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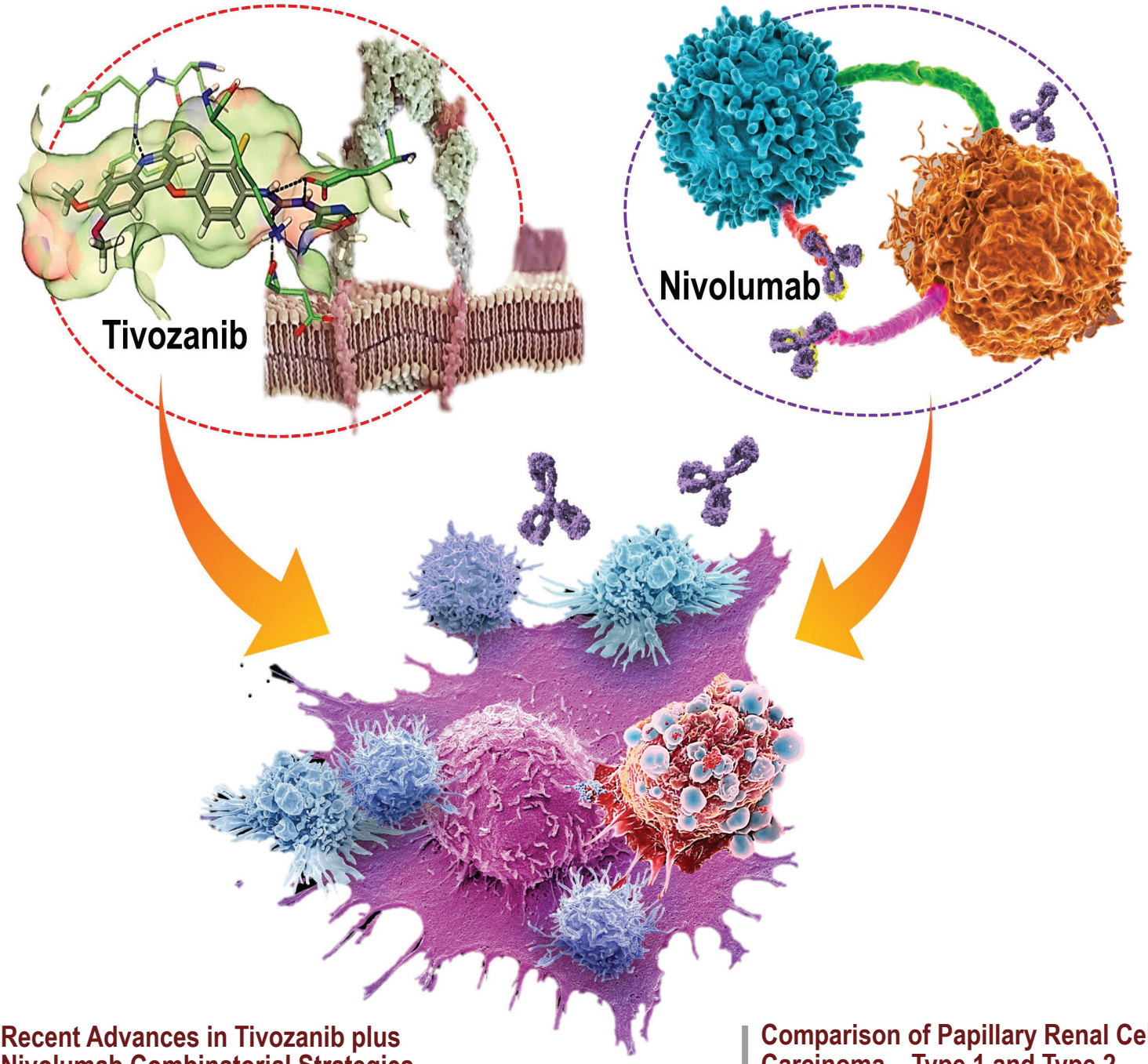
Kidney Cancer JOURNAL

Official Journal of The Kidney Cancer Association

Volume 20
Number 2
2022

Kidney-Cancer-Journal.com



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A graphic illustration of Tivozanib (VEGF TKI) plus Nivolumab (anti-PD-1 antibody) synergistically act to enhance the immune response against renal cell carcinoma

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A USA Based Publication

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Kidney Cancer Journal (ISSN 1933-0863) is published quarterly by BMG (BioMedz Global).
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Recent Advances in Tivozanib plus Nivolumab Combinatorial Strategies in Advanced Renal Cell Carcinoma

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doi.org/10.52733/KCJ20n2-rt

ABSTRACT

The treatment landscape of advanced renal cell carcinoma (aRCC) has witnessed significant benefits from the introduction of VEGF TKI/ICI (vascular endothelial growth factor receptor tyrosine kinase inhibitor/immune checkpoint inhibitor) combination in the first-line treatment. Such outcome benefits could extend to the relapsed/refractory setting with an effective, well-tolerated novel combination. Since the U.S. FDA approval of tivozanib monotherapy for the treatment of adult patients with relapsed or refractory advanced RCC following two or more prior systemic therapies,[1] there is growing interest in exploring its full potential in combination with anti-PD-1 like ICI agents. In this roundtable discussion, internationally renowned cancer experts brainstorm the potential immunomodulatory capabilities of tivozanib plus nivolumab combination as first-line and beyond settings in patients with metastatic RCC. The expert panel also explore potential data from previous and ongoing clinical trials and shared their perspectives about a tolerable safety profile and promising antitumor efficacy

KEYWORDS: Tivozanib, vascular endothelial growth factor receptor, tyrosine kinase inhibitor, nivolumab, immune checkpoint inhibitor, renal cell carcinoma, kidney cancer.

INTRODUCTION

In recent years, tyrosine kinase inhibitor/immune checkpoint inhibitor/ (ICI/TKI) combination regimens have emerged as novel treatment options for metastatic renal cell carcinoma (mRCC). However, it remains unclear how such combinations fit into the larger landscape of mRCC management, both in the first-line and beyond. Moreover, several clinical trials exploring such combinations have largely focused on the treatment-naïve population. Besides, the efficacy and toxicity of the combination beyond the first-line settings remain poorly defined.

Tivozanib, a highly selective and potent VEGF TKI, has demonstrated single-agent efficacy in advanced renal cell carcinoma.[2, 3] In addition, tivozanib exhibits minimal off-target toxicities and a favorable adverse event (AE) profile.[2-5] Based on these data, tivozanib monotherapy was approved by the FDA on March 10th, 2021 for the treatment of adult patients with relapsed or refractory advanced RCC who have received two or more prior systemic therapies.[1] As such, TKI/ICI combination regimens represent rationally designed novel therapeutic combinations built upon earlier work showing the individual efficacy of each class of drugs in RCC. Tivozanib and nivolumab are ideal candidates for combination therapy owing to their efficacy, safety profile, and synergy between VEGFR and programmed death-1 (PD-1) inhibition in RCC.[6] Tivozanib therapy facilitate immune-mediated responses through the decrease in regulatory T cells (Tregs).[7, 8] The selectivity and favorable tolerability of the VEGFR TKI tivozanib[9] may allow it to be used more readily as a combination therapy with an immune checkpoint inhibitor (ICI). Nivolumab an anti-PD-1 monoclonal antibody blocks the immune checkpoint protein PD-1 from interacting with its ligands programmed death ligands (PD-L1 and PD-L2). These mechanisms may act synergistically to potentially enhance the immune response that mediates antitumor activity.[4]

Following the FDA approval of tivozanib in renal cell carcinoma, tivozanib was explored in combination with the PD-1 inhibitor nivolumab in the Phase 1/2 TiNivo study,[6] where it demonstrated favorable tolerability and prolonged

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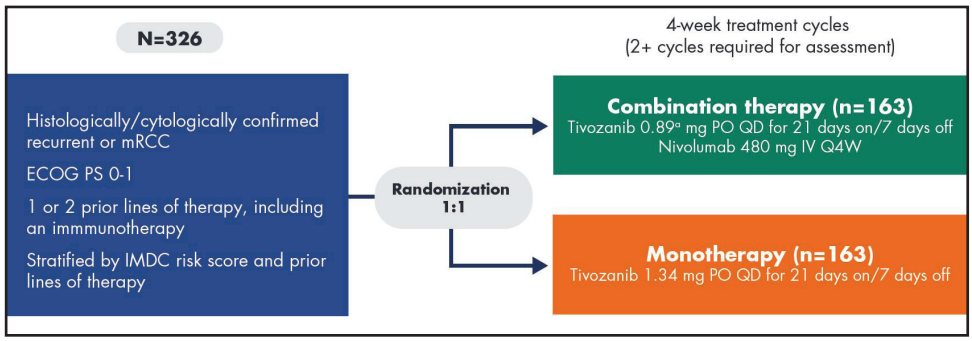

Figure 1 | Study design of TiNivo-2 trial. *ECOG PS, Eastern Cooperative Oncology Group performance status; IMDC, International Metastatic RCC Database Consortium; IV, intravenous; mRCC, metastatic renal cell carcinoma; PO, orally; Q4W, every 4 weeks; QD, once daily.*

PFS using the combination of tivozanib and nivolumab in both treatment naïve and previously treated patients with advanced RCC. Currently, the TiNivo-2 trial (NCT04987203)[10] is exploring immunomodulatory effects and differentiated tolerability profile of the tivozanib plus nivolumab combination versus tivozanib monotherapy in a phase 3, randomized, controlled, multicenter, open-label study.[10]

The objective of this roundtable program is to further gain insights into the efficacy and tolerability of tivozanib plus nivolumab combination therapy for advanced renal cell carcinoma patients. Also, leading oncology panelists share their insights that would enable clinicians to better understand the full potential of tivozanib plus ICI combinations in a rapidly changing treatment paradigm of kidney cancers. The panel includes Drs. Robert Motzer, MD, Dr. Toni Choueiri, and Dr. Laurence Albiges, MD, and our editor-in-chief Robert A. Figlin, MD chaired the meeting discussion.

Below is an excerpt from the discussion edited for brevity and clarity.

ROUNDTABLE DISCUSSION

Dr. Figlin:
Welcome, everybody. This is Robert Figlin, the Steven Spielberg Family Chair in Hematology-Oncology, Professor of Medicine and Biomedical Sciences, and Deputy Director of the Samuel Oschin Comprehensive Cancer Institute at Cedars-Sinai Medical Center in Los Angeles. On behalf of the *Kidney Cancer Journal*, I am delighted today to have a roundtable with some distinguished investigators

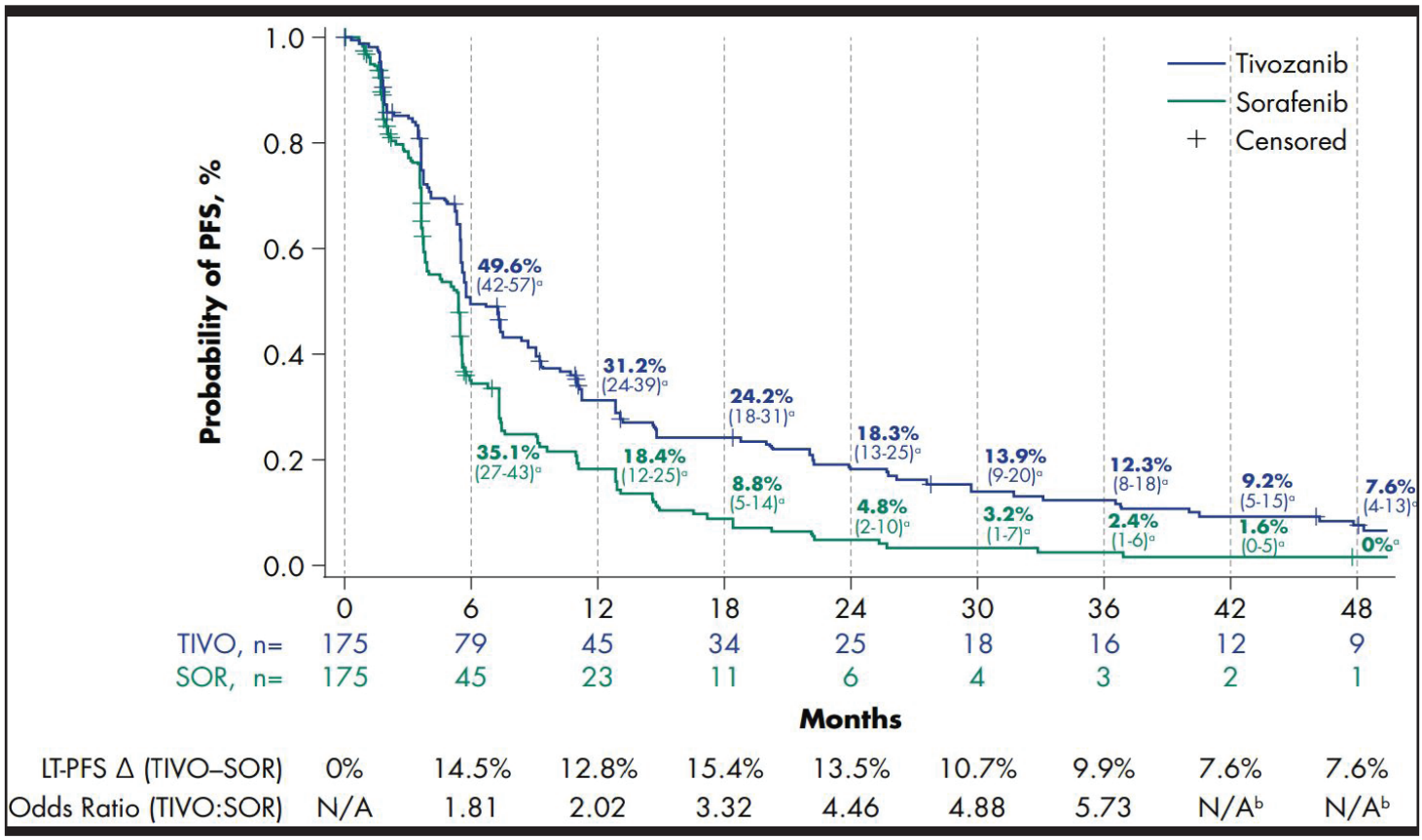

Figure 2 | Landmark Rates (95% CI) of LT-PFS in TIVO-3: TIVO vs SOR. a% (95% CI). bOR not calculated at months 42 and 48 due to insufficient number at risk. HR: 0.624 (95% CI: 0.49–0.79); log-rank P<.0001

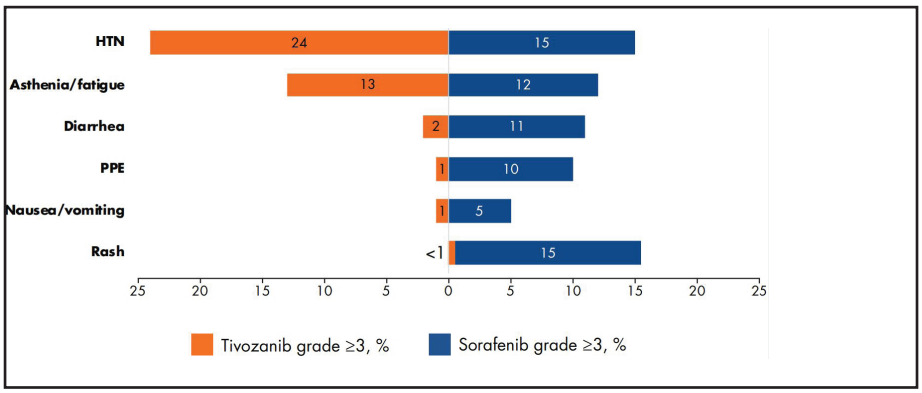

Figure 3 | Incidence of VEGFR TKI Class Effect Grade ≥3 TEAEs. *HTN, hypertension; PPE, palmar-plantar erythrodysesthesia.*

with great experience in the utility of tivozanib and its combination strategies, both in the clinical and research setting. So let me welcome Dr. Robert Motzer, Dr. Toni Choueiri, and Dr. Laurence Albiges. Please introduce yourself to the audience.

Dr. Motzer:
I am an attending physician and Kidney Cancer Section Head in the Genitourinary Service, Department of Medicine, and Jack and Dorothy Byrne Chair in Clinical Oncology at Memorial Sloan Kettering Cancer Center in New York.

Dr. Choueiri:
I am the Director of the Lank Center for Genitourinary (GU) Oncology at Dana-Farber Cancer Institute (DFCI), co-leader of the Kidney Cancer Program at Dana-Farber/ Harvard Cancer Center, and the Jerome and Nancy Kohlberg Chair and Professor of Medicine at Harvard Medical School.

Dr. Albiges:
I am Laurence Albiges a medical oncologist. I am head of the Medical Oncology Departmentat the Gustave Roussy Institute in France.

Dr. Figlin
You are a distinguished group of panelists who join us today to discuss the roles of tivozanib. Dr. Motzer, let's start with you. You are a pioneer in the development of tyrosine kinase inhibitors (TKI) and other potential therapeutics for the treatment of kidney cancers. Can you help us understand where tivozanib, a VEGF-TKI fits in that spectrum and the clinical trial that resulted in its approval in second-line therapy patients that had received prior therapy?

Dr. Motzer:
Tivozanib is a potent and highly selective VEGF receptor tyrosine kinase inhibitor. It was developed at a very exciting time with many advances in our therapeutic armamentarium between 2005 and 2012. At that time, there were several different VEGF TKIs including sunitinib, sorafenib and pazopanib which were studied in phase 3 trials and some of which were approved. Outstanding attributes of tivozanib in addition to efficacy are its tolerability and lack of off-target toxicities that had been seen with some other approved TKIs like sorafenib. Tivozanib was studied in a randomized phase III TiVo-1 trial compared to sorafenib in treatment naïve or prior cytokine-treated subjects with metastatic RCC

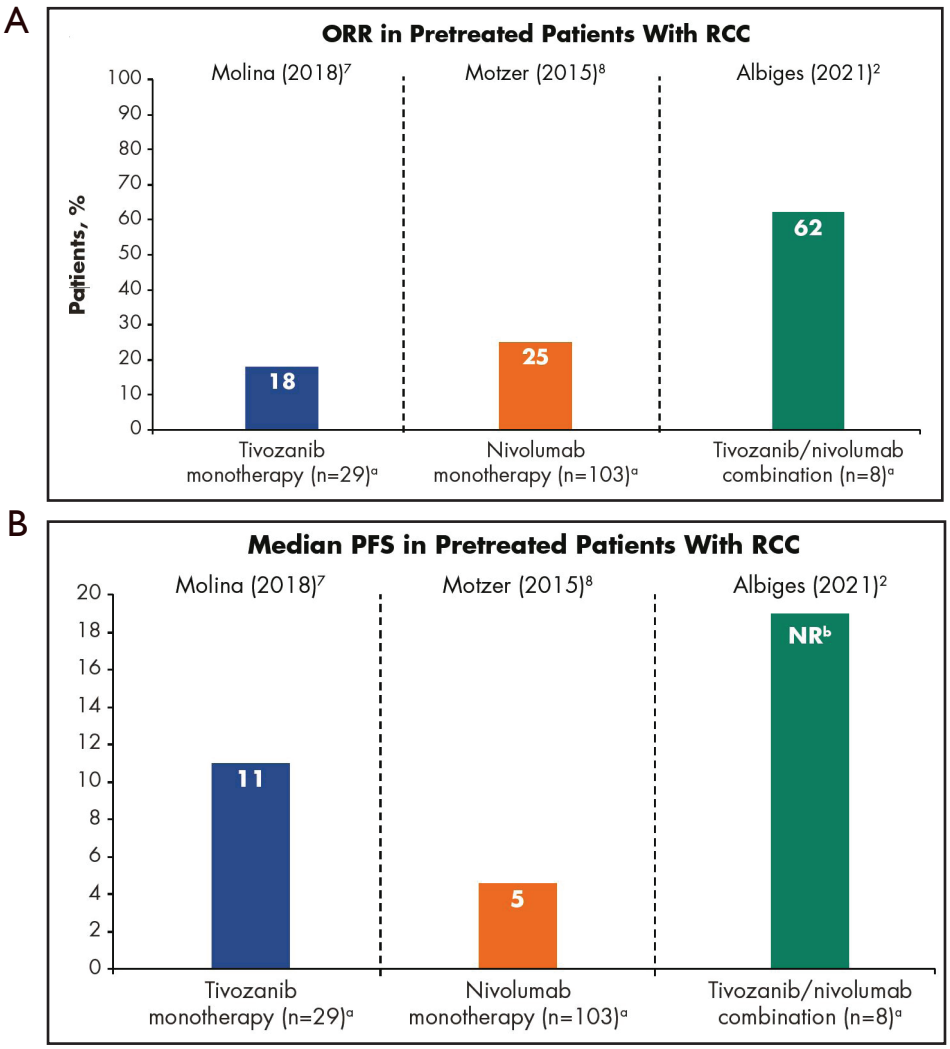

Figure 4. Antitumor Activity in Pretreated Patients from different studies[6, 11, 12]
(A) ORR was higher with tivozanib/nivolumab combination therapy than with either ingle agent alone; **(B)** PFS was longer with tivozanib/nivolumab combination therapy than with either monotherapy alone

(mRCC). Based on the improved progression-free survival (PFS), tivozanib was approved in Europe for first-line treatment of mRCC. However, due to conflicting OS results, approval was put on hold in the United States. Given the potential efficacy in later lines of therapy, TIVO-3 was designed as an open-label phase 3, randomized, controlled, multicenter study to compare tivozanib to sorafenib in 350 subjects with refractory advanced renal cell carcinoma. The patients were heavily pretreated patients had two or three prior treatments, including a TKI and some patients who have progressed on checkpoint inhibitors.

TIVO-3 met its primary endpoint by showing improvement in progression-free survival compared to sorafenib among favorable and intermediate IMDC risk patients, indicating ongoing responsiveness to VEGFR inhibition. In the heavily pretreated population, the tivozanib arm had a favorable safety profile which is a hallmark of tivozanib with fewer grade three or four adverse events, particularly those that are most troublesome to patients including hand -foot syndrome and fatigue. The issue around overall survival was resolved, with both arms showing similar overall survival, and the tivozanib arm having a superior response rate and progression-free survival.

A

	Treatment Naïve (n=12)	Pre-Treated (n=13) Includes 2 Prior CPI Pts	Overall (n=25)
CR	8%	-	4%
PR	42%	**62%**	52%
ORR (CR+PR)	50%	**62%**	56%
DCR (CR+PR+SD)	92%	**100%**	96%
mPFS	18.9 mo (4.7, NR)	**NR* (11.0, NR)**	18.9 mo (16.4, NR)
Dose reductions			**17%**

*19 months median follow up

Second Line Monotherapy Outcomes**

Tivozanib Mono[1]		Nivolumab Mono[2]
ORR 18% PFS 11.0	+	ORR 25% PFS 4.6

B

Event	Any grade n (%)	Grade 3/4 n (%)
	Patients (N = 25)	
Total	25 (100)	20 (80)
Hypertension	17 (68)	13 (52)
Asthenia	15 (60)	0
Diarrhea	11 (44)	0
Dysphonia	11 (44)	0
Pruritus	11 (44)	0
Arthralgia	11 (44)	0
Stomatitis	10 (40)	0
Anorexia	10 (40)	0
Palmar-plantar erythrodysesthesia syndrome	9 (36)	2 (8)
Dry skin	8 (32)	0
Myalgia	8 (32)	0
Fatigue	4 (16)	2 (8)
Rash	4 (16)	1 (4)
Increased ALT	4 (16)	1 (4)
Increased AST	4 (16)	1 (4)
Increased amylase	2 (8)	2 (8)
Pain in extremity	2 (8)	1 (4)
Malignant hypertension	2 (8)	2 (8)

5A. Anti-tumor activity seen in both treatment naive and previously treated RCC patients.[11, 12] **5B.** Treatment-related AEs of any grade (AEs in ‡30% of patients) and grade 3/4 (all AEs)[a]**.** *AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SIRS, systemic inflammatory response syndrome.* [a] *All grades (AEs in 30% of patients) and grade 3 (all AEs).*

Dr. Figlin:
Toni, let me turn to you. You are a leader in combination therapies that have transformed the kidney cancer landscape in recent years. Can you help us understand the preclinical biological mechanism when combining a TKI with an IO? Do they become additive or synergistic? Are there effects on the tumor microenvironment that make those combinations better than either of those drugs alone?

Dr. Choueiri:
I can tell you that beyond seeing if there's synergy or additive effect, we are combining two drugs endowed with single-agent activity of their own in the frontline as well as refractory settings. Based on the clinical data, we cannot confirm that if there has been synergy or if each drug works on its own. Having said so, we know that in preclinical models, T-cell mediated cancer cell killing, which is how immune checkpoint inhibitor largely works, may be enhanced through a reversal of VEGF mediated immunosuppression and other multiple steps in the immunity cycle. For example, the promotion of T cell priming and activation through the maturation of dendritic cells can happen by inhibiting VEGF. In addition, inhibiting VEGF can lead to the normalization of the tumor vasculature so that T cells could infiltrate the tumor better. VEGF inhibition can also lead to an immune permissive tumor microenvironment by decreasing the Myeloid-derived suppressor cells (MDSCs) and regulatory T (Treg) cells.

Dr. Figlin:
That is quite a nice summary, Toni Choueiri! Thank you. So Laurence let me turn to you. You're the first

author on the TiNivo-2 trial. It's the Phase 1/2b trials that you've reported. So dive into that trial in terms of what you was the patient populations that you studied, the outcomes that you observed, and why that pivotal early trial has led to a larger trial in the phase III setting.

Dr. Albiges:
It's actually building on two previous developments from Drs. Motzer and Choueiri based on the survival benefits obtained from single-agent activities from both potent VEGF-TKI and immune checkpoint inhibitor and also as Dr. Choueiri highlighted that there is an immunological standpoint as well. Based on such rationale and also because of other combinations that were similarly developed, we launched an open-label, multicenter study of tivozanib in combination with nivolumab in patients with metastatic RCC (NCT03136627). In this study, patients initially received tivozanib 1.0 mg once daily for 21 days of treatment followed by 7 days off treatment. A standard dose of Nivolumab (240 mg) was administered as an infusion every 2 weeks starting on day 1 of cycle 1, and again on day 15. Overall, 25 patients have been treated as part of this phase I. patients with advanced RCC who received tivozanib plus nivolumab demonstrated a tolerable safety profile with minimal off-target effects when used as first-line and beyond treatment in patients with advanced RCC.

We assessed that 80% of our patients had some degree of remission, and the disease control rate was 96%. So overall, we were able to achieve a response rate of 56% in patients who received the tivozanib. Ultimately, the early signs of progression-free survival were very enthusiastic with a median PFS of 18.9 months. So clearly, we observed a great signal of activity. What I can tell you from a clinical standpoint is that the tolerability was great, thanks to the potency of tivozanib. The most frequent treatment-related toxicity was hypertension which was consistent with the toxicity profiles of both drugs. Therefore it does require close monitoring. However, as medical oncologists in the field of RCC had been exposed to hypertension for many years, hypertension was manageable from a clinical standpoint. The adverse events are comparable with other VEGFR TKI-PD-(L) and generally tolerable in a combination setting.

Dr. Figlin:
Albiges, Do you have any follow-up data in terms of durable responses in those 25 patients that you've observed in your clinic?

Dr. Albiges:
The answer is yes. I could not speak for the entire study as it was a multi-centric study in France. However, I can tell you that I had seen a very long, sustained response in my hospital. In some patients, we were able to discuss treatment discontinuation. So clearly what we're seeing is a great disease control during the follow-up.

Dr. Figlin:
Before we turn to Toni and talk about the phase III trial. I think it's important that we circle back and talk about the quality of life benefits of tivozanib. Dr. Motzer, I know that you've reported on Quality of life data and the safety profile of tivozanib in the clinical setting. Please summarize some key objective data that you've reported on.

Dr. Motzer:
We performed quality of life analysis from the TiVo-1 trial, also accounting for efficacy and adverse event profile. In that direct comparison to sorafenib, tivozanib was associated with a significant improvement in PFS and a favorable quality of life profile when administered to patients with metastatic RCC. In fact the tolerability and safety profile is one of the greatest attributes of tivozanib. Tivozanib resulted in lower rates of certain side effects that are associated with a decline in quality of life, including hand-foot skin reaction, rash and diarrhea. There were fewer dose reductions and interruptions for tivozanib compared with sorafenib. On the other hand, tivozanib was characterized by higher rates of hypertension and dysphonia, but it was generally well tolerated.

Dr. Figlin:
Dr. Choueiri, let me get back to you. As the first author of TiNivo-2 study, please help us understand where you think that trial fits, what the goals and objectives are, and how that might offer our patients some continued immune modulation with positive outcomes in patients with mRCC?

Dr. Choueiri:
First, we were essentially looking into the unmet need in advanced RCC. One of the unmet needs is a treatment for those patients whose tumors progressed after prior immune checkpoint inhibitors That's why we launched TiNivo-2 study in this population based on the quite encouraging data from a phase 1/2b study that Dr. Albiges just mentioned. In the TiNivo-2 trial, patients will be randomized to tivozanib monotherapy as the standard and the experimental arm have the combination of tivozanib plus Nivolumab. Patients should have progressed through at least one prior line of therapy including an immune checkpoint inhibitor. Subjects will be stratified by IMDC risk category and whether ICI was received in most recent line of treatment or not. Subjects will receive tivozanib (1.34 mg orally once daily) for 21 consecutive days followed by 7 days off. In the combination arm, subjects will also receive Nivolumab 480 mg intravenously every 4 weeks. The dose of tivozanib will be comparatively lower when delivered in combination with nivolumab as compared to tivozanib monotherapy. Ultimately, our goal here is to find a niche of completely unmet need and see if adding nivolumab on a backbone of VEGF-TKI of tivozanib would result in improved outcomes in terms of progression-free survival (PFS) in patients with renal cell carcinoma who have progressed

following 1-2 lines of therapy including an immune checkpoint inhibitor.

Dr. Figlin:
We all recognize that you are to be congratulated along with Drs. Motzer, Dr. Albiges, and other colleagues who are part of that study for addressing the critical unmet need. So let me just go around the table and ask each of you. We have accomplished so much in kidney cancer during the last two decades, through the era of the tyrosine kinase inhibitors and currently through the era of the immune checkpoint inhibitors and their combination strategies. I know that many of us are looking at triplets that we would never have thought about it in kidney cancer a couple of decades ago. Here we're trying to combine it with agents such as v inhibitors for example. Where do you see us going from here Dr. Motzer? So how do you see the field evolving?

Dr. Motzer:
The identification of new agents with a novel mechanism of action is critical. One new class of drugs which Dr. Choueiri has been pivotal in terms of bringing forward is the hypoxia-inducible factor 2α (HIF-2α) inhibitors. As a class, these drugs are active and seem to be very well-tolerated and combine well with other agents. In one study with HIF-2α belzutifan plus cabozantinib, the preliminary results showed good antitumor activity and tolerability for the combination. Given the positive outcomes from tivozanib combination studies, as a next step, I would like to see one of the HIF-2α inhibitors added to the tivozanib and nivolumab as first-line therapy. I am even an advocate for a study of tivozanib plus nivolumab combination in the adjuvant setting. I recognize that TKIs as single-agent certainly did not pan out in the adjuvant setting because of poor tolerability. However, tivozanib may have a better chance, particularly in combination with a checkpoint inhibitor in the adjuvant setting. Lastly, we need a better understanding of underlying biology to see if we can identify patient subpopulations that will respond best to such combination settings.

Dr. Figlin:
Dr. Choueiri, without putting you on the spot, but putting you on the spot. You have articulated nicely an increasing role of IO-TKI as a second-line after prior IO therapy in the high-risk resected population. How do you think the field is going to evolve if there is an increased uptake of immune checkpoint inhibition in the high-risk resected population?

Dr. Choueiri:
Absolutely, this is why we need studies in the post-IO setting. In TiNivo-2 which we are talking about, we may include a subgroup to assess outcomes in the prior adjuvant IO setting. I tend to believe it will not be different if patients progressed within a year after therapy. But it will be different biology if progression happens after a year. If this strategy is successful, then we have to look at that whether we have a drug approved with the same construct as the design of TiNivo-2, but strictly in the adjuvant setting. And that's something we have been working on because what if the biology is different.

Dr. Figlin:
Absolutely. Dr. Albiges, one of the challenges is we still have to navigate through patients with brain metastases and bone metastases. Any insights on whether there are now evolving populations of patients that we need to address because of unmet needs?

Dr. Albiges:
I agree with you that there is an unmet need in those patients with brain and/or bone metastasis and obviously, we need to think about those patients that are difficult to treat. Now, we know the role of the multimodal approach combining stereotactic radiation therapy on top of our systemic treatment and maybe define the optimal systemic treatment.We may likely want to combine VEGF-TKI with immune checkpoint inhibitors so that we would be able to induce more tumor shrinkage in that subset of the population. In addition to a subset of the patient with metastasis, there are also other tumor types such as non-clear cell renal cell carcinoma and other different tumor entities. For those, we clearly need to have more clinical trials being developed and test some of those combinations in such patient populations that usually have very aggressive features. So beyond clear cell RCC, there are challenges from different pathological, and specific tumors that need to be addressed. I feel that we have made a long way but we still have a lot to go and especially with how to sequence those different agents and work on the rescue strategy.

Dr. Figlin:
Let me just summarize by saying that our distinguished colleagues have shared their insights regarding the survival benefits, tolerance profile, quality of life, and the rationale for combining tivozanib with immunotherapy along with some key perspectives about prospective pivotal trials for both adjuvant as well as systemic therapeutic settings. I would like to thank Drs. Motzer, Choueiri and Albiges for joining with us for this stimulating roundtable discussion.

CONCLUDING REMARKS

An unmet need remains for developing a novel therapeutic combination that produces effective, durable responses without adding substantial toxicity in patients with relapsed or refractory advanced RCC. Anti-angiogenic therapy in combination with ICIs in the first-line setting has demonstrated not only favorable efficacy, but also improved tolerability in patients with advanced RCC. For example, the tivozanib plus tivozanib combination demonstrated a promising safety and efficacy profile with minimal off-target effects as first-line and beyond treatment in patients with advanced RCC. In this roundtable discussion, renowned

experts convened to examine the immunomodulatory potential of tivozanib and also its synergistic potential when combined with nivolumab as a treatment option in patients with treatment-naïve or previously treated metastatic RCC. Also, panelists shared their perspectives about the recent TIVO-3 and ongoing TiNivo-2 trial with regards to safety and efficacy.

CONFLICT OF INTERESTS

RJM reports consulting fees from Aveo, Calithera, Eisai, Eli Lilly, EMD Serono, Genentech, Merck, Novartis AG, Pfizer, and Roche, and contracted research to employer MSKCC for Bristol Myers Squibb, Eisai, Exelixis, Genentech, Merck, Pfizer, and Roche. **TKC** reports grants received from Pfizer during the conduct of the study; personal fees received from Agensys, Alexion, Alligent, American Society of Clinical Oncology, Analysis Group, AstraZeneca, Bayer, Bristol Myers Squibb, Celldex, Cerulean, Clinical Care Options, Corvus, Dana-Farber Cancer Institute, EMD Serono, Inc., Eisai, Exelixis, Foundation Medicine, Genentech/Roche, GSK, Harborside Press, Heron, Ipsen, Kidney Cancer Association, Kidney Cancer Journal, Lpath, Lancet Oncology, Lilly, Merck & Co., Michael J. Hennessy Associates, National Comprehensive Cancer Network, Navinata Health, New England Journal of Medicine, Novartis, Peloton Therapeutics, Pfizer, PlatformQ Health, Prometheus Laboratories, Sanofi, Seattle Genetics/Astellas, and UpToDate outside the conduct of the study; grants received from AstraZeneca, Bayer, Bristol Myers Squibb, Calithera, Cerulean, Corvus, Eisai, Exelixis, Foundation Medicine, Genentech/Roche, GSK, Ipsen, Merck & Co., Novartis, Peloton Therapeutics, Pfizer, Prometheus Laboratories, Takeda, and TRACON outside the conduct of the study; and medical writing and editorial assistance provided by ClinicalThinking, Envision Pharma Group, Fishawack Group of Companies, Health Interactions, and Parexel, funded by pharmaceutical companies. **LA** reports consulting fees compensated to their institution from Amgen, Astellas, AstraZeneca, Bristol Myers Squibb, Corvus Pharmaceuticals, Exelixis, Ipsen, Merck KGaA, Merck & Co., Novartis, Peloton Therapeutics, Roche, and Pfizer outside the submitted work. HM has declared no conflicts of interest. **RAF:** No relevant conflicts to report for this roundtable.

CONTRIBUTIONS

The roundtable panelists (authors) were invited to participate in this discussion by the journal. All authors listed in the manuscript contributed significantly to KCJ roundtable. All authors have read and approved the final version. The final content and article is the sole work of the authors. The figures were obtained from AVEO ONCOLOGY database.

ACKNOWLEDGMENTS

This educational roundtable program is supported by AVEO Oncology. www.aveooncology.com/

ONLINE CONTENT

Full online contents with additional information including conflict of interests will be available at https://kidney-cancer-journal.com/KCJ20n2-rt.php

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Comparison of Papillary Renal Cell Carcinoma Type 1 and Type 2: A Secondary Data Analysis

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doi.org/10.52733/KCJ20n2-a1

ABSTRACT

OBJECTIVE: The overall aim of this study was to determine if there are significant differences between type 1 and type 2 papillary renal cell carcinoma (PRCC) that can be utilized by healthcare providers.

MATERIALS AND METHODS: This study performed a secondary data analysis using The Cancer Genome Atlas Kidney Renal Papillary Cell Carcinoma data to determine if there are clinically significant differences in survival, demographics (age, ethnicity, gender, and race), increased risk factors (body mass index [BMI] smoking history, neoplasm history, and malignancy history) and preferential genetic pathways between type 1 and type 2 PRCC tumors.

RESULTS: Descriptive statistics were performed on a total of 156 cases to determine demographics, increased risk factors and genetic pathways. The hazard ratio, with type 1 as the reference group, was 2.459 (with 95% CI 0.9723, 6.217). Of the risk factor variables investigated, we found that smoking appeared to be associated with an increased risk of type 2 (OR 3.241 95% CI 1.066, 9.853). In the pathways analysis, we observed one significant difference between MAPK and PI3K, with the latter being significantly associated with type 2 (OR 4.968 95% CI 1.759, 14.031 Table 6).

CONCLUSION: This study provides the framework for future more comprehensive research on the demographic, increased risk factor and genetic pathway differences between PRCC type 1 and type 2 tumors. Future investigations should include a more complete dataset with additional potential risk factors.

KEYWORDS: Kidney Cancer, The Cancer Genome Atlas, Cancer Epidemiology, Risk Factors, Genetic Pathways

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INTRODUCTION

Renal cell carcinoma (RCC) is the 14th most common cancer worldwide and was the cause of 175,098 deaths in 2018.[1] RCC consists of numerous subtypes including clear cell renal carcinoma, papillary renal cell carcinoma and most recently clear cell papillary renal cell carcinoma. Currently, papillary renal cell carcinoma (PRCC) is the second most common type of RCC, after clear cell renal cell carcinoma, comprising approximately 15-20% of all RCC cases.[2,3]

PRCC is considered a heterogeneous disease consisting of two subtypes; type 1 and type 2. These subtypes are primarily distinguished by their histology and vary in prognosis, treatment and patient outcomes. Type 1 is histologically characterized by a single layer of cells with sparse basophilic cytoplasm and small oval shaped nuclei that are present in either the renal tubules or renal papillae. This type can be associated with both hereditary and sporadic PRCC.[4,5] Conversely, type 2 tumors are histologically characterized by large pseudostratified cells with eosinophilic cytoplasm with large spherically shaped nuclei that are present in the renal papillae. These tumors can be associated with hereditary PRCC but are more often associated with the sporadic form of PRCC.[6] Furthermore, research has shown that patients with PRCC

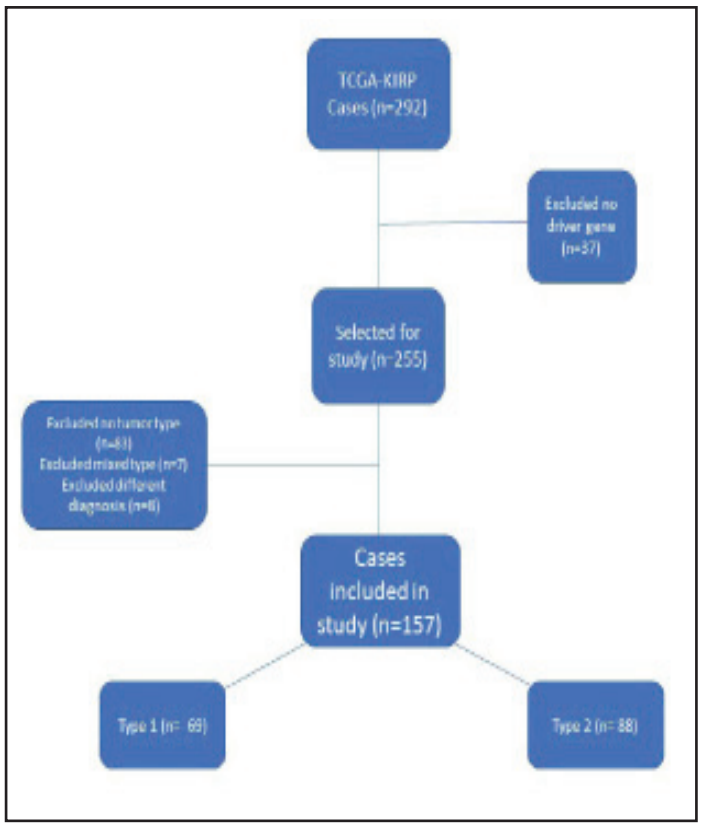

Figure 1 | A schematic consort diagram describing TCGA-KIRP data extraction.

type 2 tumors are correlated with a higher rate of metastasis and have a lower overall survival rate compared with patients with type 1 tumors.[7]

The overall aim of this study was to determine if there are significant differences between type 1 and type 2 PRCC that can be utilized by healthcare providers. Specifically, this study sought to determine if there are clinically significant differences in survival, demographics (age, ethnicity, gender, and race), increased risk factors (body mass index [BMI] smoking history, neoplasm history, and malignancy history) and preferential genetic pathways between type 1 and type 2 PRCC tumors.

The epidemiology and risk factors for PRCC are largely based on the broader RCC. However, there are certain conditions that may increase an individual's risk of developing PRCC. For instance, individuals with Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) have a greater chance of developing PRCC type 2. There is some evidence that suggests individuals with renal insufficiencies have a greater risk of developing PRCC.[8,9] Ethnicity is also linked to increased risk of developing RCC with African Americans having the highest incidence of RCCs. Sankin *et al.* (2011) found that African Americans had a four times greater incidence of PRCC as compared to non-African Americans.[10,11]

Research has demonstrated that malignant tumors utilize a wide variety of genetic alterations to modify the normal cell cycle in order to be able to divide and grow without restrictions. These modifications are accomplished by altering cell signaling pathways to promote cell growth, angiogenesis and obstruct apoptosis.[12] Considering the heterogeneous nature of PRCC, there are numerous genetic alterations that occur within both type 1 and type 2 PRCC. Approximately 20% of hereditary type 1 tumors have been associated with variations in the protooncogene mesenchymal epithelial transition (MET). However, sporadic type 1 tumors have numerous genes associations as well as chromosomal abnormalities. Type 2 tumors have also been correlated with a large number of genetic and chromosomal alterations.[4,13] Similarly, research has shown that renal cancers in general utilize several signaling pathways. The alteration of MET has been shown to activate the MAPK and PI3K pathways as well as other proteins involved with tumor growth.[14] Gaps in research still exist for determining if there are pathway preferences between type 1 and type 2 PRCC tumors.

Most research on PRCC has either been umbrellaed under RCC or focused on developing a basic understanding of the disease with minimal attention to the differences between type 1 and type 2 PRCC tumors. Recently, Wong et al.

	TYPE 1	TYPE 2
Gender (n=158)		
Male	50	61
Female	19	27
Race (n=149)		
White	46	66
Black or African American	18	15
Other	0	4
Mean Age (n= 156)	60 (Range 28 to 82)	64.5 (Range 28-88)
Ethnicity (n= 144)		
Hispanic or Latino	2	5
Not Hispanic or Latino	62	75

Table 1 | Descriptive Statistics for Demographic Factors

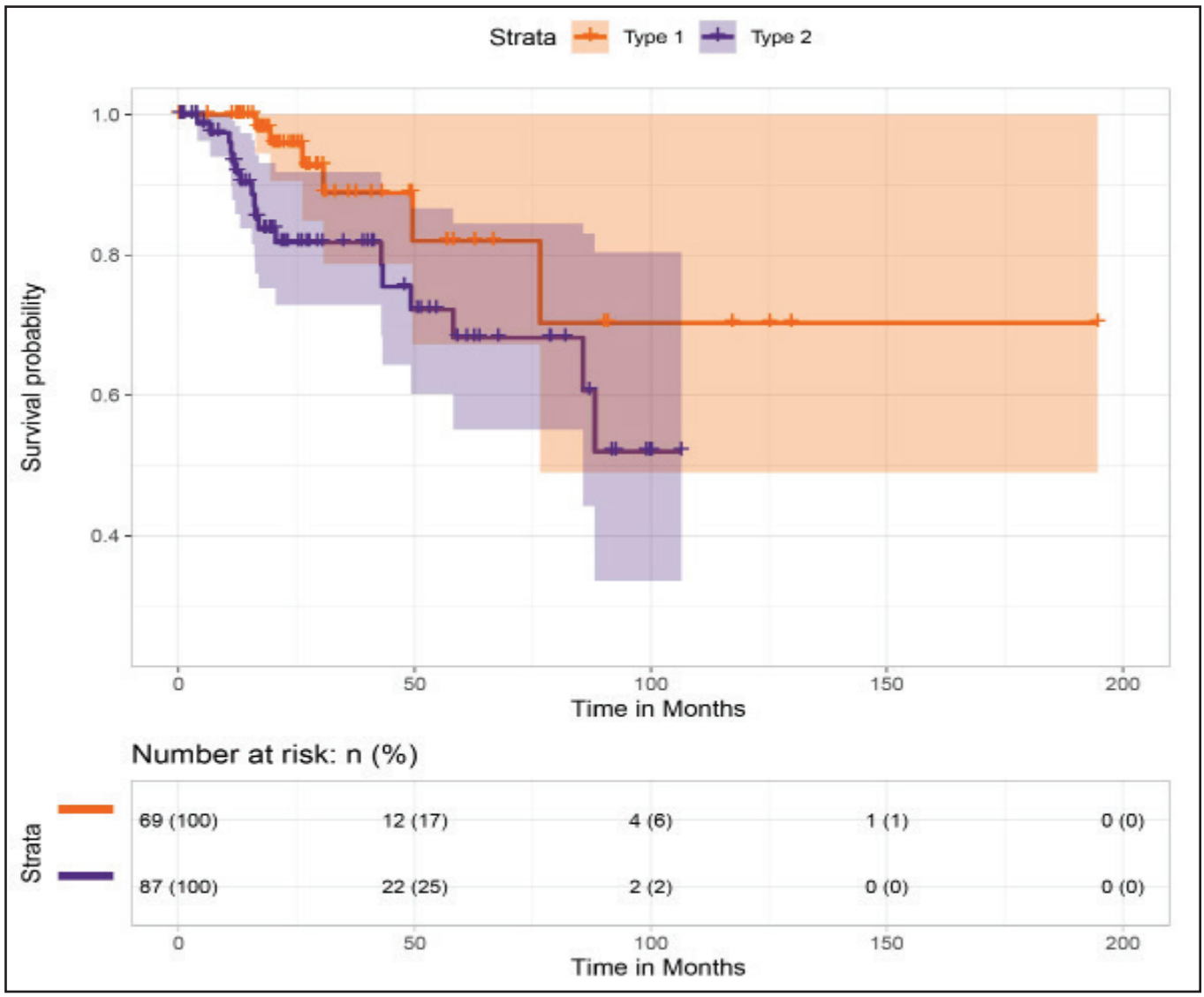

Figure 2 | Kaplan Meier curves for Type 1 and 2 PRCC survival

(2019) investigated survival rates associated with type 1 and type 2 PRCC. The researchers found that type 2 PRCC was associated with a higher all-cause mortality rate as well as with worse reoccurrence rates as compared to type 1.7 As part of our research, we analyzed the all-cause mortality for discrepancies in survival rates between type 1 and 2 PRCC. Next, we selected a demographic (baseline) model to identify a set of demographic variables that are likely to be associated with the different types of PRCC. Lastly, we investigated environmental and gene pathway associations with prevalence of the two types of PRCC.

	TYPE 1	TYPE 2
Smoking History Category (n=146)		
1	**30**	**36**
2	**10**	**11**
3	**10**	**14**
4/5	**7**	**20**
Prior Neoplasm (n= 95)		
Yes	**2**	**9**
No	**36**	**48**
Prior Malignancy (n= 156)		
Yes	**16**	**14**
No	**55**	**77**
Mean BMI (n=123)	**35.88**	**27.72**

Table 2 | Descriptive Statistics for Increased Risk Factors

METHODS

Sample

This study was a secondary data analysis using data from The Cancer Genome Atlas Kidney Renal Papillary Cell Carcinoma (TCGA-KIRP). A review of the literature was conducted to determine the appropriate inclusion criteria which included: 1) PRCC tumors, 2) distinguishes between type 1 and type 2, 3) demographics data, gender, race, age and ethnicity, 4) clinical data, prognosis, treatment,

	TYPE 1	TYPE 2
Pathway (n=157)		
MAPK	31	23
HIPPO	2	3
PI3K	8	27
P53	13	16
WNT	7	6
NOTCH	5	9
TGF	2	3
TNF	1	1
Pathway (n=157)		
MAPK	31	23
HIPPO	2	3

Table 3 | Descriptive Statistics for Pathways

preexisting conditions, 5) increased risk factors, smoking history, BMI, prior neoplasms and prior malignancies, and 6) genetic analysis of the tumors. A further review of the literature revealed that TCGA-KIRP is the most current and appropriate dataset to use for this secondary data analysis. The *cBioPortal* for cancer genomics (*cBioPortal*) was used in conjunction to analyze the TCGA-KIRP data.

TCGA-Kidney Renal Papillary Cell Carcinoma (KIRP) data was collected from 41 institutions from 1996 to 2013. The database adheres to a strict inclusion policy; TCGA tumors are untreated samples that were snap frozen. Each tumor sample has to have a matched normal sample from the same patient which generally comes in the form of the patient's blood. The tumors and subsequent molecular data are cross referenced by Biospecimen Core Resource (BCR) to ensure validity. Furthermore, the BCR analyzes each sample for pathological quality control. This maintains that TCGA has a high-quality tumor samples as well as consistent molecular data.[15] Additionally, each sample was reviewed by a panel of six experienced pathologist to in order to be classified into type 1, type 2 or unclassified PRCC. Moreover, any samples that were pre-classified were reassessed by the same panel to ensure proper classification.[15]

	OR	95% CI for OR	
Age at Diagnosis	1.045	1.014	1.078
White	Reference	-	-
Black or African American	0.677	0.301	1.525
Other	5.601	0.54	58.089

Table 4. Demographics Model

The *cBioPortal* is a resource that incorporates data from TCGA as well as actively curates data sets from the literature into a research-friendly source. The cBioPortal separates PRCC genetic variations into categories such as copy number variations and mutations. Furthermore, the cBioPortal predetermines and denotes driver genes through specific algorithms.16 The cBioPortal allows the user to analyze specific genes, as opposed to TCGA, which only allows users to view the dataset as a whole and does not denote potential driver genes.16 Even though the cBioPortal contains the same data as TCGA, the cBioPortal was used to aid in the analysis of TCGA data.

Data Extraction

Both databases showed the same cases which totaled 292. The first step in evaluating the dataset was determining the demographic and clinical data. TCGA contained a manifest of demographic, clinical, and environmental data. This manifest was downloaded and converted into an Excel file. Once retrieved, the dataset was reviewed and irrelevant data was removed; such data included serum levels, blood cell counts, IDH level, tumor laterality, lymph node data, tumor dimensions, treatment data, tissue collection data, sample weights, calcium levels, and vial numbers. Data categories that were redundant were also eliminated.

Next, the *cBioPortal* resource was used to determine pertinent genetic information related to PRCC. The first step was to download the copy number alteration (CNA) data from this resource. A total of 10,837 genes exhibited a copy number variation. Genes that were not considered to be driver genes according to the GISTIC algorithm were eliminated from the dataset. This elimination left a total of 426 driver genes with CNA. The driver genes were then put into the BCG query to determine how many cases included one or more of the driver CNA genes. A total of 193 of the cases (66%) contained one of the driver CNA genes. In order to increase the sample population, mutated driver genes (as determined by *Mutsig*) were added to the query bringing the total of genes to 517 and 255 (87%) cases. Thirty-six cases did not have an association with one of the 517 driver genes and were eliminated. The driver genes were divided into categories based on their cytoband for future reference.

The remaining 255 cases were reviewed to determine whether or not they were designated type 1 or type 2 PRCC. Out of the 255 cases, 115 cases had no designation in the type category. The pathology report of each of the 115 cases was reviewed to see if a pathologist had designated the tumor as either type 1 or type 2. Seven more cases were determined to be a mix of type 1 and type 2 histology and were also removed. Additionally, eight more cases were either mislabeled as PRCC or determined to favor a different cancer type per the reviewing pathologist. These eight cases did not include a TCGA addendum that disputed the cancer

Variable	Level	OR	95% CI for OR	
BMI (n=121)		0.989	0.963	1.015
Smoking (n=131)	Smoke 1	Reference	-	-
	Smoke 2	1.141	0.381	3.415
	Smoke 3	0.916	0.322	2.611
	Smoke 4 or 5	3.241	1.066	9.853
Malignancy (n=150)	No	Reference	-	-
	Yes	0.614	0.265	1.421
Neoplasm (n=91*)	No	Reference	-	-
	Yes	3.736	0.698	19.999

Table 5 | Increased Risk Factor Model

typing and therefore were removed from this dataset. (See Figure 1). At the conclusion of this analysis, 88 cases were designated as type 2, 69 cases were type 1, and 83 cases were undesignated. The 83 undesignated cases were subsequently removed from the dataset in order to preserve the validity and continuity of the data.

ANALYSIS

Descriptive Statistics and Survival Analysis

Descriptive statistics were utilized to determine demographics, increased risk factors and genetic pathways. The survival analysis was conducted for the TCGA-KIRP analytic file using R version 3.6.2. , the survival(v3.2-13) and the survminer (v0.4.9) packages.[21-23] A cox-proportional hazard model was fitted on the overall survival times of 156 patients (1 had a survival time of 0 indicating that they were diagnosed post-mortem or there was an error in entry) to determine if there were evidence that survival rates differ between type 1 and 2 PRCC.

Logistic Regression

For the next three phases of our statistical analysis, SASTM software, Version 9.4 of the SAS system for Windows was utilized. The demographic model selection included age at diagnosis, race, ethnicity and sex, as candidate descriptors relating to PRCC tumor type. The demographic model selection utilized forward selection with a relaxed p value (<0.1) to determine the appropriate variables to be included in the model. The selected demographic model included Age at Diagnosis (OR 1.045 95% CI 1.014, 1.078, Table 5) as well as 3 Category Race (White, Black or African American and Other) was used as the baseline model for the increased risk factor variables. Each increased risk factor variable; BMI, smoking status, prior neoplasms and prior malignancies, were added univariately to the demographic model controlling for age at diagnosis and race to identify associations.

RESULTS

Descriptive Statistics

For the 69 patients designated as type 1 tumors, 50 were male and 19 were female with a median age of 60 (range 28 to 82). In terms of race, 46 were white, 18 were black or African American, and 5 were unspecified. Ethnicity was reported as 62 non-Hispanic or Latino, 2 were Hispanic or Latino and 5 were unspecified. Table 1.

For the 88 patients designated as type 2 tumors, 61 were male and 27 were female with a median age of 65 (range 28 to 88). In terms of race, 66 were white, 15 were black or African American, and 7 were unspecified. Ethnicity was reported as 75 were non-Hispanic or Latino, 5 were Hispanic or Latino and 8 were unspecified (Table 1). Due to the sparsity in the demographic factor levels, the following variable levels were collapsed; Asian and American Indian. Table 1.

Smoking categories were defined as life-long non-smoker (1), current smoker (2), reformed smoker >15years (3), reformed smoker <15 years (4) and reformed smoker unknown length (5). Table 2 describes the smoking status of type 1 and type 2 PRCC tumors. Smoking categories 4 and 5 were collapsed together due to data sparsity in the increased risk factor variables.

The existence of prior neoplasm was defined in the database as 'yes' or 'no'. Two patients with type 1 PRCC had known prior neoplasm were as 9 patients with Type 2 reported prior neoplasm. Similarly, prior malignancies were also defined as 'yes' or 'no'. Sixteen patients with type 1 reported prior malignancies and 14 patients with type 2 reported prior malignancies (Figure 2). The most common pathway in type 1 was the MAPK pathway and in type 2 was the PI3K pathway Table 3).

Overall Survival

The hazard ratio, with type 1 as the reference group, was 2.459 (with 95% CI 0.9723, 6.217). This result did not provide sufficient evidence that the two types differ significantly in all-cause survival (α=.05). However, given the relatively small sample size and high rate of censoring, it is not surprising that our results do not provide as striking a contrast between the two as supported by Wong et al. (2019). (Censoring rates were 91.3% for Type 1 and 79.5% for type 2, respectively, which consequently prevents us from being able to report median survival without making parametric

assumptions). Survival rates are illustrated via the Kaplan Meier curve included in Figure 2.

Logistic Regression

Odd ratios (OR) and confidence intervals (CI) are reported in Tables 5 and 6 for each variable in the increased risk factor and pathway analyses. Of the risk factor variables investigated, we found that smoking appeared to be associated with an increased risk of type 2. Specifically, being a reformed smoker of unknown length or less than 15 years, was positively associated with type 2 PRCC compared to life-long non-smokers (OR 3.241 95% CI 1.066, 9.853 Table 5). None of the other increased risk factors had significant association with tumor type. In the pathways analysis, we observed one significant difference between MAPK and PI3K, with the latter being significantly associated with type 2 (OR 4.968 95% CI 1.759, 14.031 Table 6). All pairwise comparisons were made between pathways and the MAPK/PI3K comparison was the only one found to be significant. In all analyses, type 1 was used as the reference level for each model and the OR corresponds to odds of type 2 Vs 1.

DISCUSSION

It is important to note that current findings from the International Society of Urological Pathology (ISUP) suggests that the PRCC type 1 subtype is the most uniform morphologically, immunohistochemically, and in terms of molecular features. ISUP also suggests that PRCC type 2 is not a distinct neoplasm but rather a combination of multiple distinct neoplasms. As such, type 2 PRCC is a distinctly different disease as compared to type 1 and contains multiple clinically and molecularly heterogeneous subtypes.24 Additionally, the use of type 1 and type 2 terminology is evolving as PRCC becomes better understood.

To the best of our knowledge, our study is the first to collectively examine the demographic, increased risk and pathway associations between type 1 and type 2 PRCC tumors. Furthermore, while our findings with respect to the survival analysis were not significant, it does provide marginal evidence to confirm the findings of Wong et al. (2019) in that survival rates for type 2 are shorter than those diagnosed with type 1. 7 While our analysis was limited by small sample size, certain variables were linked to increased probability of type 2 PRCC tumors. The age at diagnosis variable was considered significant with an older adult having increased risk of type 2. Our result is consistent with Wong et al. (2019) who reported a higher age at time of nephrectomy for patients with type 2 tumors as compared with type 1 tumors.[7]

Smoking was the only increased risk factor that was significant in determining the probability of having the type 2 tumor type versus type 1. Individuals who were reformed smokers of less than 15 years (as well as reformed smokers of unknown length) had a greater risk of developing a type 2 tumors as compared to lifelong non-smokers. Furthermore, type 2 PRCC tumors tend to be sporadic as compared to type 1, meaning that increased risk factors may have a greater impact on the development of type 2 tumors.6 However, further research needs to be conducted on the effects of smoking on the growth of specific tumor subtypes.

Although smoking was the only significant increased risk factor variable, further research should be conducted on a larger sample size with less missingness to better compare increased risk factors variables between tumor types. Specific focus should be put on prior neoplasms since they have been associated with a number of renal cell cancer syndromes that are considered to increase the risk of PRCC. For example, the most common renal cell cancer syndrome, von Hippel-Lindau syndrome, is characterized by benign tumor growths and has a 40% chance of developing renal cancer, including type 2 PRCC. Additionally, hereditary leiomyomatosis and renal cell cancer (HLRCC), is characterized by harmatomas with an increased risk of developing type 2 PRCC. 8,17 Considering the number of renal cell cancer syndromes that are both associated with an increased PRCC risk and are characterized by neoplasms; further research should be conducted to determine if prior neoplasms is a determining factor in PRCC subtype.

The findings in this study have potential implications for future treatment options. The higher rate of MAPK pathway in type 1 supports ongoing studies of the role of the MET gene in clinical trials. The MET gene codes for c-Met, a tyrosine kinase protein that is involved with the MAPK pathway. When c-Met binds to its ligand, HGF, a downstream cascade is started that leads to the activation of the MAPK pathway which promotes cell migration and tumor proliferation. 18 Seeing as 20% of type 1 tumors contain a MET mutation, it is not surprising that MAPK is the preferred pathway of type 1 tumors. Furthermore, the PI3K pathway was found to be significant in the probability of having a type 2 tumor as well as being the preferred pathway of type 2. The findings in this study support the ongoing efforts in determine drug treatment therapies that target the PI3K pathway. PI3K is comprised of lipid kinases that once activated, begin a downstream cascade that leads to cell growth and survival. PI3K pathway has a strong association with the inactivation of PTEN, which has been correlated poor patient outcomes.[19,20]

CONCLUSION

Despite the imperfect database this study found that there is a trend in the data that is clinically significant.

Furthermore, this study provides the framework for future more comprehensive research on the demographic, increased risk factor and genetic pathway differences between PRCC type 1 and type 2 tumors. Future investigations should include a more complete dataset with additional potential risk factors. Given the differences in survival rates, such investigations will provide clinicians a better understanding of tumor types allowing for quicker more accurate diagnosis and evidence-based treatment plans.

CONFLICT OF INTEREST

All authors listed on this study have no conflicts of interest that may be relevant to the contents of this manuscript.

FUNDING

None

ACKNOWLEDGMENTS

None

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KCJ REVIEW ARTICLE

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Engineered T-Cell Therapy: The Next Direction for RCC Immuno-oncology?

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doi.org/10.52733/KCJ20n2-r1

ABSTRACT

Synthetic biology in the form of engineered antigen specific T-cells for cancer immunotherapy has demonstrated its potential to revolutionize cancer treatment. However, whereas engineered T-cell therapy is already well established in the treatment of hematologic malignancies, it remains only in the pre-clinical and early clinical development stages in solid organ cancers including RCC. In this review, we consider three T-cell target antigens that have already reached the clinic for kidney cancer, and discuss future novel directions including harnessing the immune system against patient specific neoantigens.

KEYWORDS: T Cell Therapy, CAR T-cells, neoantigens, tumor antigen targets, renal cell carcinoma, kidney cancer.

INTRODUCTION

Synthetic biology in the form of engineered antigen specific T-cells for cancer immunotherapy holds promising potential to revolutionize the treatment of advanced solid malignancies. Chimeric Antigen Receptor T-cells, or CAR T-cells, are engineered to express chimeric antigen receptors to target tumor-associated antigens independently of the major histocompatibility complex (MHC).[1] Hence, they mimic both antibody-based antigen recognition with T-cell receptor function to enable antitumor activity by lysis of the target cells. The genetically engineered CAR fusion protein is transduced ex vivo by means of retroviral or lentiviral vectors into autologous T-cells collected by leukapheresis. Subsequently, CAR T-cells are re-infused into patients following a lymphodepleting conditioning regimen to enable further T-cell expansion and personalized targeted therapy.[2]

The primary advantage of CARs is their ability to recognize tumors based on binding with a single chain variable fragment (scFv) derived from a tumor-specific antibody, and therefore to target antigens expressed on the cell surface without MHC restriction. Autologous CAR T-cell therapy eliminates the potential risk of allogeneic reaction at the expense of a longer manufacturing time due to leukapheresis requirement for every patient, leading to treatment delays and higher manufacturing costs.[3] The concept of adoptive transfer of allogeneic CAR T-cells using "off the shelf" as opposed to "made to order," personalized T-cells aims to address these limitations. The use of allogeneic CAR T-cells from healthy donors has been explored with distinct advantages over autologous therapies, including the potential for standardization of CAR T-cell therapy, increased availability of therapy, ease of re-dosing or combination of CAR T-cells against multiple targets, decreased time and potentially decreased cost.3 However, one prominent drawback of allogeneic T-cells is the risk of a life-threatening graft vs host disease (GVHD) necessitating further gene editing techniques to avoid the native TCRs of the donor cells recognizing and attacking recipient host tissues as foreign. The second drawback of allogeneic T-cells includes risk of rapid elimination by the host immune system, leading to treatment failure.[3]

T cell receptor-engineered T-cells (TCR-T) represent an alternative way to utilize autologous T lymphocytes to target tumor cells. Mechanistically they differ from CAR-T as they rely on antigen specificity derived from recombinant transduced antigen-specific T-cell receptors rather the antibody binding and recognition, which therefore requires MHC co-presentation of the tumor antigens to initiate a further intracellular immune signaling cascade.[4] This is potentially advantageous as targets are not limited to cell surface proteins but can be expanded to include intracellular antigen fragments that are presented by MHC proteins. In order to design an effective TCR-T, unique polypeptides that are presented by tumors cells must be identified and then a TCR with a higher affinity to that specific antigen can be genetically engineered.[5] If an appropriate target is selected, TCR-T can be a highly effective therapy because only a small amount of tumor antigen is needed to stimulate a robust response as TCR-T rely on native T-cell signaling transduction mechanisms.[6] However, similarly to CAR-T, polypeptides that are also cross-expressed in normal tissue must be screened out to limit on target, off tumor toxicity resulting from cytotoxicity of normal cells sharing expression of the target antigen. For example, TCR-T cells targeting MART-1 and MAGE-A3 led

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to lethal cardiotoxicity in patients with metastatic melanoma in clinical studies, as both target antigens are highly expressed in cardiac tissue.[7,8] Both TCR-T and CAR-T have demonstrated striking advancements in the treatment of hematologic malignancies resulting in new standard of care paradigms and the potential for long-term durable cures of refractory liquid tumors, but currently with only limited efficacy in the treatment of solid tumors.[2,4]

Background

CAR T-cells have evolved over three generations of CAR constructs to improve the antitumor cytotoxicity and CAR-T cell persistence through the addition of costimulatory domains.[1,2,9] The first-generation CAR construct includes a single-chain variable fragment (scFv) antigen-recognition domain, a transmembrane domain, and an intracellular T-cell activation domain derived from CD3 zeta chain. The 2nd generation CAR that is utilized by commercial CAR T-cell products in hematologic malignancies included the addition of a costimulatory domain (either CD28 or 4-1BB). Finally, the 3rd generation CAR incorporates two distinct costimulatory domains (e.g., both CD28 and 4-1BB).[2,9] The choice of costimulatory domain may affect T-cell proliferation and persistence.[1,10]

The earliest established clinical use of CAR T-cells lies in Hematologic malignancies including leukemias and lymphomas.[2] The Landmark Phase II ELIANA trial of anti-CD19 CAR T-cell therapy Tisagenlecleucel-T demonstrated 81% overall remission within 3 months11 and led to the FDA approval of tisagenlecleucel-T in August 2017 for Acute Lymphoblastic Leukemia (ALL) in pediatrics and adults up to age 25.11 The first CAR T-cell therapy for lymphoma was FDA approved after the ZUMA-1 trial of Axicabtagene ciloleucel that demonstrated efficacy of autologous anti-CD19 CAR T-cell therapy in patients with relapsed, refractory large B-cell lymphoma after failure of conventional therapy.[12] In total, three CAR T-cell products have been approved to treat relapsed or refractory aggressive B-cell lymphomas: Tisagenlcleucel, axicabtagene ciloleucel, and lisocabtagene maraleucel.[13] In contrast, data on CAR T-cell therapy in solid tumors thus far suggests less robust responses and greater challenges.[2,14] To date, no CAR T-cell products have been FDA approved for treatment of solid organ malignancies, but some progress has been achieved in pre-clinical and clinical studies of CAR-T and TCR-T in osteosarcoma and gynecologic malignancies.[15,16] Ovarian cancer TCR-T candidate targets have focused on melanoma-associated antigen 4 (MAGE-A4) and New York esophageal squamous cell carcinoma 1 (NY-ESO-1) both commonly expressed by ovarian cancer cells. The ongoing NCT03132922 clinical trial for MAGE-4 TCR-T in multiple cancers including ovarian, bladder, esophageal, head and neck, bladder, melanoma, and synovial sarcoma demonstrated interim partial response in 7 of 28 patients and stable disease in 11 of 28 patients at the cost of significant adverse events.17 Clinical studies have been conducted to evaluate human epidermal growth factor receptor 2 (HER2)-specific CAR T-cells in patients with HER2-positive sarcoma, demonstrating T-cell persistence for at least 6 weeks without significant toxicity.[16] A positive clinical response was demonstrating by administering a single agent ultra-low dose of HER2-Car T-cells to 19 sarcoma patients with recurrent or refractory metastatic disease, with subsequent dose escalation to bypass the need for concurrent lymphodepleting chemotherapy.16 However, none of the 19 patients demonstrated a complete response although 4 of 17 measurable patients had stable disease for 12 weeks to 14 months by RECIST criteria.[16]

CAR T-cells for Renal Cell Carcinoma

The utilization of CAR T-cells for solid organ malignancies, including renal cell carcinoma (RCC), is subject to numerous challenges including suppression of T-cell function, inhibition of T-cell localization, toxicity leading to adverse events, and lack of therapeutic response. As of 2020, there were 196 clinical trials of CAR T-cells targeting 57 unique solid tumor entities registered at *clinicaltrials.gov*, the majority of which were performed in the USA and China.9 Clear cell renal cell carcinoma (ccRCC) is an immunogenic tumor type with moderate tumor mutational burden of 1.42 mutations per megabase[18] that has proven to benefit from both cytokine-based and checkpoint inhibitor immunotherapies in advanced and metastatic disease.[19,20] However, despite its theoretical promise as an immune-sensitive malignancy, no large clinical trials yet exist for CAR T-cell therapy in RCC. Safety and efficacy are two major limitations that prevent CAR-T therapy from proceeding to clinical trials in RCC. To maximize both safety and efficacy of CAR T-cell immunologic response, antigen selection is vital to reduce off-target toxicity. In the current review, we examine the furthest developed candidates for CAR-T therapy in RCC.

CAIX

Carbonic anhydrase-IX (CAIX) is a 54/58 kDa transmembrane tumor-associated antigen and marker of hypoxia that belongs to the family of carbonic anhydrases, a family of zinc metalloenzymes that catalyzes hydration of CO2 for pH balance in living organisms.[21] The CAIX gene is directly activated at a transcriptional level by hypoxia-inducible factor (HIF)-1a leading to proton transport to extracellular medium to lower pH. Therefore CAIX expression serves as a surrogate marker for hypoxia in some tumors.[21,22] Specifically for RCC, CAIX is overexpressed in over 90% of ccRCC and over 80% of metastases but not on neighboring normal renal parenchyma.[21,23] Patients with Von Hippel Lindau (VHL) mutation characterized by predisposition to ccRCC have also been demonstrated to have higher CAIX expression than those with wildtype VHL.[24] CAIX serves as an important prognostic biomarker in patients with ccRCC, with high CAIX score on immunohistochemical staining associated with improved disease free survival and overall survival.[25] Conversely, low CAIX expression and absence of VHL mutation is associated with more advanced disease and decreased survival.[24] In addition to RCC, CAIX is overexpressed in several other solid tumor types including carcinomas including ovarian, breast, esophageal, bladder, colon, non-small cell lung, dysplasia of cervix and others.21 CAIX has also been proposed historically to be a prognostic marker for favorable response in IL-2 treated patients with RCC,[26] though this was not demonstrated prospectively when tested in the SELECT study.

Prior to preclinical studies, in vitro and in vivo studies focused on constructing CAR using anti-CAIX scFv.[21,27] Lo *et al* evaluated five anti-CAIX single chain antibodies as candidates for CAR construction and constructed two generations of anti-CAIX CARs using the selected scFvG36 CAR-targeting moiety. They reported in vitro comparisons of both21 to confirm superior effector functions of second generation G36-CD28z CAR T-cells compared with first generation constructs in all in vitro assays including IFN-y, IL-2, and IL-17 cytokine secretion, cytolytic activity, proliferation, and clonal expansion.21 The same group then reported in vivo superior antitumor activity of second generation CAR T-cells against RCC21 after adoptive transfer of CAR T-cells combined with high-dose interleukin (IL)-2 into RCC-established mice, demonstrating tumor cell apoptosis and

regression of CAIX+sk-rc-52 tumors in vivo.[21]

The first clinical study of T-cells genetically modified to express a CAR against CAIX was published in 2006 as a proof of principle that autologous CAR T-cell transfer can be accomplished in metastatic RCC to provide tumor-specific immunity.28 A single chain antibody-type receptor construct that recognizes CAIX was transduced into primary human T-cells. These autologous genetically retargeted T-lymphocytes were administered to three patients with CAIX-positive metastatic clear cell carcinoma who had already undergone radical nephrectomy with metastasis refractory to treatment with interferon alpha.[28] The study was not designed to assess clinical efficacy but did confirm off-tumor T-cell mediated cytotoxic effects: two of three patients required cessation of therapy due to hepatotoxicity per NCI Common Toxicity Criteria grades 2-4.[28] Liver biopsy confirmed cholangitis with T-cell infiltration of bile ducts and CAIX expression on bile duct epithelial cells, suggesting antigen-specific immunologic mechanism.[28] A follow-up study by the same group utilized CAIX CAR-T in 12 patients with CAIX-expressing metastatic RCC and demonstrated increased plasma levels of interferon-gamma, IL-2, and tumor necrosis factor (TNF)-alpha. Similar to prior study, they confirmed grade 2-4 hepatotoxicity at the lowest CAR T doses with CAIX expression and T-cell infiltration on bile duct epithelium, but with the notable novel finding that pre-treatment with CAIX monoclonal antibody G250 helped to circumvent CAR-specific hepatotoxicity.[29] This provided additional proof of principle that the on-target toxicity is antigen-directed, as blockage of CAR-specific antigen expressed on normal tissue improved the toxicity profile to allow higher doses.[29] There is a dose escalation and expansion clinical trial of CAIX-targeted CAR-T cells in the treatment of advanced RCC that is ongoing at The Affiliated Hospital of Xuzhou Medical Center (ClinicalTrials.gov Identifier NCT04969354).[30] New progress has been made in creating CAIX-targeted CAR T-cells with different cellular composition in the ccRCC mouse model, more specifically with a CD4/CD8 ratio of 2:1 (CAR 4/8) to balance cytolytic CD8 T-cell killing capacity with cytokine-induced effect of CD4 T-cells.[31] Indeed, early results demonstrated superior antitumor efficacy in the ccRCC orthotopic mouse model, increased memory phenotype, and decreased exhaustion genes compared to CAR8 T-cell groups.31 More recent attempts to target CAIX with CAR-T cells while avoiding the observed on-target off-tumor toxicities noted above have led to the development of dual-targeted CAR-T constructs that require targeting and binding of two unique antigens to mediate cellular cytotoxicity. Early pre-clinical data on such a dual construct that targets both CAIX and CD70 (see section below) has been reported.[32]

CD70

CD70, a ligand for CD27, is a costimulatory receptor involved in T-cell proliferation and survival.[33,34] CD70 was initially identified as a diagnostic marker for ccRCC by gene expression profiling, real time RT-PCR and IHC.[35] A postulated mechanism of CD70 overexpression is due to dysregulated pVHL/HIF pathway in RCC.36 RCC and other solid tumors can constitutively overexpress CD70, making it an effective target of CAR-T cells in vitro and in vivo.[37,38] Clinical studies of CD70-expressing RCC and other targeted treatment modalities have demonstrated its potential as a target: an antibody-drug conjugate targeting CD70 (SGN-CD70A) has been tested in a phase I clinical trial for patients with CD70-positive metastatic RCC demonstrating modest clinical results including 13 of 18 with stable disease but only 1 with partial response per RECIST 1.1.[39] Aside from RCC, other CD70-expressing tumors include glioblastoma, and hematologic malignancies.

Published preclinical data supports the feasibility and safety of using anti-human CD70 CAR to treat cancer patients whose tumors express CD70.[40] Seven candidate anti-human CD70 CARs consisting of extracellular binding portion of CD27 fused with 41BB and/or CD3-zeta were constructed for in vitro studies and in vivo adoptive transfer into a CD27-CD3-zeta CAR murine model. In vitro results demonstrated that the CAR consisting of extracellular binding portion of CD27 fused with 41BB and CD3-zeta conferred the highest IFNy production against CD70-expressing tumors.40 In vivo data for renal cell carcinoma demonstrates that mouse xenografts treated with CD70 CAR-T cells showed significantly decreased RCC burden, longer survival times than mice treated with controls (PBS, T-cells, or mock CAR-T cells). In addition, higher cytokine levels of IL-2, TNF-alpha, and IFNy were secreted in peripheral blood of mice treated with CD70 CAR-T cells compared to controls, suggesting that CD70 CAR-T cells may be effective in treating CD70+ RCCs in vivo.38 Clinical trials with CD70 CAR-T cells have recently entered the clinic, with the TRAVERSE trial using allogeneic, TALEN gene edited ALLO-316 anti-CD70 T-cells being given Fast Track Designation for the US FDA based on its potential to address an unmet medical need for patients with advanced RCC who have progressed on approved therapies.[41–43]

HERV-E

VHL-deficient ccRCC commonly express transcripts derived from novel human endogenous retrovirus HERV-E. In current literature there are no in-vitro or in-vivo studies of CAR-T targeting HERV-E in RCC, but advancements have been achieved in the development of TCR-T targeting HERV-E.44–47 HERV-E was first identified as a target antigen of RCC-specific CD8+ T-cells due to expression in RCC cell lines and fresh RCC tissue but not in normal kidney or other tissues.[47] To provide a clinical proof of principle, T-cells targeting to HERV-E family antigens mediated regression of metastatic RCC in a stem cell transplant recipient.47 Subsequently, HERV-E expression was demonstrated to restrict to ccRCC by mechanism of inactivation of the VHL tumor suppressor and stabilization of HIFs.[46] HERV-E expression in ccRCC demonstrated linear correlation to HIF-2alpha levels, while transfection of normal VHL successfully silenced HERV-E expression.[46] Cherkasova *et al* confirmed that T-cells could recognize HLA-A+0201-positive HERV-E-expressing kidney tumor cells suggesting HERV-E envelope peptides as tumor-restricted targets.[45] In a separate paper, RNA-seq analysis was performed on RCC tumor samples to determine whether response to Nivolumab was associated with HERV expression, with finding of no association between T-cell reactivity to HERVs and nivolumab response,[48] though other published data have supported such an association.[49] Taken collectively, these studies suggest prominent potential for future TCR-T or CAR-T against HERV-E in ccRCC. Studies of other tumors have demonstrated the feasibility of CAR T-cell specific for other HERV subtypes: In vivo studies of CAR T-cell generated for breast cancer demonstrated downregulation of HERV-K expression in tumors of mice treated w/ CAR T-cell for HERV-K, upregulation of 53, downregulation of MDM2 and p-ERK.[50] Additionally, HERV-K env-specific CAR T-cells demonstrated lysis of HERV-K env(+) tumor targets in melanoma.[51] A clinical trial at National Institutes of Health (NCT03354390) is currently ongoing to evaluate the effectiveness and safety of HERV-E TCR transduced

autologous T-cells when infused in patients with metastatic ccRCC.[52]

Neoantigens and other Tumor Antigen Targets

Personalized neoantigen-based immunotherapy, based on a patient's tumor-specific somatic mutational profile, represents the most individualized form of immunotherapy when incorporated into neoantigen long peptide vaccines, dendritic cell vaccines, and neoantigen-reactive T-cells (NRTs).[53] Neoantigens are epitope peptides that originate from somatic variants in tumor cells and bind with a patient's MHC to elicit T-cell mediated antitumor response. Neoantigen candidates may be identified for a specific patient through genomic and transcriptomic profiling of the tumor and administered via personalized neoantigen vaccination. Neoantigens are advantageous as immunologic targets due to specific expression in tumor cells and not normal cells, thereby minimizing the risk of autoimmunity.[53] Neoantigen-based cancer immunotherapy has demonstrated therapeutic efficacy in multiple solid tumors including small cell lung cancer[54] and glioblastoma.[55] Robust data has been published in the pancreatic cancer literature utilizing TCR-T cells targeting neoantigen mutant KRAS G12D expressed in a patient's tumors, leading to overall partial response of 72% by RECIST criteria at 6 months.[56] There is currently limited data on neoantigen-based immunotherapy in renal cell carcinoma, but at least one case report has demonstrated the feasibility of neoantigen-reactive T-cells in a patient with metastatic collecting duct carcinoma refractory to tyrosine kinase inhibitor. Post-therapy biopsy demonstrated reduction in mutant allele frequency corresponding to 12/13 of the neoantigens compared to pre-therapy biopsy, indicating therapeutic efficacy against tumor cells carrying these neoantigens. The patient demonstrated stable tumor burden and significant reduction in bone pain within 3 months.[53]

Renal cell carcinoma has a relatively low tumor mutational burden (TMB) but discrepantly high response to PD-1 inhibition, which counters the association between high TMB and response to immune checkpoint blockade.[57] This discordance may lie in small insertions and deletions (indels), as whole-exome sequencing data demonstrates the highest proportion of indels in RCC when compared to a pan-cancer cohort including 5777 solid tumors.[58] Therefore, neoantigen-based therapy may be particularly beneficial for renal cell carcinoma due to high immunogenicity of RCC despite relatively low mutation load: neoantigens derived from indel mutations were found to be 9x enriched for mutant specific binding compared to single nucleotide variant derived neoantigens, suggesting that Indels may be the key to activating increased neoantigens and increased mutant-binding specificity in RCC.[58]

Other specific tumor-associated antigens highly aberrantly expressed and mutated in RCC have been identified as potential RCC-specific neoantigen targets for mRNA vaccine development including DNA topoisomerase II alpha (TOP2A), neutrophil cytosol factor 4 (NCF4), formin-like protein 1 (FMNL1) and docking protein 3 (DOK3).[59] Other potential tumor antigen candidates for engineered T-cell therapy in RCC include vascular endothelial growth factor receptor 1 (VEGFR1) associated with RCC angiogenesis that has demonstrated good peptide-specific cytotoxic lymphocyte response when administered in a phase I vaccine trial.[57] Hypoxia-inducible protein 2 (HIG2) is a growth factor expressed in 86% of RCC that demonstrated HIG2-specific CTL response in 8 of 9 patients after vaccination of a specific HIG2 peptide.[57]

CONCLUSIONS

Engineered T-cell therapy is well established in hematologic malignancies but remains in pre-clinical and early clinical development for clinical applicability in solid organs including RCC. Current literature suggests that CAIX, CD70 are the primary candidate target antigens for CAR T-cell design for RCC, and HERV-E has demonstrated great promise as a target in ccRCC TCR-T therapy. Future strategies should direct towards finding an optimal target antigen for RCC and minimizing off-target toxicity prior to large-scale clinical trials. The current clinical studies of CAR T-cell therapy in other solid organs include patients with refractory or recurrent metastatic disease after failure of conventional chemotherapy. In this landscape and in part due to the risk of adverse events, we anticipate that the optimal CAR T-cell therapy candidate in the RCC space should also demonstrate failure of conventional approved therapies. CAR T-cells for RCC should be intended to target advanced and refractory disease, or those with strict contraindication to more established immunotherapy. Furthermore, future directions of CAR T-cell therapy include its potential use in combination with established immune checkpoint blockade for synergistic effect. With potential life-threatening adverse events representing a major barrier to CAR T-cell therapy in RCC, we emphasize a need to confirm safety and efficacy before progressing to large clinical trials.

DISCLOSURES

A.J.P. is a consultant for T Cure, a company that has licensed and is developing HERV-E CAR-T for renal cell carcinoma. No additional disclosures

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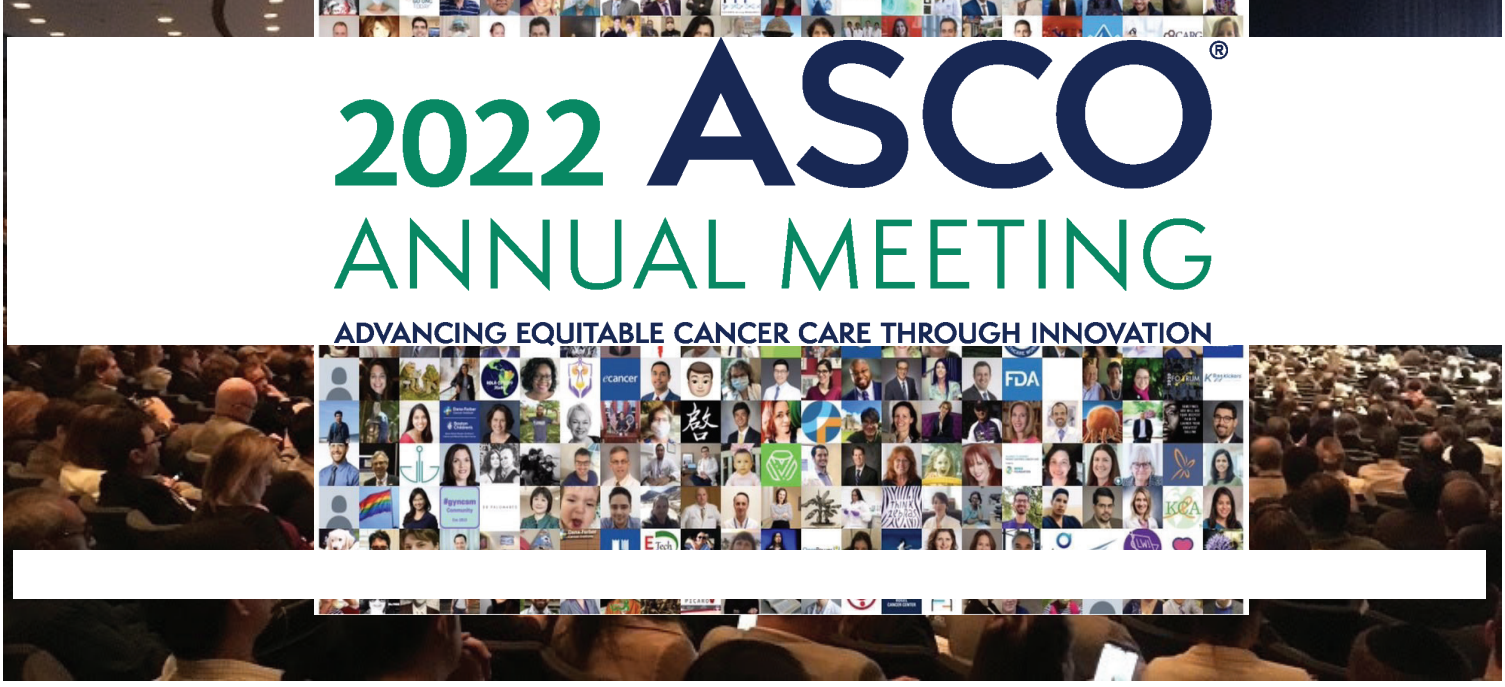

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ASCO 2022: Sets the Stage for Improved and Practice-Changing Results

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https://doi.org/10.52733/KCJ20n2-e

Dear Colleagues,

This year's annual meeting of the American Society of Clinical Oncology (ASCO22) held June 3 through 7, was hybrid in nature with attendees joined both in-person and virtually from over 100 countries. Tens of thousands of physicians, clinical trial investigators, R&D scientists, academics, patient advocates, and biopharma leaders descended upon Chicago for the first in-person ASCO meeting after a two-year hiatus due to the COVID-19 pandemic. This year's ASCO22 has provided an opportunity to explore the latest advancements in cancer research, treatment, and patient care with featured abstracts in more than 120 subcategories including all major disease sites and research areas. Presentations at ASCO22 have unearthed a wealth of exciting data across the oncology spectrum, especially for oncologists and physicians around the world, and also gave glimpses into what is next for the field. With a mix of live and on-demand content, there was no shortage of cutting-edge research available to attendees —including more than 2,000 abstracts, 85 live stream sessions, and more than 2,500 poster presentations and poster discussion sessions, clinical science symposia, education sessions, etc. Topics span the spectrum of hematology/oncology, including new drugs; treatment advances in prostate, breast, lung, and blood cancers, as well as screening, prevention, access to care, immunotherapy, and precision medicine.

The theme for ASCO 2022 was "Advancing Equitable Cancer Care Through Innovation" with more than 200 sessions offering resources and research on this topic. Inequitable access to cancer care and management, compounded by the unprecedented effects of global COVID-19 impact, presents a daunting, global challenge for both governments and stakeholders —as well as opportunities for innovative solutions. Presentations at the meeting sought to address inequitable access issues and develop equitable cancer strategies through innovation. "The COVID-19 pandemic has laid bare the inequities that exist in our global health care systems," noted Everett E. Vokes, MD, FASCO, 2021-2022 ASCO President, in his program communication to attendees. "It has also provided us an opportunity to reinvent cancer care delivery and test promising approaches to a more equitable future in health care. In oncology, innovation can be seen around every corner. Opportunities range from new therapies and smarter use of existing treatments and offering patients broader and easier access through telemedicine, to rethinking clinical trial eligibility and much more" he concluded. ASCO'22 provided the perfect backdrop to dive into strategies we can collectively drive patient-centric oncology research and drug development. Many important discussions on how to help address inequities in cancer care have drawn leaders in the field to seek solutions quickly.

The science of immunotherapy has come a long way in the last decade since the approval of the first checkpoint immunotherapy in 2011, as the meeting presentations highlighted that tremendous scientific advances are unlocking more of immunotherapy's potential each passing year. While the immuno-oncology combinations continued their impressions, newly developed strategies viz. HIF2a inhibitor and GAS6-AXL inhibitor also showcased their promising outcomes in renal cell carcinoma. More than 160 abstracts and talks focused on therapies for renal cell carcinoma were delivered during poster and oral sessions. Following high-profile clinical

trials have delivered some interesting and impactful data at the meeting: EVEREST (everolimus, SWOG S0931, NCT01120249; abstract LBA4500), CheckMate 9ER (nivolumab plus cabozantinib; NCT03141177; abstract 4501), CheckMate 214 (nivolumab plus ipilimumab; NCT02231749; abstract 4502), CALYPSO (durvalumab plus savolitinib; NCT02819596; abstract LBA4503), LITESPARK-001 (belzutifan; NCT02974738; abstract 4509), AVB-S6-500 (batiraxcept; NCT04300140; abstract 4511), KEYNOTE-564 (pembrolizumab; NCT03142334; abstract 4512), KEYNOTE-426 (Pembrolizumab plus axitinib; NCT02853331; abstract 4513), TiNivo-2 (tivozanib plus nivolumab; NCT04987203; abstract TPS4605) and CLEAR (lenvatinib plus pembrolizumab; NCT02811861; abstract 4514) etc. A full list of abstracts that I have picked is available in the special ASCO22 section in detail. These studies presented at ASCO22 demonstrated statistically significant and clinically meaningful benefits or deeper responses over their respective comparator drug as well as made tremendous strides in the renal cancer space. Altogether, ASCO 2022 offered impactful novel data that will continue to transform clinical practice and cancer drug development for a variety of cancers. Most importantly, the implementation of the scientific advances we learned at ASCO 2022 will improve the quality of life and length of our cancer patients.

In this issue, an exclusive roundtable discussion that I chaired, provide key perspectives on the efficacy and tolerability of tivozanib plus nivolumab combination therapy. Following distinguished kidney cancer investigators joined the conversation: Dr. Robert Motzer, Dr. Toni Choueiri, and Dr. Laurence Albiges discuss the full potential of tivozanib plus ICI combinations in a rapidly changing treatment paradigm of renal carcinoma. A manuscript by Paquin et al provides the framework for comprehensive research on the demographic, increased risk factor and genetic pathway differences between papillary renal cell carcinoma type 1 and type 2 tumors. In another review work, Zhang *et al* outlined the current state of using engineered T cell therapy especially CAR-T cell therapy for the treatment of patients with advanced RCC and also described the toxicity and challenges and CAR-T cell therapy. Also, Dr. Yasser Ged and Dr. Nirmish Singla provided meeting coverage for our featured ASCO22 section in this issue.

Sincerely,
Robert A Figlin, MD

Kidney Cancer Research Highlights from ASCO 2022 Annual Meeting

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doi.org/10.52733/KCJ20n2-ASCO22

ABSTRACT

The 2022 American Society of Clinical Oncology (ASCO) annual meeting was held June 3-7, 2022, in Chicago, Illinois. This hybrid meeting gathered international cancer experts across multidisciplinary specialties and was held both virtually and in-person. Here, we highlight key kidney cancer research updates presented at the meeting. Slides from the meeting's presentations are available on the ASCO meeting library website.

Adjuvant Therapy Updates

Locally advanced kidney cancer has traditionally been managed surgically alone1. However, approximately 30% of patients develop recurrent metastatic disease after surgical resection despite curative intent, and the optimal approaches to integrate surgery with systemic therapies in a neoadjuvant or adjuvant approach to reduce the risk of recurrence has been an area of active research.[2] The U.S. Food and Drug Administration (FDA) has approved two adjuvant therapies in renal cell carcinoma (RCC) thus far, including sunitinib in 2017 and most recently pembrolizumab in 2021.[3,4] The use of adjuvant sunitinib has been limited despite FDA approval because of its increased toxicity and lack of overall survival benefit.[5] Pembrolizumab is the first approved adjuvant immunotherapy for clear cell RCC patients with intermediate-high or high risk of recurrence after nephrectomy based on the phase 3 double-blind, multicenter, randomized KEYNOTE-564 study (NCT03142334).[4]

Updated analysis from KEYNOTE-564 was presented at the meeting evaluating the time to first

Figure 1. Oral presentation at the 2022 American Society of Clinical Oncology (ASCO22).

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subsequent drug treatment or any-cause death (TFST) and time from randomization to progression on next line of therapy or any-cause death (PFS2) after treatment with pembrolizumab or placebo in the study.[6] Overall 67 patients (13.5%) in the pembrolizumab group and 99 patients (19.9%) in the placebo group received ≥1 line of subsequent anticancer drug therapy. A total of 108 PFS2 events were observed, 40 (8.1%; 12 death events and 28 progression events) in the pembrolizumab group and 68 (13.7%; 14 death events and 54 progression events) in the placebo group. PFS2 was also delayed with pembrolizumab compared with placebo (HR, 0.57; 95% CI, 0.39-0.85; medians not reached). The authors concluded that treatment with adjuvant pembrolizumab reduced risk for TFST and PFS2 compared with placebo. LITESPARK-022 (NCT05239728) is the next iteration of the KEYNOTE-564 study which is a phase 3 study designed to compare the efficacy and safety of belzutifan plus pembrolizumab with that of placebo plus pembrolizumab as adjuvant treatment for clear cell RCC after nephrectomy, and this study is currently actively enrolling.

Multiple adjuvant and neoadjuvant vascular endothelial growth factor tyrosine kinase inhibitors (VEGF-TKIs) studies in RCC were reported previously.[5] To better understand the role of mammalian target of rapamycin (mTOR) inhibitors in the adjuvant setting, the *Southwest Oncology Group* (SWOG) launched the phase 3 study of everolimus in treating patients with kidney cancer who have undergone surgery (EVEREST) study (NCT01120249), which was reported at ASCO 2022.[7] Individuals with clear or non-clear cell RCC immediately post-nephrectomy whose tumors show intermediate high-risk to high risk features were included in the study. Between 4/2011 and 9/2016, 1545 patients were randomized to either 12 months of adjuvant everolimus (n = 775) or placebo (n = 770) including 83% with clear cell RCC and 17% with non-clear cell RCC. With a median follow-up of 76 months, the recurrence free survival was improved with everolimus compared to placebo (HR 0.85, 95% CI, 0.72 – 1.00; P (one sided) = 0.0246), narrowly missing the pre-specified, one-sided significance level of 0.022 which accounted for interim analyses, and the effect of everolimus was especially pronounced in patients with very high risk disease. Adverse events were consistent with safety profiles of everolimus, although there was a high discontinuation rate of everolimus in this population (47%).

First Line Metastatic Kidney Cancer Treatment Updates

The first line treatment landscape of metastatic RCC has rapidly evolved in recent years.[8] New updates on some of the registration first line metastatic RCC studies were

Figure 2. ASCO poster session

presented during the meeting.

The CheckMate 9ER trial is a phase 3 trial which compared nivolumab plus cabozantinib versus sunitinib in patients with untreated advanced clear cell RCC and demonstrated superior overall survival (OS), progression free survival (PFS) and objective responses of the nivolumab plus cabozantinib combination9. Updated analysis from the depth of response was presented at ASCO 2022.[10] Patients' responses were classified as complete response (CR) or partial response (PR) subdivided by a tumor reduction of ≥80%–<100% (PR1), ≥60%–<80% (PR2), or ≥30%–<60% (PR3). Overall, greater proportions of patients receiving nivolumab plus cabozantinib had deeper responses versus sunitinib (CR, PR1, PR2), and deeper responses with nivolumab plus cabozantinib were associated with improved 12-months PFS rate versus sunitinib for CR (94.9% vs 82.4%), PR1 (81.3% vs 37.5%), and PR2 (72.1% vs 53.2%).

Updates on health-related quality of life (HRQoL) from the CheckMate-214 phase 3 clinical trial, which compared nivolumab plus ipilimumab versus sunitinib in patients with untreated advanced clear cell RCC, were also presented during the meeting.[11,12] As previously reported, nivolumab plus ipilimumab was associated with improved HRQoL compared to sunitinib. At ASCO 2022, the investigators reported on a post-hoc analysis on the prognostic ability of HRQoL to inform the risk of disease progression or death. The results of the analysis showed that higher (better) baseline scores were associated with significantly reduced risk of death (HR [95% CI] for FKSI-19 Total Score and DRS score was 0.83 [0.80-0.87] and 0.80 [0.76-0.84], respectively). Furthermore, patients with improved/stable HRQoL had a 52% reduction in risk of death compared to patients who had worsened (HR 0.48 [95% CI: 0.39-0.59]).

Post-hoc exploratory analyses of PFS2 were conducted in the KEYNOTE 426 (phase 3 study comparing pembrolizuamb plus axitinib versus sunitinib in patients with untreated advanced clear cell RCC)[13,14] and the CLEAR (phase 3 study comparing pembrolizumab plus lenvatinib versus sunitinib in patients with untreated advanced clear cell RCC)[15,16] studies. Both analyses demonstrated prolongation of PFS2 in patients who received pembrolizumab plus axitinib in KEYNOTE 426 study and pembrolizumab plus lenvatinib in the CLEAR study.

Novel Kidney Cancer Therapies Highlights

Several exciting data were presented on novel therapies in RCC. Batiraxcept is a GAS6-AXL inhibitor, a pathway which is overexpressed in clear cell RCC.[17] Interim results of a phase 1b study of batiraxcept plus cabozantinib 60 mg daily were presented at the meeting.[18] A total of 26 patients were enrolled in the phase 1b study so far, and the recommended phase 2 dose of batiraxcept was identified as 15 mg/kg every 2 weeks. Encouraging early anti-tumor efficacy results of the combination were observed with an objective response rate of 67% and 6 months PFS of 79%.

Hypoxia-inducible factor 2α (HIF-2α) is a key oncogenic driver in RCC.[19] Belzutifan is a HIF-2α inhibitor which was recently approved by the FDA for patients with VHL syndrome and currently under investigation in sporadic RCC.[20,21] LITESPARK-001 is a phase 1 study which was designed to evaluate belzutifan in heavily pretreated RCC and showed durable antitumor activity and an acceptable safety profile.[21] An update of the clear cell RCC cohort in the study with more than 3 years of total follow-up was presented at the meeting.[22] With extended follow-up of 41 months, the objective response rate was 25% with 80% disease control rate and median PFS of 14.5 months (95% CI, 7.3-22.1). Belzutifan monotherapy continued to show a high rate of disease control and durable responses in this heavily pre-treated population.

The CALYPSO study results were presented at the meeting as well.[23] This is a randomized phase II study of durvalumab alone or with savolitinib or tremelimumab in previously treated advanced clear cell RCC. Savolitinib is a potent MET inhibitor with established dosing and activity in papillary RCC; however, its role in clear cell RCC is unclear.[24] Between 2017 and 2021, 139 patients were randomized across the treatment arms. Savolitinib alone and in combination with duravlumab was associated with modest confirmed response rates (5% and 13%, respectively) compared to confirmed response rates of 10% for durvalumab and 28% for durvalumab plus tremelimumab. All regimens studied in the trial appeared to be safe and tolerable.

SUMMARY

In summary, ASCO 2022 was enriched with novel results and concepts continually expanding the field of kidney cancer research. Indeed, the data presented are both hypothesis-generating and practice-informing. Herein, we highlighted a snapshot of some of the oral presentations from the meeting in the kidney cancer space; however, there are considerably more exciting abstract and poster presentations that are available for review on the meeting's website. In addition to the scientific content, ASCO 2022 also provided ample opportunities for networking and collaborations among the academic kidney cancer community, with the first in-person option since the beginning of the COVID-19 pandemic.

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https://doi.org/10.52733/KCJ20n2-ASCO22abs

These recommended abstracts from ASCO22 Annual meeting have been selected by Robert A. Figlin, MD, 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.

ABSTRACT LBA4500: EVEREST: Everolimus for renal cancer ensuing surgical therapy—A phase III study (SWOG S0931, NCT01120249). *Ryan CW et al.*

BACKGROUND: Patients (pts) who undergo resection of renal cell carcinoma (RCC) with curative intent remain at risk for disease relapse. We conducted a phase III, double-blind, placebo (PB)-controlled, intergroup study to determine the effect of adjuvant treatment with the mTOR inhibitor everolimus (EVE) on recurrence-free survival (RFS).

METHODS: Pts with treatment-naïve, non-metastatic, fully-resected RCC at intermediate high- (pT1 G3-4 No to pT3a G1-2 No) or very high-risk (pT3a G3-4 to pT4 G-any or N+) for recurrence were randomized 1:1 to EVE 10 mg PO daily x 54 weeks or PB within 12 weeks of radical or partial nephrectomy. Randomization was stratified by risk group, histology (clear vs. non-clear cell), and performance status (0 vs. 1). RFS was the primary end point; secondary endpoints included overall survival (OS) and adverse events (AEs). The study was designed to detect an 18% reduction in the risk of RFS with EVE compared to PB, corresponding to an improvement of median RFS from 6.75 (based on E2805 ASSURE) to 8.23 years. Final analysis, using a stratified logrank test, was to occur after 804 total events or by 3/2022, whichever occurred first.

RESULTS: Between 4/2011 and 9/2016, 1545 pts were randomized to EVE (n = 775) or PB (n = 770). Overall pt characteristics included: intermediate high-/very high-risk 45%/55%; clear cell/non-clear cell 83%/17%. The DSMC recommended study continuation after each of 4 pre-specified interim analyses. 556 DFS events among 1499 eligible pts occurred by the time of final study analysis on 2/23/2022. The median follow-up was 76 months. RFS was improved with EVE vs. PB (HR 0.85, 95% CI, 0.72 – 1.00; P1-sided= 0.0246), narrowly missing the pre-specified, one-sided significance level of 0.022 which accounted for interim analyses. Median RFS was not reached; the 6-year RFS estimate was 64% for EVE and 61% for PB. RFS improvement with EVE vs. PB was observed in the very high-risk group (HR 0.79, 95% 0.65-0.97; P1-sided= 0.011) but not in the intermediate high-risk group (HR 0.99, 95% CI 0.73-1.35, P1-sided= 0.48) (P for interaction = 0.22). With 290 deaths, OS was similar between arms (HR 0.90, 95% CI, 0.71 – 1.13; P1-sided= 0.178). Fewer pts completed all 54 weeks of study treatment in the EVE group (45% v 69%). In the EVE group, 37% withdrew due to AEs (vs 5% in PB). Grade 3-4 AEs occurred in 46% of pts treated with EVE and 11% with PB. The most common grade 3-4 AEs were mucositis (14% v 0%), hypertriglyceridemia (11% vs. 2%), and hyperglycemia (5% vs. 0%).

CONCLUSIONS: Adjuvant EVE improved RFS in RCC pts after nephrectomy, but the nominal significance level was narrowly missed. The RFS improvement was seen despite a high rate of early treatment discontinuation. A 21% improvement in RFS with EVE was observed in pts with very high-risk disease, a group for whom adjuvant therapy may be most relevant. Clinical trial information: NCT01120249.

ABSTRACT 4501- Association between depth of response (DepOR) and clinical outcomes: Exploratory analysis in patients with previously untreated advanced renal cell carcinoma (aRCC) in CheckMate 9ER. *Suárez C et al.*

BACKGROUND: Among patients (pts) with untreated aRCC in the CheckMate 9ER trial, superior progression-free survival (PFS; hazard ratio [HR], 0.56) and overall survival (OS; HR, 0.70) were maintained, and objective response and complete response (CR) rates were doubled for nivolumab plus cabozantinib (N+C) vs sunitinib (SUN) with extended 25.4 mo minimum (32.9 mo median) follow-up. This exploratory analysis evaluated the relationship between DepOR and clinical outcomes in CheckMate 9ER.

METHODS: Eligible pts received N (240 mg) every 2 weeks plus C (40 mg) once daily or SUN (50 mg once daily; 4 weeks of each 6-week cycle). In this analysis, DepOR subgroups were based on best overall response (blinded independent central review [BICR] per RECIST v1.1) and best tumor reduction threshold, as follows: CR; partial response subdivided by a tumor reduction of ≥80%–<100% (PR1); ≥60%–<80% (PR2); or ≥30%–<60% (PR3); stable disease (SD); and progressive disease (PD). PFS (per BICR) and OS by DepOR subgroups were analyzed after a 6-mo post-randomization landmark. Treatment-related adverse events (TRAEs) were assessed in DepOR subgroups.

RESULTS: Of 323 and 328 pts randomized to N+C or SUN, 236 and 157 pts were progression-free and alive and 293 and 253 pts were alive at the 6-mo landmark and were categorized by DepOR subgroup. Overall, greater proportions of pts receiving N+C had deeper responses vs SUN (CR, PR1, PR2; Table). Deeper responses with N+C were associated with improved 12-mo PFS rate vs SUN for CR (94.9% vs 82.4%), PR1 (81.3% vs 37.5%), and PR2 (72.1% vs 53.2%). In both arms, an increasingly deeper response led to better OS outcome; yet OS rates and medians were comparable between arms for CR, PR1, PR2, and PR3 (Table). No meaningful patterns for overall TRAE rates by DepOR subgroup were identified in either arm.

CONCLUSIONS: In CheckMate 9ER, more pts receiving N+C achieved deeper responses vs SUN. Deeper responses were generally associated with improved PFS and OS. Clinical trial information: NCT03141177.CONCLUSIONS: At 30 months of follow-up, adjuvant pembrolizumab continued to demonstrate a consistent and clinically meaningful improvement in DFS vs placebo in pts with RCC at high risk of recurrence. No new safety signals were observed with pembrolizumab in the adjuvant setting. Clinical trial information: NCT03142334.

	N+C						SUN					
	PFS[a] N = 236			OS[a] N = 293			PFS[a] N = 157			OS[a] N = 253		
DepOR	n	12 morate, %[b,c]	Median (95% CI), mo	n	18 morate, %[c]	Median (95% CI), mo	n	12 morate, %[b,c]	Median (95% CI), mo	n	18 morate, %[c]	Median (95% CI), mo
CR	40	94.9	NR (26.0–NE)	40	97.5	NR (NE–NE)	17	82.4	NR (15.9–NE)	17	100	NR (30.2–NE)
PR1	32	81.3	24.3 (17.0–NE)	33	97.0	NR (28.9–NE)	8	37.5	6.5 (0.9–NE)	9	100	NR (19.7–NE)
PR2	37	72.1	24.8 (13.4–NE)	38	83.5	NR (31.7–NE)	18	53.2	12.0 (7.9–NE)	18	88.2	NR (NE–NE)
PR3	62	46.7	10.4 (5.5–14.0)	69	78.3	NR (30.5–NE)	45	57.0	15.9 (6.8–21.6)	49	75.3	NR (25.1–NE)
SD	65	33.5	6.3 (4.0–10.6)	99	59.6	28.7 (17.8–NE)	69	22.6	5.2 (3.7–6.7)	123	68.0	NR (24.6–NE)
PD	0	–	–	14	35.7	10.1 (4.8–25.1)	0	–	–	37	39.1	13.7 (6.4–18.6)

[a]At the 6 mo landmark. [b]12 mo PFS rate is presented due to low patient numbers at later timepoints. [c]12 mo and 18 mo rates are from 6 mo landmark.CI, confidence interval; NE, not evaluable; NR, not reached.

ABSTRACT 4502: The relationship between health-related quality of life (HRQoL) and clinical outcomes in patients with advanced renal cell carcinoma (aRCC) in CheckMate (CM) 214. *Cella D et al.*

BACKGROUND: In CM 214, when compared to sunitinib (S), nivolumab plus ipilimumab (N+I) was associated with both clinical benefit and improved HRQoL as first-line treatment for intermediate/poor (I/P)-risk patients (pts). This analysis investigates the direct association between HRQoL and clinical outcomes in aRCC pts.

METHODS: I/P-risk population included 425 and 422 pts in the N+I and S arms, respectively. HRQoL was assessed using the FKSI-19 (Total Score and Disease Related Symptoms [DRS]). Three separate analyses (A, B, and C) were conducted. A: Changes in individual item scores from baseline to last assessment prior to progression were descriptively assessed. B: For each FKSI-19 score, multivariable Cox regression, adjusted for treatment and stratification factors, was used to evaluate the prognostic significance of baseline and time-dependent HRQoL scores in separate models. Hazard ratios (HR) were calculated based on the risk of death per improvement in HRQoL scores, defined using the clinically meaningful change threshold (5 points for FKSI-19 Total and 3 points for DRS). Pts with overall survival (OS) events were censored if their survival event was not within 12 weeks of the last available HRQoL assessment. C: The association between HRQoL change status (ie, improvement or maintenance vs. worsening from baseline in the FKSI-19 Total Score), irrespective of treatment arm, and OS was further assessed using a landmark analysis at the month 6 (mo-6) landmark. Additional landmark time points were explored in sensitivity analysis.

RESULTS: Items related to fatigue and perceived bother of the side-effects of treatment had the largest percentage of pts worsening prior to progression. In both baseline and time-dependent HRQoL analyses, OS was independently associated with both HRQoL measures. Higher (better) baseline scores were associated with significantly reduced risk of death (HR [95% CI] for FKSI-19 Total Score and DRS was 0.83 [0.80-0.87] and 0.80 [0.76-0.84], respectively). Every 5-point increase (improvement) in FKSI-19 Total Score and 3-point increase in DRS was associated with a 31% decreased risk of death (P< 0.01). At mo-6, 301 pts showed improvement or maintenance in HRQoL. Pts with improved/stable HRQoL had a 52% reduction in risk of death compared to pts who had worsened (HR 0.48 [95% CI: 0.39-0.59]).

CONCLUSIONS: Results demonstrate there is an association between HRQoL and clinical outcomes in CM 214. Baseline HRQoL scores are a potential predictor for survival in aRCC, and HRQoL changes are informative for pts' expected survival. HRQoL change status at mo-6 was significantly and positively associated with subsequent survival. Thus, patient-reported outcomes may be useful for both describing pt experience in clinical trials and providing valuable clinical insights during routine practice. Clinical trial information: NCT02231749.

ABSTRACT LBA4503 - CALYPSO: A three-arm randomized phase II study of durvalumab alone or with savolitinib or tremelimumab in previously treated advanced clear cell renal cancer. *Powles T et al.*

BACKGROUND: New drug combinations are required in advanced clear cell renal cancer (RCC). These potentially include MET inhibition with savolitinib (S) or CTLA-4 inhibition with tremelimumab (T). In this study these agents were given alone or in combination with the PD-L1 inhibitor durvalumab (D).

METHODS: A multinational open-label randomised phase II study assigning patients to one of D, S, DT or DS was performed. Patients with RCC, who had previously received VEGF targeted therapy but not immune checkpoint inhibitors or MET inhibitors were included. Confirmed response rate (cRR) was the primary endpoint. A response rate of at least 50% was required for further exploration. The S arm was closed early due to a lack of efficacy. DNA alterations were measured using Foundation One and PD-L1 analysis was performed with SP263. This abstract details the pre-planned 12-month interim analyses after the cohort completed randomisation.

RESULTS: Between 2017 and 2021, 139 patients were randomised (D N=39, S N=22, DT N=39, DS N=39). The median age was 62 years (range: 28 – 85). cRRs for the 4 arms were D=10%, S=5%, DT=28%, DS=13%, which did not meet the primary objective. cRRs in the MET-driven patients (N=17) were D=0% (0/7), S=0% (0/2), DT=50% (1/2), DS=17% (1/6). cRRs in PD-L1+ves for DT and D were 14% (1/7) and 33% (2/6) respectively. 12-month progression-free survival (PFS) rates were D=26% (80% confidence interval [CI]: 17% - 36%), S=21% (80% CI: 10% - 35%), DT=33% (80% CI: 24% - 43%), DS=17% (80% CI: 10% - 26%). Median overall survival for D=26.1 (80% CI: 16.2 – 32.0) months, S=23.1 (80% CI: 20.6 – 29.7) months, DT=21.9 (80% CI: 16.3 – 31.5) months, DS=16.1 (80% CI: 10.3 – 18.8) months. There was 1 treatment related death in the DT arm. Of the 136 patients who received treatment, grade 3 or more treatment related adverse events occurred in D=10% (4/39), S=26% (5/19), DT=23% (9/39), DS=23% (9/39).

CONCLUSIONS: This randomised phase II study did not demonstrate significant efficacy for S alone or in combination with D in RCC. The addition of T to D did not demonstrate clearly superior efficacy to D in this setting. Clinical trial information: NCT02819596.

ABSTRACT 4509: Phase 1 LITESPARK-001 (MK-6482-001) study of belzutifan in advanced solid tumors: Update of the clear cell renal cell carcinoma (ccRCC) cohort with more than 3 years of total follow-up. *Jonasch E et al.*

BACKGROUND: Hypoxia-inducible factor 2α (HIF-2α) is a key oncogenic driver in RCC. Antitumor activity of the HIF-2α inhibitor belzutifan has been observed in RCC and is approved for treatment in patients (pts) with VHL disease who require therapy for associated RCC, CNS hemangioblastomas, or pNETs not requiring immediate surgery. Previous data from the phase 1 LITESPARK-001 trial (NCT02974738) designed to evaluate belzutifan in heavily pretreated RCC showed durable antitumor activity and an acceptable safety profile. After more than 3 years of follow-up for pts with ccRCC still receiving treatment, updated data are presented.

METHODS: Pts enrolled in the ccRCC cohort were previously treated with ≥1 therapy, had RECIST-measurable disease, ECOG PS score of 0 or 1, adequate organ function, and life expectancy of ≥6 months. Pts received oral belzutifan 120 mg once daily. The primary end point was safety. Secondary end points were ORR, DCR (CR + PR + SD), PFS, and DOR per RECIST v1.1 by investigator. The data cutoff date was July 15, 2021.

RESULTS: Of 55 pts enrolled in the ccRCC cohort, 9 (16%) remain on treatment as of the data cutoff date of July 15, 2021; the primary reason for discontinuation was progressive disease (n = 34; 62%). Pts received a median of 3 prior therapies (range, 1-9); 39 (71%) received prior VEGF and immunotherapy. Pts were followed while on treatment and for 30 days after the last dose for a median of 41.2 months (range, 38.2-47.7). Twenty-two pts (40%) experienced grade 3 TRAEs. The most common (≥10%) grade 3 TRAEs were anemia (n = 13; 24%) and hypoxia (n = 7; 13%). There were no grade 4 or 5 TRAEs. ORR was 25%, with 1 confirmed CR (2%) and 13 PRs (24%); DCR was 80%. Median DOR was not reached (range, 3.1+ to 37.9+ months); 8 of 14 responding pts (57%) remain in response as of the data cutoff date. Per IMDC risk, 4 of 13 pts with favorable risk achieved response (ORR = 31%; all PRs) and 10 of 42 pts with intermediate/poor risk achieved response (ORR = 24%; 1 CR, 9 PRs). DCR was 92% for pts with favorable risk and 76% for pts with intermediate/poor risk. For pts who received prior VEGF and immunotherapy, 8 of 39 pts achieved response (ORR = 21%; 1 CR; 7 PR); DCR was 74%. For the 16 pts who did not receive prior VEGF/immunotherapy, 6 achieved response (ORR = 38%; all PRs); DCR was 94%. Median PFS for the total cohort was 14.5 months (95% CI, 7.3-22.1); PFS rate at 156 weeks (36 months) was 34%.

CONCLUSIONS: As seen after a median follow-up of > 3 years for pts still receiving treatment, belzutifan monotherapy continued to show a high rate of disease control and durable

responses in previously treated pts with advanced ccRCC. Belzutifan exhibited a favorable safety profile, and no new safety signals were observed. In several phase 3 studies, belzutifan is being evaluated as monotherapy and combined therapy for ccRCC. Clinical trial information: NCT02974738.

ABSTRACT 4511: A phase 1b/2 study of batiraxcept (AVB-S6-500) in combination with cabozantinib in patients with advanced or metastatic clear cell renal cell (ccRCC) carcinoma who have received front-line treatment (NCT04300140).

Shah N et al.

BACKGROUND: AXL is up-regulated by hypoxia-inducible factor-1 signaling in both VHL-deficient and hypoxic tumor cells and plays a critical role in the metastatic phenotype of ccRCC. Batiraxcept is a recombinant fusion protein containing an extracellular region of human AXL combined with the human immunoglobulin G1 heavy chain (Fc), demonstrating highly potent, specific AXL inhibition.

METHODS: Batiraxcept at doses of 15 and 20 mg/kg, plus cabozantinib 60 mg daily, was evaluated using a 3+3 dose escalation study design. The primary objective was safety; secondary and exploratory objectives included identification of the recommended phase 2 dose (RP2D), overall response rate (ORR), and duration of response (DOR). Correlation of serum soluble AXL (sAXL)/GAS6 with ORR was evaluated. Key eligibility criteria include previously treated (2L+) ccRCC patients; prior treatment with cabozantanib was not allowed. sAXL/GAS6 was evaluated at baseline.

RESULTS: Data as of 4-February-2022, Phase 1b enrolled 26 patients, 16 patients treated with 15 mg/kg and 10 patients with 20 mg/kg dose of batiraxcept. Baseline characteristics: median age 60 (40-81); male 22 (85%); median prior line of therapy 1 (1-5); IMDC risk group of favorable 6 (23%); prior VEGF inhibitor 15 (58%); 100% with prior immunotherapy. At median follow up of 4.9 months, 92% (n=24) patients remained on the study. No dose limiting toxicities were observed at either 15 mg/kg or 20 mg/kg dose. Batiraxcept and cabozantinib related adverse events (AEs) occurred in 17 subjects (65%). Most common related AEs include decreased appetite 31% (n=8), diarrhea and fatigue 23% (n=6). Grade 3 related AEs occurred in 4 patients (15%) including diarrhea, thromboembolism, hypertension, small bowel obstruction, and thrombocytopenia (n=1, 4% each) being most common. No grade 4 or 5 related AEs were observed. The ORR was 46% (n=12, partial response [PR]; Table). No patients had primary progressive disease. Among the patients who had a baseline sAXL/GAS6 ratio of ≥ 2.3, the ORR was 67% (12/18). Regardless of baseline sAXL/GAS6 ratio, 3-month DOR was 100%; and 6-month progression free survival was 79%. Batiraxcept PK levels were similar across both doses and GAS6 levels suppressed through the dosing period.

CONCLUSIONS: Batiraxcept plus cabozantinib is well tolerated. The RP2D of batiraxcept was identified as 15 mg/kg. Early efficacy signals were observed including 100% DOR at 3 months. Baseline sAXL/GAS6 may serve as a potential biomarker to enrich the population. Clinical trial information: NCT04300140.

	Entire cohort	Batiraxcept 15 mg/kg cohort	Batiraxcept 20 mg/kg cohort
	N=26 (%)	N=16 (%)	N=10 (%)
ORR (confirmed + unconfirmed)	12 PR (46)	9 PR (56)	3 PR (30)
DOR (3-month)	26 (100)	26 (100)	Not reached
Any grade-related AEs	17 (65)	11 (69)	6 (60)
Grade ≥3 related AEs	4 (15)	2 (13)	2 (20)

ABSTRACT 4512: Adjuvant pembrolizumab for postnephrectomy renal cell carcinoma (RCC): Expanded efficacy analyses from KEYNOTE-564.

Choueiri TK et al.

RESULTS: Of 994 patients, 496 were randomly assigned to receive pembrolizumab and 498 to placebo. Median time from randomization to the data cutoff date (June 14, 2021) was 30.1 months (range, 20.8-47.5). Overall, 67 patients (13.5%) in the pembrolizumab group and 99 patients (19.9%) in the placebo group received ≥1 line of subsequent anticancer drug therapy. Of patients who received ≥1 line of subsequent drug therapy, most in the pembrolizumab group (90.0% [60/67]) and placebo group (85.9% [85/99]) received a VEGF/VEGFR-targeted therapy; 23.9% of patients (16/67) in the pembrolizumab group and 59.6% (59/99) in the placebo group received an anti–PD-1/PD-L1 agent. Seventy-seven TFST events were observed in the pembrolizumab group; 110, in the placebo group. Compared with placebo, adjuvant treatment with pembrolizumab delayed TFST (HR, 0.67; 95% CI, 0.50-0.90; medians not reached). A total of 108 PFS2 events were observed, 40 (8.1%; 12 death events and 28 progression events) in the pembrolizumab group and 68 (13.7%; 14 death events and 54 progression events) in the placebo group. PFS2 was also delayed with pembrolizumab compared with placebo (HR, 0.57; 95% CI, 0.39-0.85; medians not reached).

CONCLUSIONS: Treatment with adjuvant pembrolizumab reduced risk for TFST and PFS2 compared with placebo. Results of this exploratory analyses suggest sustained clinical benefit of adjuvant pembrolizumab and support the use of adjuvant pembrolizumab after nephrectomy as standard of care for patients with localized RCC at increased risk for recurrence. Clinical trial information: NCT03142334.

ABSTRACT 4513: Pembrolizumab (pembro) plus axitinib (axi) versus sunitinib as first-line therapy for advanced clear cell renal cell carcinoma (ccRCC): Analysis of progression after first subsequent therapy in KEYNOTE-426.

Powles T et al.

BACKGROUND: The randomized, open-label, phase 3 KEYNOTE-426 study (NCT02853331) met its primary and key secondary end points of improved OS, PFS, and ORR with pembro + axi versus sunitinib as first-line treatment for patients with advanced ccRCC. Extended follow-up (42.8-mo median follow-up) continued to show the superior efficacy of pembro + axi versus sunitinib in this patient population. We describe the results of PFS2 for all randomly assigned patients and across IMDC risk categories.

METHODS: Treatment-naive patients with advanced ccRCC, Karnofsky Performance Status Scale score ≥70% and measurable disease per RECIST v1.1 were randomly assigned 1:1 to receive pembro 200 mg IV every 3 weeks for up to 35 doses (˜ 2 y) + axi 5 mg orally twice daily or sunitinib 50 mg orally once daily on a 4-wk on/2-wk off schedule. The end point of this exploratory analysis was PFS2, defined as time from randomization to progression after first subsequent therapy or any-cause death. The Kaplan-Meier method was used to estimate PFS2 and hazard ratios were estimated using a Cox regression model.

RESULTS: Of 861 patients, 432 were assigned to receive pembro + axi; 429, to sunitinib. Median time from randomization to the database cutoff date (January 11, 2021) was 42.8 mo (range, 35.6-50.6). Overall, 47.2% of patients (204/432) in the pembro + axi arm and 65.5% of patients (281/429) in the sunitinib arm received ≥1 line of subsequent anticancer therapy. For patients who received subsequent therapy, anti–PD-1/PD-L1 agents were the first subsequent treatment for 11.3% of patients (23/204) in the pembro + axi arm and 54.8% of patients (154/281) in the sunitinib arm. In the pembro + axi arm, 82.8% of patients (169/204) received a VEGF/VEGFR inhibitor as first subsequent therapy, as did 43.4% (122/281) in the sunitinib arm. PFS2 results are displayed in the Table.

CONCLUSIONS: In this exploratory analysis, PFS2 was longer for patients randomized to pembro + axi compared to sunitinib. Results were consistent across IMDC risk groups. These data support use of pembro + axi for the first-line treatment of patients with advanced ccRCC. Clinical trial information: NCT02853331.

	ITT		IMDC favorable risk		IMDC intermediate/poor risk	
	Pembro + axi N = 432	Sunitinib N = 429	Pembro + axi n = 138	Sunitinib n = 131	Pembro + axi n = 294	Sunitinib n = 298
Received ≥1 line of subsequent anticancer therapy, n (%)	204 (47.2)	281 (65.5)	64 (46.4)	87 (66.4)	140 (47.6)	194 (65.1)
Median (95% CI) PFS2, mo	40.1 (34.9–43.8)	27.7 (23.1–29.9)	46.0 (43.8 to NR)	39.9 (33.5 to NR)	32.1 (27.9–39.3)	20.1 (15.9–25.1)
HR (95% CI)	0.63 (0.53–0.75)		0.68 (0.47–0.98)		0.62 (0.51–0.76)	

ABSTRACT 4514: Impact of subsequent therapies in patients (pts) with advanced renal cell carcinoma (aRCC) receiving lenvatinib plus pembrolizumab (LEN + PEMBRO) or sunitinib (SUN) in the CLEAR study. *Voss MH et al.*

BACKGROUND: In the open-label, randomized, phase 3 CLEAR study, LEN + PEMBRO had significant PFS (primary endpoint) and OS (key secondary endpoint) benefits over SUN among pts with aRCC in the 1L setting (Motzer 2021, NEJM). We evaluated PFS on next-line therapy ("PFS2") and explored the effect of subsequent anticancer therapy on OS in the LEN + PEMBRO and SUN treatment arms of CLEAR.

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

RESULTS: Among pts who received subsequent anticancer therapy in the LEN + PEMBRO (n=117 pts) and SUN (n=206 pts) arms (Table), median time to next-line therapy was 12.2 mos (range 1.45–37.36) and 6.4 mos (range 0.39–28.52), respectively. Median duration of first subsequent anticancer therapy was 5.2 mos (range 0.10–30.23) in the LEN + PEMBRO arm and 6.8 mos (range 0.03–30.72) in the SUN arm. Among all pts, PFS2 was longer with LEN + PEMBRO than with SUN (median not reached vs 28.7 mos; HR, 0.50; 95% CI 0.39–0.65; nominal P<0.0001); PFS2 rates at 24 and 36 mos are in the Table. The unadjusted OS HR for LEN + PEMBRO vs SUN (from the primary analysis [Motzer 2021, NEJM]) was 0.66 (95% CI 0.49–0.88); the HR for OS adjusted for subsequent therapy was 0.54 (bootstrap 95% CI 0.39–0.72).

CONCLUSION: LEN + PEMBRO had a statistically significant and clinically meaningful benefit over SUN in the CLEAR study. These findings remained consistent after accounting for subsequent therapies, as evidenced by prolonged PFS2 and adjusted OS. Results further support LEN + PEMBRO as a standard of care in 1L aRCC. Clinical trial information: NCT02811861.

Parameter	LEN + PEMBRO (n=355)	SUN (n=357)
Pts receiving any subsequent systemic anticancer therapy[a], n (%)	117 (33.0)	206 (57.7)
Anti-VEGF	108 (30.4)	120 (33.6)
PD-1/PD-L1 checkpoint inhibitor	29 (8.2)	154 (43.1)
MTOR Inhibitor	6 (1.7)	17 (4.8)
CTLA-4 Inhibitor	6 (1.7)	18 (5.0)
Other	12 (3.4)	20 (5.6)
PFS2, median (95% CI)	Not reached (NE–NE)	28.7 mos (23.0–NE)
PFS2 HR (95% CI)	0.50 (0.39–0.65)	
Nominal *P* value	<0.0001	
PFS2 rate at 24/36 mos, % (95% CI)	72.7 (67.3, 77.4) / 61.9 (53.7, 69.0)	54.2 (48.4, 59.6) / 42.9 (32.8, 52.5)

[a]Monotherapy or in combination. NE, not estimable.

ABSTRACT TPS4605 TiNivo-2: A phase 3, randomized, controlled, multicenter, open-label study to compare tivozanib in combination with nivolumab to tivozanib monotherapy in subjects with renal cell carcinoma who have progressed following one or two lines of therapy where one line has an immune checkpoint inhibitor. *Choueiri et al.*

BACKGROUND: Tivozanib, a highly selective and potent vascular endothelial growth factor receptor tyrosine kinase inhibitor, has demonstrated single-agent efficacy in advanced renal cell carcinoma (aRCC) along with minimal off-target toxicities and a favorable adverse event (AE) profile (Rini et al Lancet Oncol 2020). Tivozanib was approved by the FDA on March 10, 2021, for the treatment of patients with aRCC who had progressed on 2 or more prior systemic therapies. Tivozanib was combined with Nivolumab in the phase 1b/2 TiNivo trial (NCT03136627), showing an objective response rate of 56%, disease control rate of 96%, median PFS of 18.9 months and a tolerable safety profile (Albiges et al Ann Oncol. 2021).

METHODS: TiNivo-2 (NCT04987203) is a phase 3, randomized, controlled, multicenter, open-label study to compare tivozanib in combination with nivolumab to tivozanib monotherapy in subjects with renal cell carcinoma who have progressed following 1-2 lines of therapy including an immune checkpoint inhibitor. Eligibility criteria include age >18 years, clear cell RCC, ECOG PS 0-1, and disease progression during or following at least 6 weeks of treatment with ICI for RCC. Subjects will be stratified by IMDC risk category and whether ICI was received in most recent line of treatment or not. Subjects will receive tivozanib 1.34 mg orally once daily for 21 consecutive days followed by 7 days off, on the monotherapy arm, and tivozanib 0.89 mg at the same schedule in addition to nivolumab 480mg intravenously every 4 weeks on the combination arm. Study assessments include CT scan or MRI of the chest, abdomen, and pelvis every 8 weeks following Cycle 1 Day 1 for 2 years and every 12 weeks thereafter until disease progression is confirmed by independent radiology review (IRR). The primary objective is to compare the progression-free survival (PFS) of tivozanib in combination with nivolumab to tivozanib. A sample size of 326 subjects, with 191 events will provide at least 80% power to detect a 50% improvement in PFS, 12 mos v. 8 mos, as assessed by an IRR. Secondary endpoints include assessment of overall survival (OS), objective response rate (ORR), and duration of response (DoR), as well as safety and tolerability. Exploratory endpoints are to assess the quality of life (FKSI-DRS and EORTC QLQ C-30) and to investigate the pharmacokinetics of tivozanib. TiNivo-2 is actively enrolling and planning to open at 190 sites in the United States, and the European Union. Clinical trial information: NCT04987203.

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https://doi.org/10.52733/KCJ20n2-jc

Nivolumab, nivolumab-ipilimumab, and VEGFR-tyrosine kinase inhibitors as first-line treatment for metastatic clear-cell renal cell carcinoma (BIONIKK): a biomarker-driven, open-label, non-comparative, randomised, phase 2 trial. *Vano YA et al. Lancet Oncol. 2022 May;23(5):612-624. doi: 10.1016/S1470-2045(22)00128-0*

FINDINGS: Between June 28, 2017, and July 18, 2019, 303 patients were screened for eligibility, 202 of whom were randomly assigned to treatment (61 to nivolumab, 101 to nivolumab–ipilimumab, 40 to a VEGFR-TKI). In the nivolumab group, two patients were excluded due to a serious adverse event before the first study dose and one patient was excluded from analyses due to incorrect diagnosis. Median follow-up was 18·0 months (IQR 17·6–18·4). In the ccrcc1 group, objective responses were seen in 12 (29%; 95% CI 16–45) of 42 patients with nivolumab and 16 (39%; 24–55) of 41 patients with nivolumab–ipilimumab (odds ratio [OR] 0·63 [95% CI 0·25–1·56]). In the ccrcc4 group, objective responses were seen in seven (44%; 95% CI 20–70) of 16 patients with nivolumab and nine (50% 26–74) of 18 patients with nivolumab–ipilimumab (OR 0·78 [95% CI 0·20–3·01]). In the ccrcc2 group, objective responses were seen in 18 (50%; 95% CI 33–67) of 36 patients with a VEGFR-TKI and 19 (51%; 34–68) of 37 patients with nivolumab–ipilimumab (OR 0·95 [95% CI 0·38–2·37]). In the ccrcc3 group, no objective responses were seen in the four patients who received a VEGFR-TKI, and in one (20%; 95% CI 1–72) of five patients who received nivolumab–ipilimumab. The most common treatment-related grade 3–4 adverse events were hepatic failure and lipase increase (two [3%] of 58 for both) with nivolumab, lipase increase and hepatobiliary disorders (six [6%] of 101 for both) with nivolumab–ipilimumab, and hypertension (six [15%] of 40) with a VEGFR-TKI. Serious treatment-related adverse events occurred in two (3%) patients in the nivolumab group, 38 (38%) in the nivolumab–ipilimumab group, and ten (25%) patients in the VEGFR-TKI group. Three deaths were treatment-related: one due to fulminant hepatitis with nivolumab–ipilimumab, one death from heart failure with sunitinib, and one due to thrombotic microangiopathy with sunitinib.

Health-related quality-of-life outcomes in patients with advanced renal cell carcinoma treated with lenvatinib plus pembrolizumab or everolimus versus sunitinib (CLEAR): a randomised, phase 3 study. *Motzer R et al.* Lancet Oncol. 2022 Jun;23(6):768-780. doi: 10.1016/S1470-2045(22)00212-1.

FINDINGS: Between Oct 13, 2016, and July 24, 2019, 355 patients were randomly assigned to the lenvatinib plus pembrolizumab group, 357 to the lenvatinib plus everolimus group, and 357 to the sunitinib group. Median follow-up for HRQOL analyses was 12·9 months (IQR 5·6-22·3). Because of the promising efficacy and safety results of lenvatinib plus pembrolizumab in the first-line setting, we focus the HRQOL results in this report on that combination versus sunitinib. Mean change from baseline in the lenvatinib plus pembrolizumab group compared with the sunitinib group was -1·75 (SE 0·59) versus -2·19 (0·66) for FKSI-DRS, -5·93 (0·86) versus -6·73 (0·94) for EORTC QLQ-C30 global health status/quality of life (GHS/QOL), and -4·96 (0·85) versus -6·64 (0·94) for the EQ-5D visual analogue scale (VAS). Median time to first deterioration in the lenvatinib plus pembrolizumab group compared with the sunitinib group was 9·14 weeks (95% CI 6·43-12·14) versus 12·14 weeks (9·14-15·29; HR 1·13 [95% CI 0·94-1·35], log-rank p=0·20) for FKSI-DRS, 12·00 weeks (7·29-15·14) versus 9·14 weeks (6·29-12·14; 0·88 [0·74-1·05], log-rank p=0·17) for EORTC QLQ-C30 GHS/QOL, and 9·43 weeks (6·43-12·29) versus 9·14 weeks (6·29-12·00; 0·83 [0·70-0·99], log-rank p=0·041) for the EQ-5D VAS. Median time to definitive deterioration in the lenvatinib plus pembrolizumab group compared with the sunitinib group was 134·14 weeks (95% CI 120·00-not estimable) versus 117·43 weeks (90·14-131·29; HR 0·70 [95% CI 0·53-0·92], log-rank p=0·0081) for FKSI-DRS, 114·29 weeks (102·14-153·29) versus 75·14 weeks (57·29-105·14; 0·60 [0·47-0·77], log-rank p<0·0001) for EORTC QLQ-C30 GHS/QOL, and 124·86 weeks (94·71-134·57) versus 74·86 weeks (54·14-96·00; 0·67 [0·53-0·85], log-rank p=0·0012) for the EQ-5D VAS. No outcomes on any of the instruments significantly favoured sunitinib over lenvatinib plus pembrolizumab. Most HRQOL comparisons of lenvatinib plus everolimus versus sunitinib were similar or favoured sunitinib.

Efficacy and safety of avelumab plus axitinib in elderly patients with advanced renal cell carcinoma: extended follow-up results from JAVELIN Renal 101. *Tomita Y. ESMO Open . 2022 Apr;7(2):100450.*

RESULTS: In the avelumab plus axitinib and sunitinib arms, 271/138/33 and 275/128/41 patients aged <65, ≥65 to <75, and ≥75 years, respectively, were randomized. At data cut-off (January 2019), median PFS [95% confidence interval (CI)] with avelumab plus axitinib versus sunitinib in these respective age groups was 11.6 (8.4-19.4) versus 6.9 (5.6-8.4) months [hazard ratio (HR), 0.63; 95% CI 0.501-0.786], 13.8 (11.1-18.0) versus 11.0 (7.8-16.6) months (HR, 0.88; 95% CI 0.627-1.231), and 13.8 [7.0-not estimable (NE)] versus 9.8 (4.3-NE) months (HR, 0.76; 95% CI 0.378-1.511). Median OS (95% CI) in the respective age groups was not reached (NR) (NE-NE) versus 28.6 (25.5-NE) months (HR, 0.74; 95% CI 0.541-1.022), 30.0 (30.0-NE) versus NR (NE-NE) months (HR, 0.89; 95% CI 0.546-1.467), and 25.3 (19.9-NE) versus NR (19.4-NE) months (HR, 0.87; 95% CI 0.359-2.106). ORR (95% CI) in the respective age groups was 49.4% (43.3% to 55.6%) versus 27.3% (22.1% to 32.9%), 60.9% (52.2% to 69.1%) versus 28.9% (21.2% to 37.6%), and 42.4% (25.5% to 60.8%) versus 22.0% (10.6% to 37.6%). In the avelumab plus axitinib arm, grade ≥3 adverse events (AEs) and immune-related AEs occurred in 76.9%/81.2%/72.7% and 45.5%/48.1%/36.4% in the respective age groups.

CONCLUSIONS: First-line avelumab plus axitinib demonstrated favorable efficacy across age groups, including patients aged ≥75 years. OS data were still immature; follow-up is ongoing. The safety profile was generally consistent across age groups..

Bempegaldesleukin plus nivolumab in first-line renal cell carcinoma: results from the PIVOT-02 study.
Tannir NM, et al. J Immunother Cancer. 2022 Apr;10(4):e004419. doi: 10.1136/jitc-2021-004419.

RESULTS: At a median follow-up of 32.7 months, the ORR was 34.7% (17/49 patients); 3/49 patients (6.1%) had a complete response. Of the 17 patients with response, 14 remained in response for >6 months, and 6 remained in response for >24 months. Median PFS was 7.7 months (95% CI 3.8 to 13.9), and median OS was not reached (95% CI 37.3 to not reached). Ninety-eight per cent (48/49) of patients experienced ≥1 treatment-related adverse event (TRAE) and 38.8% (19/49) had grade 3/4 TRAEs, most commonly syncope (8.2%; 4/49) and increased lipase (6.1%; 3/49). No association between exploratory biomarkers and ORR was observed. Limitations include the small sample size and single-arm design.

CONCLUSIONS: BEMPEG plus NIVO showed preliminary antitumor activity as first-line therapy in patients with advanced clear-cell RCC and was well tolerated. These findings warrant further investigation.

A phase 1-2 trial of sitravatinib and nivolumab in clear cell renal cell carcinoma following progression on antiangiogenic therapy. *Msaouel P. Sci Transl Med. 2022 Apr 20;14(641):eabm6420.*

ABSTRACT: The accumulation of immune-suppressive myeloid cells is a critical determinant of resistance to anti-programmed death-1 (PD-1) therapy in advanced clear cell renal cell carcinoma (ccRCC). In preclinical models, the tyrosine kinase inhibitor sitravatinib enhanced responses to anti-PD-1 therapy by modulating immune-suppressive myeloid cells. We conducted a phase 1-2 trial to choose an optimal sitravatinib dose combined with a fixed dose of nivolumab in 42 immunotherapy-naïve patients with ccRCC refractory to prior antiangiogenic therapies. The combination demonstrated no unexpected toxicities and achieved an objective response rate of 35.7% and a median progression-free survival of 11.7 months, with 80.1% of patients alive after a median follow-up of 18.7 months. Baseline peripheral blood neutrophil-to-lymphocyte ratio correlated with response to sitravatinib and nivolumab. Patients with liver metastases showed durable responses comparable to patients without liver metastases. In addition, correlative studies demonstrated reduction of immune-suppressive myeloid cells in the periphery and tumor microenvironment following sitravatinib treatment. This study provides a rationally designed combinatorial strategy to improve outcomes of anti-PD-1 therapy in advanced ccRCC.

Results from the INMUNOSUN-SOGUG trial: a prospective phase II study of sunitinib as a second-line therapy in patients with metastatic renal cell carcinoma after immune checkpoint-based combination therapy. *Grande E, ESMO Open. 2022 Apr;7(2):100463.*

RESULTS: Twenty-one assessable patients were included in the efficacy and safety analyses. Four patients [19.0%, 95% confidence interval (CI) 2.3% to 35.8%] showed an objective response (OR), and all of them had partial responses. Additionally, 14 (67%) patients showed a stable response, leading to clinical benefit in 18 patients (85.7%, 95% CI 70.7% to 100%). Among the four assessable patients who showed an OR, the median duration of the response was 7.1 months (interquartile range 4.2-12.0 months). The median progression-free survival (PFS) was 5.6 months (95% CI 3.1-8.0 months). The median overall survival (OS) was 23.5 months (95% CI 6.3-40.7 months). Patients who had better antitumor response to first-line ICI-based treatment showed a longer PFS and OS with sunitinib. The most frequent treatment-emergent adverse events were diarrhea (n = 11, 52%), dysgeusia (n = 8, 38%), palmar-plantar erythrodysesthesia (n = 8, 38%), and hypertension (n = 8, 38%). There was 1 patient who exhibited grade 5 pancytopenia, and 11 patients experienced grade 3 adverse events. Eight (38%) patients had serious adverse events, four of which were considered to be related to sunitinib.
CONCLUSION: Although the INMUNOSUN trial did not reach the pre-specified endpoint, it demonstrated that sunitinib is active and can be safely used as a second-line option in patients with mRCC who progress to new standard ICI-based regimens.

Telaglenastat Plus Cabozantinib or Everolimus for Advanced or Metastatic Renal Cell Carcinoma: An Open-Label Phase I Trial. *Meric-Bernstam F, et al.* Clin Cancer Res. 2022 Apr 14;28(8):1540-1548. doi: 10.1158/1078-0432.CCR-21-2972.

RESULTS: Twenty-seven patients received TelaE, 13 received TelaC, with median 2 and 3 prior therapies, respectively. Treatment-related adverse events were mostly grades 1 to 2, most common including decreased appetite, anemia, elevated transaminases, and diarrhea with TelaE, and diarrhea, decreased appetite, elevated transaminases, and fatigue with TelaC. One dose-limiting toxicity occurred per cohort: grade 3 pruritic rash with TelaE and thrombocytopenia with TelaC. No maximum tolerated dose (MTD) was reached for either combination, leading to a recommended phase II dose of 800-mg telaglenastat twice daily with standard doses of E or C. TelaE disease control rate (DCR; response rate + stable disease) was 95.2% [20/21, including 1 partial response (PR)] among 21 patients with clear cell histology and 66.7% (2/3) for papillary. TelaC DCR was 100% (12/12) for both histologies [5/10 PRs as best response (3 confirmed) in clear cell].
CONCLUSIONS: TelaE and TelaC showed encouraging clinical activity and tolerability in heavily pretreated mRCC patients.

Safety and efficacy of nivolumab plus ipilimumab in patients with advanced non-clear cell renal cell carcinoma: results from the phase 3b/4 CheckMate 920 trial. *Tykodi SS. J Immunother Cancer. 2022 Feb;10(2):e003844.*

RESULTS: Fifty-two patients with nccRCC (unclassified histology, 42.3%; papillary, 34.6%; chromophobe, 13.5%; translocation-associated, 3.8%; collecting duct, 3.8%; renal medullary, 1.9%) received treatment. With 24.1 months minimum study follow-up, median duration of therapy (range) was 3.5 (0.0-25.8) months for nivolumab and 2.1 (0.0-3.9) months for ipilimumab. Median (range) number of doses received was 4.5 (1-28) for nivolumab and 4.0 (1-4) for ipilimumab. Grade 3-4 immune-mediated AEs were diarrhea/colitis (7.7%), rash (5.8%), nephritis and renal dysfunction (3.8%), hepatitis (1.9%), adrenal insufficiency (1.9%), and hypophysitis (1.9%). No grade 5 immune-mediated AEs occurred. ORR (n=46) was 19.6% (95% CI 9.4 to 33.9). Two patients achieved complete response (papillary, n=1; unclassified, n=1), seven achieved partial response (papillary, n=4; unclassified, n=3), and 17 had stable disease. Median TTR was 2.8 (range 2.1-14.8) months. Median DOR was not reached (range 0.0+-27.8+); eight of nine responders remain without reported progression. Median PFS (n=52) was 3.7 (95% CI 2.7 to 4.6) months. Median OS (n=52) was 21.2 (95% CI 16.6 to not estimable) months.
CONCLUSIONS: Nivolumab plus ipilimumab for previously untreated advanced nccRCC showed no new safety signals and encouraging antitumor activity.

Baseline circulating unswitched memory B cells and B-cell related soluble factors are associated with overall survival in patients with clear cell renal cell carcinoma treated with nivolumab within the NIVOREN GETUG-AFU 26 study. *J Immunother Cancer. 2022 May;10(5):e004885. doi: 10.1136/jitc-2022-004885.PMID: 35640928*

RESULTS: Among the 44 patients, baseline unswitched memory B cells (NSwM B cells) were enriched in responders (p=0.006) and associated with improved OS (HR=0.08, p=0.002) and PFS (HR=0.54, p=0.048). Responders were enriched in circulating T follicular helper (Tfh) (p=0.027) and tertiary lymphoid structures (TLS) (p=0.043). Circulating NSwM B cells positively correlated with Tfh (r=0.70, p<0.001). Circulating NSwM B cells correlated positively with TLS and CD20 +B cells at the tumor center (r=0.59, p=0.044, and r=0.52, p=0.033) and inversely correlated with BCA-1/CXCL13 and BAFF (r=-0.55 and r=-0.42, p<0.001). Tfh cells also inversely correlated with BCA-1/CXCL13 (r=-0.61, p<0.001). IL-6, BCA-1/CXCL13 and BAFF significantly associated with worse OS in the discovery (n=40) and validation cohorts (n=313).
CONCLUSION: We report the first fresh blood immune-monitoring of patients with m-ccRCC treated with nivolumab. Baseline blood concentration of NSwM B cells was associated to response, PFS and OS in patients with m-ccRCC treated with nivolumab. BCA-1/CXCL13 and BAFF, inversely correlated to NSwM B cells, were both associated with worse OS in discovery and validation cohorts. Our data confirms a role for B cell subsets in the response to immune checkpoint blockade therapy in patients with m-ccRCC. Further studies are needed to confirm these findings.

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