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Kidney Cancer Journal ROUNDTABLE

Recent Advances in Tivozanib plus Nivolumab Combinatorial Strategies in Renal Cell Carcinoma

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Recent Advances in Tivozanib plus Nivolumab Combinatorial Strategies in Advanced Renal Cell Carcinoma

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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 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

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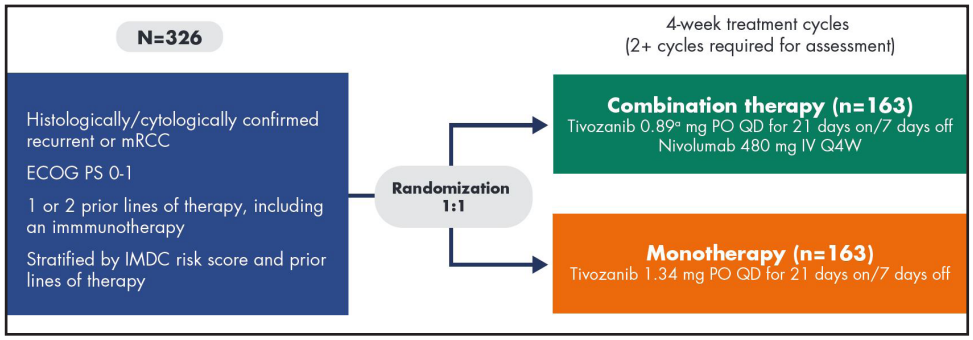

Figure 1 | Study design of TiNivo-2 trial. *ECOG PS, Eastern Cooperative Oncology Group performance status; IMDC, International Metastatic RCC Database Consortium; IV, intravenous; mRCC, metastatic renal cell carcinoma; PO, orally; Q4W, every 4 weeks; QD, once daily.*

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 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,

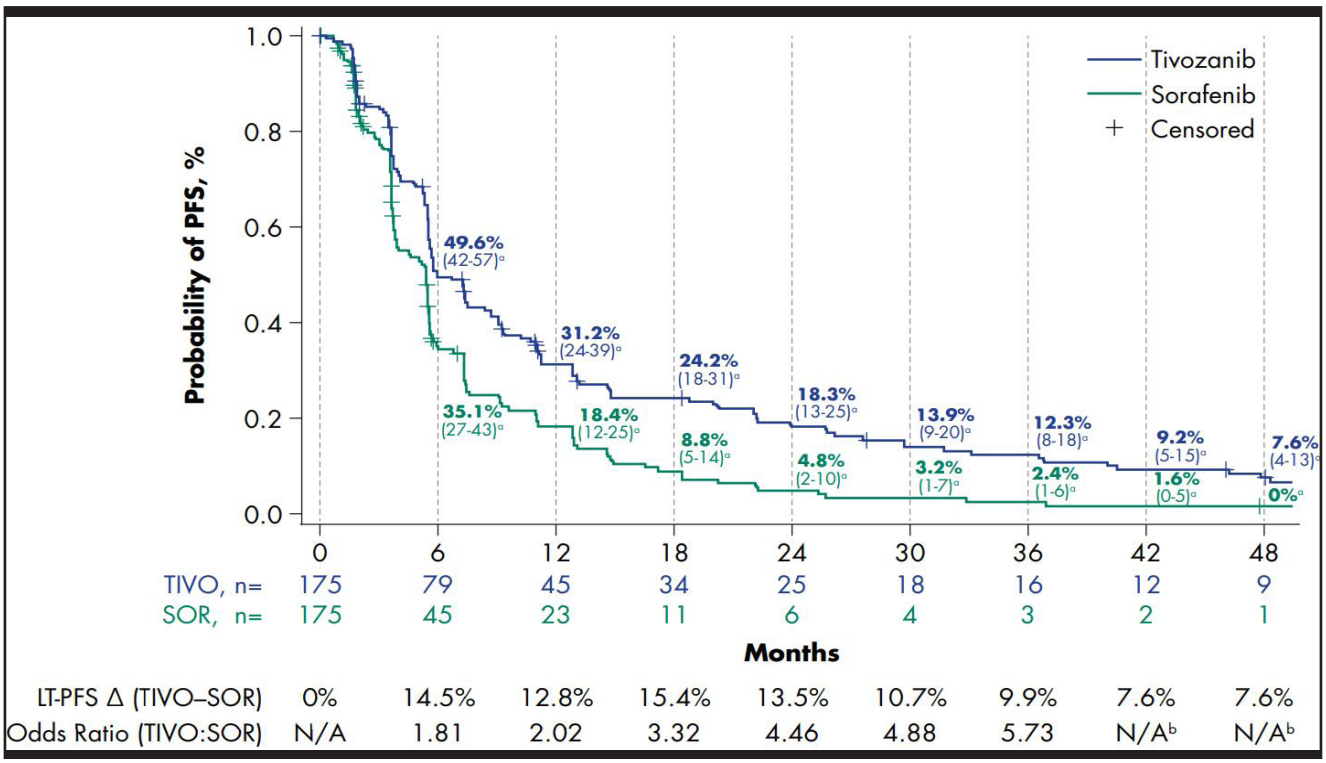

Figure 2 | Landmark Rates (95% CI) of LT-PFS in TIVO-3: TIVO vs SOR. a% (95% CI). bOR not calculated at months 42 and 48 due to insufficient number at risk. HR: 0.624 (95% CI: 0.49–0.79); log-rank P<.0001

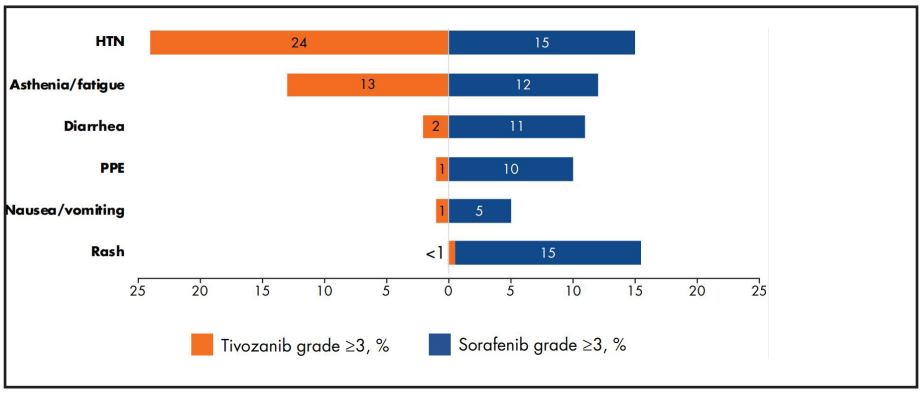

Figure 3 | Incidence of VEGFR TKI Class Effect Grade ≥3 TEAEs. *HTN, hypertension; PPE, palmar-plantar erythrodysesthesia.*

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?

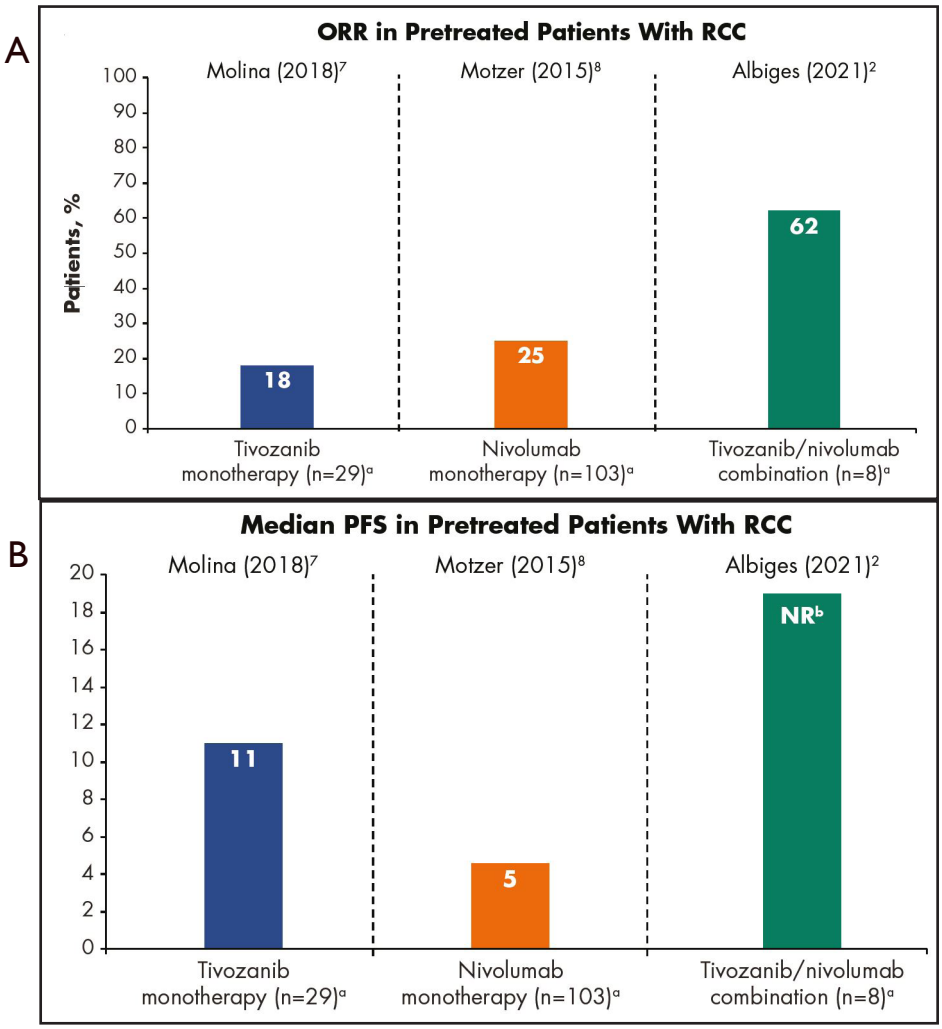

Figure 4. Antitumor Activity in Pretreated Patients from different studies.[6, 11, 12] **(A)** ORR was higher with tivozanib/nivolumab combination therapy than with either ingle agent alone; **(B)** PFS was longer with tivozanib/nivolumab combination therapy than with either monotherapy alone

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 (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.

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.

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)

(A) Anti-tumor activity seen in both treatment naive and previously treated RCC patients.[11, 12] **(B) Table 1.** 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:
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. In 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 wel-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

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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.

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ONLINE CONTENT
Full online contents with additional information will be available at https://kidney-cancer-journal.com/KCJ2on2-rt.php

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