). Belzutifan is a HIF-2a antagonist which blocks the effects of VHL inactivation leading to disease control in patients with ccRCC. Inevitably resistance develops leading to cancer growth ultimately requiring nephrectomy to prevent metastasis. We hypothesize that interrogation of genetic architecture and molecular analyses of these progressing tumors can identify new mechanisms of resistance.

METHODS: We collected 5 kidney tumors and 3 normal kidney samples from 2 patients on treatment with belzutifan who had progressing and regressing kidney lesions. At the time of surgery, 4 tumors were progressing (2 from each patient), and 1 was regressing, as defined by serial MRI scans. Samples underwent exome sequencing to an average depth of 211X, mutations and copy number alterations were identified for each patient, and phylogenetic trees constructed. We also assessed differences in CAIX, HIF2-alpha, and Ki-67 by immunohistochemistry.

RESULTS: Tumor phylogenies revealed that progressing tumors from each patient shared significant genetic alterations with one another, demonstrating the tumors progressing on belzutifan in each patient arose from a shared cell of origin. In the patient with a regressing tumor, this tumor did not share somatic mutations with the 2 progressing tumors, suggesting that by contrast it arose independently (Figure 1). No significant difference in CAIX, HIF2-alpha, and Ki-67 expression between progressing tumors and non-progressing likely reflecting our limited number of tumors/patients.

CONCLUSIONS: We conclude that in patients with VHL disease and multifocal kidney lesions, multiple kidney tumors can arise from a single cell of origin. This suggests that VHL disease may create a cancerized field within the kidney, in which there is clonal expansion of a cancerous population that is predisposed to develop resistance to belzutifan.

OPEN ACCESS

https://doi.org/10.52733/KCJ22n2-jc

Belzutifan for patients with von Hippel-Lindau disease-associated CNS haemangioblastomas (LITESPARK-004): a multicentre, single-arm, phase 2 study. *Iliopoulos O et al, Lancet Oncol. 2024 Oct;25(10):1325-1336.*

BACKGROUND: The first-in-class hypoxia-inducible factor-2a inhibitor, belzutifan, showed clinically meaningful antitumour activity in von Hippel-Lindau (VHL) disease-associated neoplasms in the ongoing, single-arm, phase 2 LITESPARK-004 study. We aimed to investigate antitumour activity with an additional 16 months of follow-up and present updated results for the subgroup of patients with CNS haemangioblastomas..

METHODS: In the multicentre, single-arm, phase 2 LITESPARK-004 study, adults (aged ≥18 years) from 11 cancer centres or hospitals in the USA, Denmark, France, and the UK, with germline VHL alterations, at least one measurable renal cell carcinoma tumour, no renal cell carcinoma tumour greater than 3 cm requiring immediate surgical intervention, an Eastern Cooperative Oncology Group performance status 0 or 1, and no previous systemic therapy received oral belzutifan 120 mg once daily until unacceptable toxicity, disease progression, or patient decision to withdraw. The primary endpoint, evaluated in patients with CNS haemangioblastomas, was the proportion of patients with an objective response per RECIST version 1.1 by an independent review committee. We assessed response using two approaches. In approach 1, we evaluated all measurable (≥1 cm maximum diameter) or non-measurable lesions at baseline, including both the solid lesion and the associated cystic component if present. In approach 2, we evaluated only baseline lesions with a measurable (≥1 cm maximum diameter) solid lesion. Antitumour activity was assessed in all patients who received at least one dose of belzutifan. This study is no longer recruiting but is ongoing, and is registered with Clinicaltrials.gov, NCT03401788.

FINDINGS: Between May 31, 2018, and March 29, 2019, of 67 patients screened, 61 (32 [52%] male and 29 [48%] female) were enrolled; 50 (82%) had at least one CNS haemangioblastoma evaluable at baseline (184 total lesions). Median follow-up for the 50 patients with CNS haemangioblastomas was 38·0 months (IQR 36·7-40·1). In approach 1, 22 of 50 patients (44% [95% CI 30-59]) had an objective response. In approach 2, 19 of 25 patients (76% [55-91] had an objective response. 23 (46%) of 50 patients had a grade 3-5 all-cause adverse event. 19 (38%) patients reported grade 3 adverse events, the most common of which was anaemia (in 6 [12%] patients). Two of 50 patients (4%) reported grade 4 events (retinal vein occlusion and embolism). Two patients died owing to adverse events not considered treatment-related (suicide and toxicity to various agents).

INTERPRETATION: Belzutifan showed meaningful antitumour activity in VHL disease-associated CNS haemangioblastomas that was sustained for more than 3 years of treatment. These results continue to support belzutifan as a systemic treatment option for patients with VHL disease-related CNS haemangioblastomas.

Tivozanib plus nivolumab versus tivozanib monotherapy in patients with renal cell carcinoma following an immune checkpoint inhibitor: results of the phase 3 TiNivo-2 Study Choueiri TK et al. *Lancet . 2024 Oct 5;404(10460):1309-1320.*

BACKGROUND: Immune checkpoint inhibitors (ICIs) and vascular endothelial growth factor receptor tyrosine kinase inhibitors are cornerstones of first-line treatment for advanced renal cell carcinoma; however, optimal treatment sequencing after progression is unknown. This study aimed to assess clinical outcomes of tivozanib-nivolumab versus tivozanib monotherapy in patients with metastatic renal cell carcinoma who have progressed following one or two lines of therapy in the post-ICI setting..

METHODS: In TiNivo-2 is a multicentre, randomised, open-label, phase 3 trial at 190 sites across 16 countries, in Australia, Europe, North America, and South America. Patients with advanced renal cell carcinoma and progression during or after one to two previous lines of therapy (including one ICI) were randomised 1:1 to tivozanib (0·89 mg per day, orally) plus nivolumab (480 mg every 4 weeks, intravenously) or tivozanib (1·34 mg per day, orally). Randomisation was stratified by immediate previous therapy (ICI or non-ICI) and International Metastatic Renal Cell Carcinoma Database Consortium risk category. The primary endpoint was progression-free

survival (PFS), defined as the time from randomisation to first documentation of objective progressive disease according to RECIST 1·1 or death from any cause, whichever came first, by independent radiology review. Efficacy was evaluated in the intention-to-treat population, and safety was assessed in patients who received one or more doses of the study drug. This trial was registered on ClinicalTrials.gov (NCT04987203) and is active and not recruiting.

FINDINGS: From Nov 4, 2021, to June 16, 2023, 343 patients were randomly assigned to tivozanib-nivolumab (n=171) or tivozanib monotherapy (n=172). Median follow-up was 12·0 months. Median PFS was 5·7 months (95% CI 4·0-7·4) with tivozanib-nivolumab and 7·4 months (5·6-9·2) with tivozanib monotherapy (hazard ratio 1·10, 95% CI 0·84-1·43; p=0·49). Among those with an ICI as their immediate previous therapy (n=244), median PFS was 7·4 months (95% CI 5·6-9·6) with tivozanib-nivolumab and 9·2 months (7·4-10·0) with tivozanib monotherapy. With non-ICIs as the most recent therapy, lower median PFS was observed, with no difference between groups (tivozanib-nivolumab 3·7 months [95% CI 2·7-5·4] and with tivozanib monotherapy 3·7 months [1·9-7·2]). Serious adverse events occurred in 54 (32%) of 168 patients receiving tivozanib-nivolumab and 64 (37%) of 171 patients receiving tivozanib monotherapy. One (<1%) treatment-related death occurred (tivozanib group).

INTERPRETATION: These data further support that ICI rechallenge should be discouraged in patients with advanced renal cell carcinoma. Furthermore, these data suggest that tivozanib monotherapy has efficacy in the post-ICI setting.

[(^{89})Zr]Zr-girentuximab for PET-CT imaging of clear-cell renal cell carcinoma: a prospective, open-label, multicentre, phase 3 trial. *Shuch B et al. Lancet Oncol.2024 Oct;25(10):1277-1287. doi: 10.1016/S1472045(24)00402-9.*

BACKGROUND: With limitations of conventional imaging and biopsy, accurate, non-invasive techniques to detect clear-cell renal cell carcinoma in patients with renal masses remain an unmet need. 89Zr-labelled monoclonal antibody ([89Zr]Zr-girentuximab) has high affinity for carbonic anhydrase 9, a tumour antigen highly expressed in clear-cell renal cell carcinoma. We aimed to evaluate [89Zr]Zr-girentuximab PET-CT imaging for detection and characterisation of clear-cell renal cell carcinoma.

METHODS: ZIRCON was a prospective, open-label, multicentre, phase 3 trial conducted at 36 research hospitals and practices across nine countries (the USA, Australia, Canada, the UK, Türkiye, Belgium, the Netherlands, Spain, and France). Patients aged 18 years or older with an indeterminate renal mass 7 cm or smaller (cT1) suspicious for clear-cell renal cell carcinoma and scheduled for nephrectomy received a single dose of [89Zr]Zr-girentuximab (37 MBq ±10%; 10 mg girentuximab) intravenously followed by abdominal PET-CT imaging 5 days (±2 days) later. Surgery was performed no later than 90 days after administration of [89Zr]Zr-girentuximab. Blinded central review, conducted by three independent readers, determined the histology from surgical samples. The coprimary endpoints, determined for each individual reader, were the sensitivity and specificity of [89Zr]Zr-girentuximab PET-CT imaging to detect clear-cell renal cell carcinoma, with histopathological confirmation as standard of truth. Analyses were on the full analysis set of patients, defined as patients who had evaluable PET-CT imaging and a confirmed histopathological diagnosis. The trial is registered with ClinicalTrials.gov, NCT03849118, and EUDRA Clinical Trials Register, 2018-002773-21, and is closed to enrolment.

FINDINGS: Between Aug 14, 2019, and July 8, 2022, 371 patients were screened for eligibility, 332 of whom were enrolled. 300 patients received [89Zr]Zr-girentuximab (214 [71%] male and 86 [29%] female). 284 (95%) evaluable patients were included in the primary analysis. The mean sensitivity was 85·5% (95% CI 81·5-89·6) and mean specificity was 87·0% (81·0-93·1). No safety signals were observed. Most adverse events were not or were unlikely to be related to [89Zr]Zr-girentuximab, with most (193 [74%] of 261 events) occurring during or after surgery. The most common grade 3 or worse adverse events were post-procedural haemorrhage (in six [2%] of 261 patients), urinary retention (three [1%]), and hypertension (three [1%]). In 25 (8%) of 300 patients, 52 serious adverse events were reported, of which 51 (98%) occurred after surgery. There were no treatment-related deaths.

INTERPRETATIONS: Our results suggest that [89Zr]Zr-girentuximab PET-CT has a favourable safety profile and is a highly accurate, non-invasive imaging modality for the detection and characterisation of clear-cell renal cell carcinoma, which has the potential to be practice changing.

Final Overall Survival Analysis of S1500: A Randomized, Phase II Study Comparing Sunitinib With Cabozantinib, Crizotinib, and Savolitinib in Advanced Papillary Renal Cell Carcinoma. *Barata P. et al. J Clin Oncol . 2024 Nov 20;42(33):3911-3916.*

BACKGROUND: Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical Trial Updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.Mesenchymal-epithelial transition (MET) signaling pathway plays a role in the pathogenesis of selected patients with papillary renal cell carcinoma (PRCC). In the phase II PAPMET trial (ClinicalTrials.gov identifier: NCT02761057), cabozantinib significantly prolonged progression-free survival and improved objective response rate compared with sunitinib in patients with advanced PRCC. Here, we present the final overall survival (OS) analysis. In this multicenter, randomized phase II, open-label trial, 147 patients with advanced PRCC who have received up to one previous therapy (excluding vascular endothelial growth factor-directed agents) were assigned to sunitinib, cabozantinib, crizotinib, or savolitinib. Ultimately, savolitinib and crizotinib arms were closed because of futility. With a median follow-up of 17.5 months, the median OS was 21.5 months (95% CI, 12.0 to 28.1) with cabozantinib and 17.3 months (95% CI, 12.8 to 21.8) with sunitinib (hazard ratio, 0.83; 95% CI, 0.51 to 1.36; P = .46). The OS landmark estimates for cabozantinib and sunitinib were 50% versus 39% at 24 months and 32% versus 28% at 36 months. In conclusion, we observed no significant difference in OS across treatment arms. Although cabozantinib represents a well-supported option for advanced PRCC, the lack of survival benefit underscores the need to develop novel therapies for this disease.

A randomized, open-label, phase 3 trial of pembrolizumab plus epacadostat versus sunitinib or pazopanib as first-line treatment for metastatic renal cell carcinoma (KEYNOTE-679/ECHO-302). *Lara PN Jr et al.* BMC Cancer. 2024 Jul 25;23(Suppl 1):1253.

BACKGROUND: Immunotherapy-based combinations have emerged as standard therapies for patients with metastatic renal cell carcinoma (mRCC). Pembrolizumab, a PD-1 inhibitor, combined with epacadostat, an indoleamine 2,3-deoxygenase 1 selective inhibitor, demonstrated promising antitumor activity in a phase 1 study in advanced solid tumors, including mRCC.

METHODS: KEYNOTE-679/ECHO-302 was a randomized, open-label, parallel-group, multicenter, phase 3 study (NCT03260894) that compared pembrolizumab plus epacadostat with sunitinib or pazopanib as first-line treatment for mRCC. Eligible patients had histologically confirmed locally advanced or metastatic clear cell RCC and had not received systemic therapy. Patients were randomly assigned 1:1 to pembrolizumab 200 mg IV every 3 weeks plus epacadostat 100 mg orally twice daily versus sunitinib 50 mg orally once daily (4 weeks on treatment followed by 2 weeks off treatment) or pazopanib 800 mg orally once daily. Original dual primary end points were progression-free survival and overall survival. Enrollment was stopped when a phase 3 study in melanoma of pembrolizumab plus epacadostat compared with pembrolizumab monotherapy did not meet its primary end point. This protocol was amended, and primary end point was changed to investigator-assessed objective response rate (ORR) per RECIST 1.1.

RESULTS: One-hundred-twenty-nine patients were randomly assigned to receive pembrolizumab plus epacadostat (n = 64) or sunitinib/pazopanib (n = 65). Median (range) follow-up, defined as time from randomization to data cutoff, was 10.3 months (2.2-14.3) and 10.3 months (2.7-13.8) in the pembrolizumab plus epacadostat and sunitinib/pazopanib arms, respectively. ORRs were similar between pembrolizumab plus epacadostat (31.3% [95% CI 20.2-44.1] and sunitinib/pazopanib (29.2% [18.6-41.8]). Grade 3-5 treatment-related adverse events occurred in 34.4% and 42.9% of patients in the pembrolizumab plus epacadostat and sunitinib/pazopanib arms, respectively. One patient in the sunitinib/pazopanib arm died of septic shock (not treatment-related). Circulating kynurenine levels decreased in the pembrolizumab plus epacadostat arm, but not to levels observed in healthy subjects.

CONCLUSIONS: ORRs were similar between pembrolizumab plus epacadostat and sunitinib/pazopanib as first-line treatment in patients with mRCC. Safety and tolerability appeared similar between treatment arms; no new safety concerns were

identified. Antitumor responses observed in patients with RCC receiving pembrolizumab plus epacadostat may be driven primarily by pembrolizumab.

Randomized phase II dose comparison LITESPARK-013 study of belzutifan in patients with advanced clear cell renal cell carcinoma. *Agarwal N, et al; J Immunother Cancer 2024 Apr 11;12(4):e008293. doi: 10.1136/jitc-2023-008293.*

BACKGROUND: Belzutifan is a first-in-class hypoxia-inducible factor subunit 2α (HIF-2α) inhibitor approved at a dose of 120 mg once daily for certain adults with VHL disease and adults with advanced renal cell carcinoma (RCC) following therapy with a programmed cell death protein 1 (PD-1) [or programmed death ligand 1 (PD-L1)] inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor. However, whether the belzutifan dose could be optimized is unclear.

METHODS: The phase II LITESPARK-013 study (NCT04489771) enrolled patients with advanced clear cell RCC whose disease progressed after one to three prior systemic therapies, including an anti-PD-(L)1 regimen. Patients were randomly assigned 1 : 1 to receive belzutifan 120 or 200 mg once daily. The primary endpoint was the objective response rate (ORR) per RECIST version 1.1. The secondary endpoints were duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety.

RESULTS: Overall, 154 patients were enrolled (120 mg: n = 76; 200 mg: n = 78). The median follow-up was 20.1 months (range 14.8-28.4). The ORR was 23.7% versus 23.1% for the 120 mg and 200 mg groups, respectively [P = 0.5312; -0.5%, 95% confidence interval (CI) -14.0% to 12.9%]. The median DOR was not reached for the 120 mg arm and was 16.1 months (2.1+ to 23.5+) for the 200 mg arm. No between-group differences were observed for PFS [hazard ratio (HR) 0.94, 95% CI 0.63-1.40] or OS (medians not reached; HR 1.11, 95% CI 0.65-1.90). Grade 3 or 4 treatment-related adverse events were observed in 35 patients (46.1%) in the 120 mg group and 36 patients (46.2%) in the 200 mg group.

CONCLUSIONS: Although overall survival was similar, favorable-risk patients treated with NIVO+IPI spent more time surviving treatment-free with and without toxicity versus SUN after 60 months of follow-up. Intermediate/poor-risk patients treated with NIVO+IPI had longer survival and longer TFS without toxicity versus SUN.

CONCLUSIONS: The efficacy of belzutifan was similar between the 120 mg dose and the 200 mg dose for previously treated clear cell RCC. Safety at both doses was consistent with the known safety profile of belzutifan. These results further support 120 mg once daily as the preferred dose for belzutifan.

Phase II Trial of Intermittent Therapy in Patients with Metastatic Renal Cell Carcinoma Treated with Front-line Ipilimumab and Nivolumab. Ornstein MC et al.

INTRODUCTION: The combination of ipilimumab/nivolumab is approved for patients with treatment-naïve, intermediate-, and poor-risk metastatic renal cell carcinoma (mRCC), but duration of therapy and safety/efficacy of reinduction at progression is unknown. A phase II trial of intermittent ipilimumab/nivolumab with reinduction at progression was conducted (NCT03126331).

PATIENTS AND METHODS: Patients with treatment-naïve mRCC were treated with induction ipilimumab/nivolumab followed by up to 24 weeks of maintenance nivolumab. Patients who achieved a complete response (CR) or partial response (PR) were eligible for inclusion and entered a treatment-free observation period. Patients were restaged every 12 weeks. Patients with no disease progression (PD) remained off therapy. Upon PD, patients were re-challenged with 2 doses of ipilimumab/nivolumab every 3 weeks. Study objectives were to estimate success rate of observation in patients who achieve a CR/PR, and to assess toxicity in patients undergoing reinduction. The study accrued slower than expected and was closed prior to the anticipated accrual goal of 20 patients.

RESULTS: Nine patients were included; 89% male, median age 57, 67% clear-cell histology, and 78% intermediate-risk by IMDC criteria. Response to ipilimumab/nivolumab followed by nivolumab maintenance prior to enrollment was 33% CR and 67% PR. Most (78%) patients have remained off therapy, with a median treatment-free interval (TFI) of 34.3 months (range, 8.7-41.8). Two patients had PD off therapy and received 2 cycles of reinduction ipilimumab and nivolumab. No grade 3 or greater toxicities occurred with reinduction. Both patients developed PD at their first scans after reinduction.

CONCLUSION: This prospective study demonstrates that patients with a radiographic response to ipilimumab/nivolumab can have prolonged treatment-free intervals. Further studies of de-escalation strategies are warranted.

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.

Manuscript Submission

Authors are required to submit their manuscripts in an electronic format, via https://kidney-cancer-journal.com/submit.php. or email at editor@kidney-cancer-journal.com. Please provide in a word processing program. Images should be submitted electronically as well. All material reproduced from previously published, copyrighted material should contain a full credit line acknowledging the original source. The author is responsible for obtaining this permission.

Contact information

List all authors, including mailing address, titles and affiliations, phone, fax, and email. Please note corresponding author.

Peer Review and Editing

Manuscripts will be peer reviewed. Accepted manuscripts will be edited for clarity, spelling, punctuation, grammar, and consistency with American Medical Association (AMA) style. Authors whose manuscripts are not initially accepted may have the opportunity to revise the manuscript based on recommendations from peer reviewers and at the discretion of the Editor-in-Chief.

Conflict of Interest

Kidney Cancer Journal policy requires that authors reveal to the Editor-in-Chief any relationships that they believe could be construed as resulting in an actual, potential, or apparent conflict of interest with regard to the manuscript submitted for review. Authors must disclose this information in the covering letter accompanying their submission.

Manuscript Preparation

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.
Spacing: One space after periods. Manuscripts should be double spaced.

References

All submissions should have references that are referred to in the text by superscripted numbers and that conform to AMA style. Example: Lewczuk J, Piszko P, Jagas J, et al. Prognostic factors in medically treated patients with chronic pulmonary embolism. Chest. 2001;119:818-823.

KCJ Open Access information

Publication ethics

As an official publication of the Kidney Cancer Association, Kidney Cancer Journal (KCJ) is committed to maintaining the highest standards of publication ethics and abides by Code of Conduct of Committee on Publication Ethics (COPE), and aims to adhere to its Best Practice Guidelines. Please refer to COPE flowcharts for further guidance. Manuscript authors, editors, and reviewers are expected to be aware of, and comply with, the best practices in publication ethics. Authors are expected to have knowledge of best practice in publication ethics in regard to, but not limited to, authorship, dual submission, plagiarism, manipulation of data/figures, competing interests and compliance with policies on research ethics.

Policy on use of human subjects

The clinical research studies involving the use of human subjects should inform that study has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The manuscript should be in line with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals and aim for the inclusion of representative human populations (sex, age and ethnicity) as per those recommendations. Authors should include a statement in the manuscript that informed consent was obtained for experimentation with human subjects. The privacy rights of human subjects must always be observed. Patients' and volunteers' names, initials, and hospital numbers should not be used.

Policy on use of animals

Studies involving experiments with animals must state that their care was in accordance with institution guidelines. All animal experiments should comply with the appropriate standard guidelines/act for the care and use of Laboratory animals and the authors should clearly indicate in the manuscript that such guidelines have been followed. Studies involving experiments with animals must state that their care was in accordance with institution guidelines. Authors must state in their manuscript how the identity of the cell line was confirmed.

CABOMETYX® (cabozantinib) tablets + OPDIVO® (nivolumab)

EXPLORE A **BALANCE OF DATA**

ACCESS THE CHECKMATE-9ER CLINICAL TRIAL RESULTS
bit.ly/view9ER

CABOMETYXhcp.com