Editor’s Memo

One of the phrases integrated into our lexicon over the last several years suggests that immunotherapy (IO) has become the “fifth pillar” of cancer therapy—enhancing the first four of surgery, chemotherapy, radiotherapy, and targeted therapy. If IO is the fifth pillar in that regard, then in the treatment of renal cell carcinoma (RCC), it is now the cornerstone as new regimens vie for the frontline space in metastatic RCC.

While the field of IO has advanced significantly, supported by pivotal trials like JAVELIN Renal 101, Check-Mate-214, and KEYNOTE-426, much more knowledge is needed to achieve a future where the potential benefit of these therapies can be maximized for the greatest number of patients. Key questions remain about how to select those patients who are most likely to respond to IO therapy, how to combine IO therapies with one another and with other treatment modalities, how to predict, limit, and mitigate IO treatment related toxicities, how to reduce resistance to IO therapies, how to use these therapies in newly defined standards of care and when to stop treatment. Some of these questions are addressed in this issue’s Round Table discussion with three experts whose knowledge of the pivotal IO studies offers key perspectives on the IO-TKI combinations promoted as part of the standard of care.

As much as the IO combinations have filled the treatment space, there is another narrative ongoing that also should capture our attention, although it may not serve as a focus as much as the clinical story.

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Kidney Cancer Journal Author Guidelines

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

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

Manuscript Submission
Authors are required to submit their manuscripts in an electronic format, preferably by email to the Editor-in-Chief, Robert A. Figlin, MD, at robert.figlin@cshs.org. Please provide in a word processing program. Images should be submitted electronically as well.

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

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

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

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

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

References
All submissions should have references that are referred to in the text by superscripted numbers and that conform to AMA style.

Example:

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**Summary:** Results are based on a prospectively maintained database for patients who underwent CN for nccRCC between 1989 and 2018. Histology was reviewed by an expert genitourinary pathologist, and nccRCC tumors were subdivided into papillary, unclassified, chromophobe, and other histology. Baseline clinicopathology, treatments, and survival outcomes were recorded. Preoperative hematological parameters including the neutrophil-to-lymphocyte ratio (NLR) were analyzed. Significant univariate predictors of OS were tested in a multivariate model. There were 100 nccRCC patients treated with CN. Median age was 61 years and 65% were male. There were 79 patient deaths with a median OS of 13.7 months (10.8-27.2). Estimated 2- and 5-year survival was 40.1% and 12.2%, respectively. Median follow-up of survivors was 13 months. On multivariate analysis, increasing NLR (hazard ratio [HR] 1.27; 95% confidence interval [CI] 1.14-1.40, P < 0.001) and sarcomatoid features (HR 2.18; 95% CI 1.19-3.97, P = 0.014) conferred worse OS and the presence of papillary features were a favorable prognostic feature (HR 0.37; 95% CI 0.21-0.65, P < 0.001).

**Conclusion:** OS outcomes in patients with nccRCC who underwent a CN were consistently modest throughout the study period. Patients with papillary features and a lower preoperative NLR may be better candidates for a CN.


**Summary:** Anti-PD1 therapy has the potential to cause immune-related adverse events (irAEs), which can be treated with corticosteroids if severe. The clinical implications of concomitant immunotherapy and systemic steroids remain unclear, as short courses of steroids do not significantly suppress T-cell function. The primary objective of this study is to determine if the use of concomitant steroids impacts the efficacy of anti-PD1 therapy. This retrospective, single-center study reviewed adult patients who received at least four cycles of nivolumab or pembrolizumab for the treatment of melanoma, non-small cell lung cancer (NSCLC), or renal cell carcinoma from November 2014 to February 2016. Patients who received steroids (prednisone equivalent >10mg) during anti-PD1 therapy were divided into two main cohorts based on the duration of steroid administration of ≤2 weeks or >2 weeks. Time to disease progression, overall response, and overall survival were assessed. Twenty-seven of 55 patients (13 melanoma, 11 NSCLC, 3 renal cell carcinoma) required steroids during anti-PD1 therapy. In patients who received steroids, median time to disease progression was 5.6 months for melanoma, 5.8 for NSCLC, and 2.0 for renal cell carcinoma. The overall response rate (ORR) was 3/13 (23%) for melanoma, 6/11 (54%) for NSCLC, and 1/3 (33%) for renal cell carcinoma. Median overall survival was 11.9 months for melanoma, 9.9 for NSCLC, and not reached for renal cell carcinoma. Thirteen patients who had received steroids expired; 11 of these patients had received prednisone >10mg/day for >2 weeks.

**Conclusion:** High-dose steroids for long durations during anti-PD1 therapy may be associated with poorer survival outcomes.


**Summary:** The use of VEGFR TKIs for the adjuvant treatment of renal cell carcinoma (RCC) remains controversial. This study investigated the effects of adjuvant VEGFR TKIs on circulating cytokines in the ECOG-ACRIN 2805 (ASSURE) trial. Patients with resected high-risk RCC were randomized to sunitinib, sorafenib, or placebo. Plasma from 413 patients was analyzed from post-nephrectomy baseline, 4 weeks, and 6 weeks after treatment initiation. Mixed effects and Cox proportional hazards models were used to test for changes in circulating cytokines and associations between disease-free survival (DFS) and cytokine levels. VEGF and PIGF increased after 4 weeks on sunitinib or sorafenib (P < 0.0001 for both) and returned to baseline at 6 weeks on sunitinib (corresponding to the break in the sunitinib schedule) but not sorafenib (which was administered continuously). sFLT-1 decreased after 4 weeks on sunitinib and 6 weeks on sorafenib (P < 0.0001). sVEGFR-2 decreased after both 4 and 6 weeks of treatment on sunitinib or sorafenib (P < 0.0001). Patients receiving placebo had no significant changes in cytokine levels. CXCL10 was elevated at 4 and 6 weeks on sunitinib and sorafenib but not on (continued on page 86)
CANTATA

An investigational first-in-clinic glutaminase inhibitor, telaglenastat (CB-839), in a phase 2 trial in combination with cabozantinib in renal cell carcinoma (RCC)

Key inclusion criteria

- Documented histological or cytological diagnosis of RCC with a clear cell component
- Karnofsky Performance Score (KPS) ≥ 70%
- Measurable disease per RECIST 1.1

1-2 lines of prior therapy for advanced or metastatic clear cell RCC, including at least 1 anti-angiogenic therapy or nivolumab + ipilimumab

Randomization

- CB-839 + cabozantinib
- Placebo + cabozantinib

Primary endpoint
Progression-free survival

Key exclusion criteria

- Prior treatment with cabozantinib (or other Met inhibitor) or CB-839
- Untreated or active brain metastases or central nervous system cancer, as defined per protocol
- Prior gastric surgery, small bowel resection, or other conditions that may impede adequate absorption of oral study drug
- Major surgery within 6 weeks prior to randomization
- Uncontrolled hypertension

For more details about CB-839 clinical trials or to refer patients:

Call: 1-650-870-1028
Visit: www.calithera.com/clinical-trials
Email: clinicaltrials@calithera.com

CB-839 is an investigational product and is not approved in the United States or any other country.

Calithera Biosciences—Our onco-metabolism approach brings an enhanced perspective to cancer.

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Positive Topline Results Achieved in Randomized Phase 2 ENTRATA Study of Telaglenastat with Everolimus in RCC

- Doubled median progression-free survival (PFS) in heavily pre-treated patients with advanced renal cell carcinoma
- Provides first clinical proof of concept for glutaminase inhibitor telaglenastat

SOUTH SAN FRANCISCO, CA—Calithera Biosciences has achieved positive results from its randomized placebo-controlled Phase 2 ENTRATA study of telaglenastat (CB-839) in combination with everolimus in patients with advanced RCC. The combination doubled the median progression-free survival (PFS) in heavily pre-treated patients with advanced RCC and had a well-tolerated safety profile. Telaglenastat is the first glutaminase inhibitor to demonstrate clinical activity for the treatment of cancer.

“The achievement of positive topline results in our first randomized trial is a significant milestone because it provides clinical proof of concept for telaglenastat,” said Susan Molineaux, PhD, president and chief executive officer of Calithera. “This study demonstrates a clinically meaningful improvement in progression free survival in patients with advanced renal cell carcinoma who have been treated with many prior lines of therapy, including immunotherapy and multiple tyrosine kinase inhibitors.”

Patients enrolled were heavily pre-treated with a median of three prior lines of therapy for advanced metastatic disease including 70% with two or more prior tyrosine kinase inhibitors (TKI), and 68% with intermediate/poor MSKCC prognostic score. Eighty-eight percent of patients received prior PD-1/PD-L1 therapy. Telaglenastat, when added to everolimus, doubled the median PFS to 3.8 months as compared to 1.9 months for everolimus alone and reduced the risk of disease progression or death by 36% (HR=0.64, P=0.079 one-sided). The primary endpoint of the trial was PFS per investigator assessment with a predetermined threshold of P≤0.2 one-sided. The secondary endpoint of overall survival is not yet mature.

Frequency of all-grade adverse events in the telaglenastat-containing arm were comparable to that of everolimus alone. Grade 3 or higher adverse events occurred in 80.4% of patients in the telaglenastat plus everolimus arm versus 60.9% in the everolimus plus placebo arm. The most frequently reported Grade ≥3 adverse events in the treatment versus control arms, respectively, were anemia (17.4% vs. 17.4%), pneumonia (6.5% vs. 4.3%), abdominal pain (6.5% vs. 0%), thrombocytopenia (6.5% vs. 0%), and fatigue (4.3% vs. 8.7%). Adverse events leading to discontinuation of any study drug were comparable (28.3% vs. 30.4%).

The ENTRATA trial (NCT03163667) is a randomized, double-blind Phase 2 trial designed to evaluate the efficacy and safety of telaglenastat in combination with everolimus versus placebo with everolimus in patients with advanced clear cell RCC who have been treated with at least two prior lines of systemic therapy, including at least one VEGFR-targeted TKI. Patients were stratified by prior TKI treatment and MSKCC prognostic score. The trial enrolled 69 patients at multiple centers in the United States. Calithera intends to present data at an upcoming medical meeting. Telaglenastat is an investigational, novel glutaminase inhibitor specifically designed to block glutamine consumption in tumor cells. RCC tumors commonly exhibit specific genetic alterations that cause cancer cells to increase metabolism of glutamine. In preclinical studies, telaglenastat produced synergistic antitumor effects when used in combination with standard-of-care RCC therapies, including everolimus and cabozantinib.

Telaglenastat is also being investigated in the CANTATA trial, a global, randomized, double-blind Phase 2 trial designed to evaluate the efficacy and safety of telaglenastat in combination with cabozantinib versus placebo with cabozantinib in patients with advanced clear cell RCC who have been treated with one or two prior lines of systemic therapy. CANTATA will enroll approximately 400 patients and is designed with registrational intent. The primary endpoint is PFS by blinded independent review. Calithera expects data from this trial in the second half of 2020.

International Kidney Cancer Symposium Scheduled for November 15-16

MIAMI—The 18th International Kidney Cancer Symposium, featuring the most comprehensive agenda and program focused on renal cell carcinoma, will be held November 15-16 at the Trump National Doral Miami Hotel. Researchers and medical staff from leading centers worldwide will gather for an exchange of ideas and information that will frame future research and treatment of RCC.

Registration and full details on the agenda is available online through the Association’s website, kidneycancer.org.

Updated Overall Survival Hazard Ratio of 0.99 Reported in Phase 3 TIVO-3 Trial of Tivozanib in Renal Cell Carcinoma

CAMBRIDGE, MA—AVEO Oncology has announced results from the second prespecified analysis of overall survival (OS) in the TIVO-3 trial. TIVO-3 is the Company’s Phase 3 randomized, controlled, multi-center, open-label study to compare tivozanib (FOTIVDA®) to sorafenib in 350 subjects with highly refractory metastatic renal cell carcinoma (RCC). These results include an OS hazard ratio (HR) below 1.00, favoring tivozanib (HR=0.99; 95% CI: 0.76-1.29; P=0.95). TIVO-3 is the first and only positive Phase 3 study in third and fourth line RCC, and the first Phase 3 study in RCC to investigate a predefined subpopulation of patients who received prior immunotherapy, an emerging standard

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Inaugural RCC ‘Think Tank’ Could Refocus Kidney Cancer Research

The Kidney Cancer Association (KCA) is launching “Think Tank: Coalition for a Cure” at this year’s International Kidney Cancer Symposium (IKCS). This first-of-its-kind event will be a unique opportunity for the experts and advocates who gather from across the globe to learn from one another and discuss the complexities of renal cell carcinoma (RCC).

Two of the KCA’s Medical Steering Committee members, Bradley Leibovich, MD, and Brian I. Rini, MD, will moderate the Think Tank, which takes place on November 14, the evening before the IKCS begins.

Key goals for the discussion include:

• Identification of the most current and important questions regarding advances and new approaches that could potentially change the treatments and outcomes for current RCC patients.
• Identification of the greatest unmet needs in kidney cancer research to help all within the RCC space eliminate overlaps in funding efforts.

Participants represent prominent experts from a range of RCC-related (and unrelated) disciplines including clinical, computational sciences, patient advocacy, pharmaceutical research and development, cancer research, and genetics. They will share their knowledge, ideas, and vision about the realities and possibilities of the next big breakthroughs in kidney cancer care and research.

The KCA has consistently brought important stakeholders together to share information about kidney cancer, define goals, and set the research agenda for the field through collaborative discussions like the IKCS as well as the 2011 Kidney Cancer Research Summit: a Symposium for Young Investigators. Think Tank participants were notified several months in advance of the meeting and provided with questions to create a framework for guiding the conversation and initiating momentum for the exercise.

“By coming together, we envision a purposeful IKCS experience,” said Christopher Wood, MD, Chair of the KCA’s Board of Directors. “We are committed to making a substantive impact in the lives of patients with kidney cancer and look forward to seeing the groundbreaking proposals for the YIA and ADA each year.”

Kidney Cancer Association Announces Recipients of $1.3 Million in Research Grants

Earlier this year, the Kidney Cancer Association (KCA) announced a meaningful increase in funding of their Young Investigator Award, alongside the news of a new grant opportunity, the Advanced Discovery Award (ADA). Following an in-depth application and review process, the KCA is pleased to reveal the recipients of these grants.

“The KCA was delighted by the high caliber of proposals received for both awards and are hopeful that this research will advance the medical community’s understanding of kidney cancer,” said Christopher Wood, MD, Chair of the KCA’s Board of Directors. “We are committed to making a substantive impact in the lives of patients with kidney cancer and look forward to seeing the groundbreaking proposals for the YIA and ADA each year.”

The YIA seeks to encourage promising researchers in urology and clinical oncology who are planning to pursue an investigative career in kidney cancer. The ADA is structured to promote collaboration between a clinician including a urologic oncologist, medical oncologist or radiation oncologist and a Ph.D. to propose new research that will make an immediate impact in the field of kidney cancer.

This year, two $500,000 ADA grants were awarded in the ADAs, while YIA funding increased from two grants worth $50,000 to four grants worth $75,000.

“It is exciting that we are simultaneously announcing our YIA recipients, a program which has long been a part of the KCA’s efforts, while at the same time introducing our inaugural class of ADA recipients,” said Gretchen Vaughan, CEO of the KCA. “We are proud of all our recipients and eager to see where their research may lead in our mission to conquer kidney cancer.”

Advanced Discovery Award (ADA) Recipients:

Research Team:
Kathleen M. Mahoney, MD, PhD - Dana-Farber Cancer Institute
Brenton Israel-Caldeon Medical Center
Gordon J. Freeman, PhD - Dana-Farber Cancer Institute
Rupal S. Bhatt, MD, PhD - Beth Israel-Deaconess Medical Center

HHLA2/KIR3DL3 as a novel therapeutic immune checkpoint pathway in renal cancer

This research team will explore a novel immune checkpoint pathway that is similar to, but non-overlapping with, the PD-1/PD-L1 pathway, which has been the key driver of advances in immunotherapy that led to much improved outcomes for many

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A consistent theme emerging from recent studies across tumor types is that a fraction of patients will potentially benefit from treatment beyond progression in terms of tumor shrinkage as well as overall survival advantage suggested by the hazard ratios from Kaplan Meier analysis. New guidelines for patient assessment after first progression are evolving as the concept of pseudoprogression underscores the pitfalls in relying on RECIST criteria alone. Careful consideration by treating physicians after informed consent to continue beyond progression is the appropriate strategy and is supported by mounting evidence in the literature. This review highlights the translational impact of pivotal studies such as CheckMate 025 and other evidence from pooled and subgroup analyses.

A dramatic shift in the treatment paradigm for renal cell carcinoma (RCC), characterized by the introduction of newer agents such as immune checkpoint inhibitors, has ushered in new thinking on the management of the disease. These newer agents such as nivolumab for the treatment of advanced RCC in patients who have received prior antiangiogenic therapy provide a unique mechanism of action as opposed to many of the traditional targeted therapies for mRCC. Although the era of targeted therapy resulted in significant improvements in objective response rate and progression-free survival (PFS), the limitations of such strategies soon became apparent because the majority of patients eventually experience treatment resistance and disease progression. As a result, the focus turned toward the need for novel treatment options and within the last 5 years, immune checkpoint inhibitors have shown durable responses and have improved OS for a broad range of patients.

The wider use of immune checkpoint inhibitors has dramatically reshaped the debate—not only on how such therapies can more effectively be applied but on the need to address many questions and uncertainties, including the criteria used to measure response and the duration of therapy needed to optimize outcomes. As part of this review, we will focus on these issues, including the extent to which standard criteria, such as the Response Evaluation Criteria in Solid Tumors (RECIST) still need to be adhered to or reexamined in the light of emerging data suggesting whether RECIST-defined first progression after immunotherapy is a valid endpoint for determining whether such treatment needs to be discontinued. And if RECIST-defined first progression is accepted as a compelling argument for discontinuing immune checkpoint therapy, would many patients have benefited from treatment beyond progression (TBP)? Although there is compelling evidence in recent literature clearly favoring TBP, there is still controversy over the practice that is becoming the standard of care. A review of the literature, including recommendations from the FDA on this question, will help put these issues in context.

In its mechanism of action, nivolumab, for example, offers a useful guide to understanding the rationale for using checkpoint inhibitors. This agent is a fully human IgG4 programmed cell death 1 PD-1) immune checkpoint inhibitor antibody that selectively blocks the interaction between PD-1 and its ligands PD-L1 and PD-L2. This interaction is the mechanism that normally leads to immune tolerance. We have abundant data supporting the use of nivolumab vs antiangiogenic therapy. In the CheckMate 025 trial, evaluating 821 patients with mRCC who had received earlier treatment with antiangiogenic regimens, the use of nivolumab produced a significant survival advantage over everolimus (25 vs 19.6 months) and this checkpoint inhibitor also had a more favorable side effect profile.

Treatment with immunomodulatory agents such as nivolumab has been controversial because of the issue of “tumor flare” (Figure 1). This phenomenon, also referred to as pseudoprogression, refers to what appears to be an increase in tumor burden or the appearance of new lesions that may be observed prior to a clinical response in patients receiving immunotherapy. The cause of tumor flare is thought to be caused by transient immune cell infiltration into the tumor or continued tumor growth that can occur while the immune system is priming for an antitumor response, according to Wolchok et al. The key concept in understanding the phenomenon has been suggested by other authors: namely, the time required to achieve an effective immune response...
MIAMI

Eighteenth International Kidney Cancer Symposium

November 15-16, 2019
Trump National Doral Miami Hotel, Miami, Florida

KidneyCancer.org
www.kidneycancersymposium.com

For more information about the Kidney Cancer Association and about the Eighteenth International Kidney Cancer Symposium in Miami go to:
www.kidneycancer.org       www.kidneycancersymposium.com
Figure 1. Potential Mechanism for Tumor Flare Associated With Immunotherapy.

may be longer than what is typically seen for response times when targeted therapies are used in RCC.2

Revisiting the RECIST Criteria

The standard for evaluating response has been the RECIST criteria. In early 2017, the RECIST working group developed a guideline of a modified RECIST 1.1 for immune-based therapeutics.7 Patterns of response based on RECIST criteria include complete response (total remission of all target and non-target lesions, including the lack of appearance of new lesions; to be confirmed no less than 4 weeks after the first assessment); partial response (a decrease of at least 30% in the total tumor burden compared to baseline; to be confirmed after at least 4 weeks); stable disease (the change of the total tumor burden is reduced of less than 30% when compared with baseline or increased less than 20% compared to baseline or nadir); unconfirmed progressive disease (increase in the total tumor burden of at least 20% compared to nadir/ baseline; further confirmation at imaging is needed to rule out PP); progressive disease (increase in the total tumor burden of at least 20% when compared to nadir confirmed by a further progression after 4–8 weeks or appearance of new lesion).8

As new reports present emerging data on TBP, the RECIST criteria have become the center of controversy as to whether they should be followed for treatment guidelines. When treatment response to immunotherapy is assessed by these criteria, tumor flare occurring with an agent like nivolumab will be viewed as disease progression. When it is considered as progression, discontinuation of treatment before the potential clinical benefit of a check point inhibition is realized will yield diminishing results. Thus, it is important to determine whether patients receiving immunotherapy may still realize benefit if treated beyond RECIST-defined progression.

Evidence for the appearance of pseudoprogression has been documented in immunotherapy studies in which treatment is associated with an initial tumor flare but reduced tumor burden and shrinkage have been reported later. When nivolumab therapy was used in melanoma and non-small-lung cancer trials a subgroup of patients treated beyond first progression showed an uncommon pattern of benefit relative to another group not treated beyond first progression.9–11

Pivotal Trials Verifying TBP

Several analyses, including results from Phase 2 and 3 trials and subgroup data, are providing a more accurate picture of clinical benefit derived from TBP. In a study by George et al,12 the authors presented a subgroup analysis of a blinded, randomized, multicenter, phase 2 trial to further delineate the potential for reduction in tumor burden after RECIST-defined first progression (Figure 2). This subgroup analysis continued the line of investigation in the initial assessment when some patients had sustained reductions or stabilization in the size of their target lesions.13 The analysis is important for several reasons: 1) it further elucidates the hypothesis that immunologic treatment may induce infiltration of immune cells and inflammation of the tumor, thereby increasing tumor size as measured objectively by imaging; (2) the transient growth of tumor during this time may result in a decrease in RECIST-defined PFS but not necessarily OS; and (3) it calls attention to the hypothesis that RECIST-defined progression may not necessarily be a marker for biologic disease progression, at least during this initial phase. This leads to proposed immune-related response criteria (irRC) that could be used to better characterize patterns of response observed with immunotherapies.6

In the subgroup analysis by George et al, 154 of 168 patients were randomized to nivolumab in the Checkmate-010 trial; 36 were treated beyond progression, 26 were treated beyond first progression for 6 weeks or less, and 92 were not treated beyond first progression.12 Of the 36 treated beyond first progression, 25 demonstrated reductions in tumor burden or stabilization in the size of target lesions after first progression. Thus, the analysis offers compelling evidence that sustained reductions in tumor burden or stabilization in the size of target lesions can be achieved if nivolumab treatment is continued after initial disease progression in mRCC is observed.

CheckMate 025 Confirms Value of TBP

If one were looking for Phase 3 results to further delineate the value of TBP then CheckMate 025 provides significant data from a large pivotal study. From this landmark study by Escudier et al,14 a subgroup analysis addressed similar questions on treatment in 406 nivolumab-treated patients, 316 of whom had progressed by RECIST criteria. Treatment beyond progression was defined as treatment for at least 4 weeks after first progression. The key “take-away” messages from CheckMate 025 are:

- Patient TBP with nivolumab had additional clinical
antibody group in the comparative trial. Furthermore, the number of patients with a delayed response during treatment beyond progression with anti-PD-1 antibodies was apparently low relative to the total population in the pooled analysis.

However, does this mean the FDA definitely recommends that TBP should unequivocally be followed as a policy? Not necessarily. The report acknowledges that the risks of continued treatment beyond progression should be balanced with the small potential of a subsequent reduction in tumor burden or prolonged disease stability. It notes that further evaluation is needed to identify patients who might benefit from continued treatment with the inclusion of various biomarkers and other criteria.

What remains to be considered, however, are significant differences between the FDA-sponsored report and results from Escudier et al which put the interpretation of the FDA findings into doubt. The FDA analysis excluded patients who responded to treatment and then progressed and excluded patients with nontarget expression even if there was a reduction in target lesions (based on personal communication with author Bernard Escudier). In a similar vein, the data from Escudier are based on all patients who were treated beyond progression. Thus, these data are more inclusive and provided a landmark analysis for a significant survival advantage derived from TBP compared to not treated beyond progression.

FDA Pooled Analysis Offers Skeptical View of TBP But It Has Limitations

Skeptics who remain unconvinced of the value of TBP point toward data from an FDA pooled analysis that concluded continuation of TBP beyond progression in the product labeling should not be recommended because the clinical benefit remains to be proven. In this pooled analysis, which should not be confused with CheckMate025) although more than half of patients with unresectable or metastatic melanoma with RECIST-defined progression received continued anti-PD-1 antibody treatment beyond progression, only a modest number of these patients (95 [14%] of 692) seemed to have subsequent decreases in their target lesion tumor burden that reached the level of a response (≥30% decrease) in this analysis.

Extrapolating from these results, the FDA analysis differs from the conclusions reached in the study by Escudier et al. The FDA paper suggests that the overall clinical benefit of treatment beyond progression with anti-PD-1 antibodies remains unclear. The report further suggests the survival of patients given such treatment seems to be similar in the chemotherapy group and the anti-PD-1 antibody group in the comparative trial. Furthermore, the number of patients with a delayed response during treatment beyond progression with anti-PD-1 antibodies was apparently low relative to the total population in the pooled analysis.

A Case Report on TBP in RCC

Although the literature is still sparse on the use of TBP in mRCC, other papers have provided additional evidence supporting such strategy. In a case report by Rebuzzi et al, for example, reviewed results from an advanced renal cell carcinoma patient treated with nivolumab who developed clinical benefit and delayed radiological response after initial progression. These authors performed a review of the literature on immunotherapy beyond progression in advanced solid tumors; 12 clinical trials were identified and showed that selected patients have subsequent response and survival benefit receiving immunotherapy beyond progression.

A Case Report on TBP in RCC

Although the literature is still sparse on the use of TBP in mRCC, other papers have provided additional evidence supporting such strategy. In a case report by Rebuzzi et al, for example, reviewed results from an advanced renal cell carcinoma patient treated with nivolumab who developed clinical benefit and delayed radiological response after initial progression. These authors performed a review of the literature on immunotherapy beyond progression in advanced solid tumors; 12 clinical trials were identified and showed that selected patients have subsequent response and survival benefit receiving immunotherapy beyond progression.

Offering a corroborating perspective in their review of the literature, Atkins et al provided an analysis on the future use of checkpoint inhibitors, including the potential value of treatment beyond progression, the potential use in earlier lines of care in combination with other agents. They also identify biomarkers that could help to guide patients selection and enable individualization of therapy.
Reexamining the RECIST Criteria and the Need for a Paradigm Shift in Assessment Guidelines

An overarching theme to virtually all of the studies examining the issue of treatment beyond progression is the focus on RECIST criteria and the need to reevaluate practical implications of their use. As Wolchok suggest in their report, increasing clinical experience indicates that traditional response criteria may not be sufficient to fully characterize activity in the new era of targeted therapies and/or biologics. The RECIST criteria were initially published nearly 20 years ago and the guidelines were updated 10 years ago.6 The criteria have become so much a part of practice and have guided the methods used in clinical trials. What can replace them? The precepts embodied by the RECIST criteria suggest why new thinking needs to be considered. For example, for cytotoxic agents, the guidelines assume that an early increase in tumor growth and/or the appearance of new lesions signal progressive disease. Thus, for cytotoxic agents, the term “progression” became synonymous with drug failure and cessation of the current treatment is recommended once PD is detected.

In contrast to the rationale for discontinuing the use of cytotoxic agents, the calculus for immunotherapeutic agents is markedly different. With chemotherapy, for example, stable disease (SD) is often transient and not considered indicative of true antitumor activity.6 With immunotherapy SD may be viewed as an indicator of a meaningful therapeutic effect. Wolchok et al also provide a valuable backdrop with which to analyze whether the traditional RECIST criteria need to be revisited. In studies with cytokines, cancer vaccines, and monoclonal antibodies (such as ipilimumab) complete response, partial response (PR), and SD have been shown to occur after an increase in tumor burden characterized as PD by the RECIST criteria.

A pivotal point in the evolution of new criteria occurred when approximately 200 oncologists, immunotherapists and regulatory experts met in a series of workshops in 2004 and 2005. The result of these workshops was a new line of thinking about immunotherapeutic agents in cancer.18 Wolchok et al present novel criteria, called immune-related response criteria (irRC) that can better capture the response patterns observed with some immunotherapies. Among the criteria suggested in this report:

- An increase in tumor burden or the appearance of new lesions points toward the need for appropriate follow-up at a subsequent point to confirm progressive disease.
- Treatment should be continued as tumors may begin to shrink during this interval.
- Patients treated with immune therapy whose performance status is stable and whose laboratory values have not significantly deteriorated, as well as those with moderate tumor growth on physical exam or radiographic imaging, should be considered for repeat confirmation scans. These scans should be done before progressive disease is defined and the immunotherapeutic agent is discontinued.

It is our practice generally to continue immunotherapy beyond the first progression, if patients are tolerating the drug and are found to have clinical benefit (after explaining the potential flare phenomenon). If progressive disease is observed a second time then immunotherapeutic agents should be discontinued. The key message is that the tail of the survival curve does not support continued immunotherapy after a second progression, we recommend discontinuation of immunotherapeutic agents.

Conclusion

The criteria for the continued use of immune checkpoint inhibitors beyond progression are changing as recent analyses begin to show a translational impact on clinical practice. The concept of tumor flare or pseudoprogression is increasingly important to consider in patient assessment. Based on data from pooled analyses and other reports in a broad range of tumors, including RCC, the traditional RECIST criteria have been reexamined and, if followed, may not provide patients with the potential clinical benefit they could receive with continuation of treatment beyond first progression. A new set of guidelines, the immune-related response criteria, need further prospective evaluation to determine the extent to which their application could be associated with sustained benefit and improved overall survival. This topic also underscores the unmet need to develop radiographic bio-marker studies to better assess early tumor changes after the introduction of immune checkpoint inhibitors. Such imaging modalities should ideally include tracking T-cell infiltration of tumors/ tumor metabolism/tumor microenvironment in parallel to the RECIST based assessments. Although it is not possible to conduct a prospective trial to definitively address many questions regarding TBP, if there are adequate resources to address this in a prospective trial, a randomized discontinuation trial would provide important perspectives.

References

age of social media and Twitter, it might not be considered “hot.” To be sure, the bulk of attention remains focused on various shifts in the treatment paradigm and how we are to appropriately integrate these shifts into our clinical practice. And yet, I am impressed by the voluminous content surrounding the use of IO therapy and the myriad issues many authors raise for us not only as clinicians but for us as part of the larger sphere of oncology and its place in the overarching public health sector.

Consider, for example, a paper published earlier this year by Kaufman, Atkins, Subedi et al (The promise of Immuno-oncology: implications for defining the value of cancer treatment, in the Journal for ImmunoTherapy of Cancer, May 2019.) As the authors address this topic, they note: “Responding to ongoing efforts to generate value assessments for novel therapies, multiple stakeholders have been considering the question of ‘What makes I-O transformative?’ Evaluating the distinct features and attributes of these therapies, and better characterizing how patients experience them, will inform such assessments.” The authors explore key aspects and attributes of IO therapies that should be considered in any assessment of their value and seek to address evidence gaps in existing value frameworks given the unique properties of patient outcomes with IO therapy. That is a tall order for anyone to take on but this report gives one of the most comprehensive analyses of IO therapy available. It delves into a broad spectrum of issues that will not only dramatically enlarge your frame of reference but deepen your understanding of the value of IO therapies, particularly as it relates to economic models. For example, the Incremental Cost Effectiveness Ratio (ICER) is used to assess and compare value in healthcare among available treatment options. ICERs are calculated by measuring or estimating the incremental costs and improvements in patient outcomes versus a therapeutic comparator through cost-effectiveness and cost utility models.

This is probably not something the average clinician will be thinking of at the bedside when deciding which IO-IO combination or IO-TKI combination to use, but economic models and metrics are essential in the allocation of health care resources and play a role in how we ultimately assess the value of IO therapy. “The definition of ‘value’ varies among stakeholders. For instance, patients and caregivers mostly overlap in how they define value, but subtle differences often exist between how patients differentially value returning to work or the impact of regaining their activities of daily living. Similarly, subtle but meaningful differences exist among how physicians, researchers, payers and employer groups define ‘value.’ In addition, the views of other stakeholders, such as drug developers, patients’ employers and family members are often not considered in the value assessment.”

As the pillar of IO therapy casts an even longer shadow over our treatment choices, the rationale for our choosing one or another or switching to another treatment class, as always, is primarily based on clinical criteria validated by evidence-based approaches. But the debate over these appropriate strategies is informed as well by the broader discussion on “the definition of value.” And the literature does not disappoint us in delineating these concepts and challenging our understanding of them.

Robert A. Figlin
Editor-in-Chief
Targeting Glutamine Metabolism: the CANTATA Trial for Patients With Metastatic Renal Cell Carcinoma (mRCC)

Andrew W. Hahn, MD
Nizar M. Tannir, MD, FACP

Department of Genitourinary Medical Oncology
Division of Cancer Medicine
MD Anderson Cancer Center
Houston, TX

Abstract
Despite the progress made in the management of advanced renal cell carcinoma with the regulatory approval of immune checkpoint inhibitor-based regimens, nivolumab plus ipilimumab, pembrolizumab plus axitinib, and avelumab plus axitinib as first-line therapies for the treatment of patients with metastatic renal cell carcinoma (mRCC), an unmet need still exists for the development of therapies with novel mechanism of action for patients with mRCC who do not respond or experience a relapse after an initial response to these first-line therapies. Altered cellular metabolism is a hallmark of cancer, and renal cell carcinoma (RCC) cells have been shown to depend on glutamine metabolism for energy demands. Telaglenastat (CB-839) is a selective glutaminase inhibitor that is being studied in combination with cabozantinib in the randomized CANTATA trial as second-line or third-line therapy in patients with mRCC who had progressive disease after prior therapy with dual immune checkpoint inhibitors or a VEGFR-TKI followed by immune checkpoint inhibitors, or the combination of an immune checkpoint inhibitor plus a VEGFR-TKI. Herein, we present a clinical vignette reflective of a patient enrolled on the CANTATA trial, review the preclinical and early phase clinical trial rationale for telaglenastat plus cabozantinib, and provide an in-depth discussion of the CANTATA trial.

Case Report
Mr. L is a 58 year-old male who initially presented with a palpable abdominal mass and was found to have a 10 x 8 centimeters (cm) right renal mass which was histologically confirmed to be clear-cell renal cell carcinoma (ccRCC). At that time, he had a right nephrectomy with radical lymph node dissection and was found to have 3 lymph nodes positive for ccRCC. Two months after his nephrectomy, a restaging CT chest, abdomen, and pelvis showed interval development of a 1.5 cm lesion in the liver and small pulmonary nodules suspected to be metastatic RCC (mRCC). He began first-line sunitinib for International Metastatic RCC Database Consortium (IMDC) intermediate-risk disease. After 8 months of stable disease, he experienced radiographic progression. He was then started on second-line nivolumab and continued this immunotherapy until radiographic progression 13 months later. Most recently, he was enrolled in a clinical trial of cabozantinib plus telaglenastat versus cabozantinib plus placebo as third-line treatment for IMDC intermediate-risk mRCC. He experienced a durable partial response on this clinical trial and remains on treatment 15 months later without any grade 3 or 4 adverse events.

In the above clinical vignette, Mr. L was enrolled on the CANTATA trial (NCT03428217), a randomized clinical study comparing telaglenastat (CB-839) plus cabozantinib versus cabozantinib plus placebo in patients with mRCC who had previously progressed on at least one line of systemic treatment. There is a growing need for novel salvage therapies for mRCC as combinations of VEGF targeted therapy and immune checkpoint inhibitors are now approved as first-line treatment. Telaglenastat is a selective glutaminase inhibitor that is designed to target one of the hallmarks of cancer, altered cellular metabolism (Figure). In cancer cells, the Warburg effect results in a deficit of essential metabolites for tumorigenesis. In RCC cells, HIF-1 and HIF-2 mediate a switch to use glutamate to fuel the tricarboxylic acid cycle (TCA) cycle. Glutamate is also used by cancer cells to synthesize amino acids and balance cellular oxidative stress. Thus, RCC cells are dependent on glutamine metabolism, and glutaminase plays a key role by converting glutamine into glutamate.

There is preclinical rationale and phase 1 clinical trial data supporting the CANTATA trial. In a preclinical study of VHL-deficient human RCC cell lines, glutaminase inhibition compromised de novo pyrimidine synthesis, increased levels of reactive oxygen species by impairing glutathione biosynthesis, and impaired cell growth by selectively inducing DNA replication stress. In a separate preclinical study, telaglenastat plus cabozantinib had synergistic antiproliferative activity in vitro and enhanced anti-tumor activity in murine RCC xenografts. These preclinical studies led to a phase 1 clinical trial of tela-
glenastat plus cabozantinib in 13 patients with metastatic clear-cell or papillary RCC who had progressed on at least one prior VEGF-targeted therapy. Telaglenastat plus cabozantinib was well tolerated with similar toxicity to cabozantinib alone and had promising antitumor activity, with an objective response rate (ORR) of 42% (5 responders out of 12 evaluable patients). Among the 12 patients evaluable for response, 10 patients had ccRCC and 2 patients had papillary RCC; 5 of the 10 patients with ccRCC achieved a partial response. Finally, telaglenastat has also been studied in combination with everolimus in 69 patients with mRCC in the ENTRATA trial. In this randomized phase 2 clinical trial using 2:1 randomization between telaglenastat plus everolimus vs placebo plus everolimus as third-line or beyond treatment, the experimental arm of telaglenastat plus everolimus met its primary endpoint by improving progression-free survival (PFS) compared to placebo plus everolimus (HR=0.64, P=0.079; median PFS 3.8 vs. 1.9 months).8

CANTATA is an international, randomized, double-blind clinical trial that is actively enrolling 416 patients to telaglenastat plus cabozantinib or placebo plus cabozantinib. Randomization is stratified by prior PD-1 or PD-L1 antibody treatment and IMDC risk group. The primary endpoint is PFS per RECIST version 1.1 by blinded independent review committee. Secondary endpoints include overall survival, investigator-assessed PFS, ORR, duration of response, disease control rate, safety, pharmacokinetics, biomarker analyses, and quality of life assessment. The trial is designed to have 85% power and a hazard ratio of 0.69 and two-sided alpha of 0.05. Key inclusion criteria include: documented histological diagnosis of clear-cell RCC, Karnofsky performance status ≥ 70%, measurable disease per RECIST version 1.1, and 1-2 prior lines of systemic treatment including at least one VEGF targeted therapy or the combination of nivolumab plus ipilimumab. Key exclusion criteria include: prior treatment with telaglenastat or cabozantinib (or other MET inhibitor), active central nervous system disease, major surgery within 6 weeks or significant bleeding event within 3 months of first dose, inability to receive oral medications, or inability to discontinue proton pump inhibitors prior to randomization. The CANTATA trial is actively recruiting patients and the estimated date of primary analysis is September 30, 2020.

**Conclusion**

In conclusion, RCC is dependent upon glutamine metabolism, making glutaminase inhibition a novel and rational therapeutic target for patients with mRCC. CANTATA is an ongoing, randomized clinical trial evaluating telaglenastat, a selective glutamine inhibitor, plus cabozantinib versus cabozantinib plus placebo in 416 patients who had previously progressed on one or two prior lines of systemic therapy. The results of this trial have the potential to improve the outcomes of patients with metastatic clear-cell RCC by expanding the therapeutic options for these patients and incorporating in our armamentarium a first-in-class agent with a novel mechanism of action.

**References**

Have we reached an inflection point in the debate over the role of cytoreductive nephrectomy (CN) in metastatic renal cell carcinoma (RCC)? Controversy remains regarding the sequencing of CN and targeted therapy in mRCC, and this controversy has been heightened with the availability of new and more promising agents for the treatment of metastatic renal cancers. The current literature also points toward an improved understanding of the most appropriate selection criteria for determining the best candidates for CN using prognostic and predictive factors to optimize clinical outcomes. Overall, there still remains a role for upfront CN in appropriately selected candidates.

From the early landmark papers in the cytokine era to recent analyses of retrospective observational data and additional studies of CN in the era of targeted therapy, the role of cytoreductive nephrectomy has undergone virtually continuous reevaluation and considerable confusion persists over the appropriate selection of surgical candidates for cytoreductive nephrectomy. Without question, the role of CN will continue to be modified by the evolution of new and more effective systemic therapies including the use of targeted therapies which have dramatically reshaped the evidence-based paradigm of advanced RCC treatment. Therefore, with the introduction of these new systemic therapies, the widely accepted rationale for the use of CN (either as an initial or delayed therapy) has been reexamined and upgraded. In addition, more information regarding the importance of prognostic risk factors and predictive markers that are associated with the value of CN has continued to evolve.

Within the last few years, the debate over CN in metastatic RCC has been reassessed, largely due to the publication of two trials (the CARMENA and SURTIME trials). Furthermore, the debate over the validity of data from these two trials has dominated the narrative on CN and targeted therapy. Therefore, the controversy surrounding these trials – particularly the limitations and flaws of each – has become a focus of the recent literature.

The CARMENA trial, a phase 3 study, concluded that overall survival (OS) in patients treated with sunitinib alone is not inferior to those treated with CN followed by sunitinib.1 Another pivotal trial, the European Organization for Research and Treatment of Cancer (EORTC) SURTIME trial explored a period of sunitinib prior to CN as an alternative approach to immediate CN. In this trial, the sequence of CN and sunitinib did not affect the progression-free rate, but higher OS was seen for deferred CN.2 These trials were also preceded by a long list of studies on the use of CN, beginning in the cytokine era. A brief chronicle of the highlights from these earlier studies offers important perspectives on how the rationale for the use of CN has evolved over the last 20 years. Furthermore, a review of the findings from these earlier studies offers a valuable vantage point from which to analyze the results of more recent reports.

Cytoreductive nephrectomy in the Cytokine Era

At the beginning of the cytokine era, surgery was the main treatment for localized RCC, but the use of nephrectomy for metastatic disease was controversial and generally considered not of value. Two pivotal studies from the cytokine era addressed the question of whether combined treatment with CN followed by systemic interferon-alpha lengthens time to progression and confers a survival benefit in patients with metastatic RCC, and, secondarily, whether nephrectomy before immunotherapy increases the response rate to immunotherapy.3,4 In one of these studies, by Flanigan et al, the median survival of 120 eligible patients assigned to surgery followed by interferon was 11.1 months, compared to was 8.1 months in 121 patient assigned to interferon alone.(4) In patients with PS0, OS with CN was 17.4 mo vs. 11.7 mo without CN. This data was supported by another study by Mickisch et al3 which demonstrated that time
to progression (5 vs 3 months) and median duration of survival (17 vs 7 months) were significantly better in patients receiving combined CN and IFN treatment vs IFN alone.

Both of the above mentioned trials found that systemic therapy in the era of interferon therapy could be given safely to patients at a short interval after nephrectomy. Both studies also addressed prognostic factors that seemed to affect outcomes, including especially performance status, lung only metastases, liver metastases and bulky retroperitoneal lymphadenopathy. Additional reports in the literature studied other risk factors that might also be useful in selecting patients less suitable for CN, including LDH > 600, albumin < 3.5, liver metastases, and retroperitoneal lymphadenopathy.

The “take-home” message from these studies in the cytokine era is that, in select patients with good performance status, absence of significant health comorbidities or central nervous system metastases, CN is associated with a low likelihood of surgical morbidity and a statistically significant 6-month survival advantage (Figure 1).

Cytoreductive Nephrectomy in the Era of Targeted Therapies

The advent of targeted therapies for cancer treatment heralded in a new era in the systemic treatment of renal cancers, and the value of role of CN was questioned anew. A study by Choueiri et al was among the first reports to suggest that CN may confer an independent survival benefit in patients with metastatic RCC who subsequently received contemporary VEGF targeted therapy. Retrospectively reviewing the outcomes of 314 patients, this report found that patients who underwent CN (n=201) demonstrated a median OS of 19.8 months vs 9.4 months for patients who did not undergo CN (n=113). When this study’s results were adjusted for established prognostic risk factors, the OS difference persisted in favor of the CN group.

Choueiri et al also studied two prognostic models; one derived in the era of VEGF targeted therapy and another from the immunotherapy era, and found that both models showed a benefit of CN on survival. Not surprisingly, on subgroup analyses, the benefit was marginal in patients with poor performance status, brain metastases, or in those categorized as poor risk by the MSKCC criteria. These authors suggested that these three groups of patients may therefore represent new criteria to help stratify patients who should or should not undergo CN.

Do the IMDC Prognostic Factors Reshape the CN Narrative?

We have, from the beginning of our experience with cytoreductive nephrectomy, insisted that all candidate patients be seen by their surgeon and a medical oncologist who was a part of our CN team. We feel that this protocol maximizes decision making and patient selection process and insures a more effective transition from surgery to systemic therapy. As CN has evolved (Figure 2) from the cytokine to the targeted therapy eras, the prognostic factors found to be important have also evolved. Compelling evidence for the importance of prognostic profiles in selecting patients for CN in the targeted therapy era emerged from the study by Heng et al. In their retrospective review of results from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC), these authors demonstrated that CN provided a significant OS benefit in patients treated with targeted therapy when adjusting for known prognostic factors. The Median OS of patients with CN vs without CN was 20.6 vs 9.5 months respectively. However, in this study, patients who received CN had better IMDC prognostic profiles (IMDC risk factors - less than 1 year from diagnosis to surgery, Karnofsky PS < 80%, hemoglobin < lower limit of normal, calcium > upper limit of normal, neutrophil > upper limit of normal and platelet count > upper limit of normal) than the patients not receiving CN. The study’s incremental benefit analysis also suggested that those with one, two, and three IMDC risk factors seemed to benefit from CN while those with four, five, and six risk factors did not. In addition, patients who were expected to survive less than 12 months also demonstrated limited benefit from a CN.

Database studies analyzing large patient populations in the targeted era (2005 and later) have also shown a
value for CN. Abern et al\textsuperscript{9} employed the Surveillance, Epidemiology, and End Results (SEER) database, describing the primary outcome of OS in patients with metastatic RCC. Out of 7,143 mRCC cases, they reported that 37\% underwent CN. Patients who underwent CN were more likely to be younger, white, male, married, and to have stage T3 tumors. Patients who underwent CN had an improved one-year survival (61\% vs 22\%). Although this report favored the role of CN in the management of metastatic RCC, the authors acknowledged limitations and confounding factors in the analysis. This analysis was not able to control for prognostic variables, the location or number or volume of metastatic sites (shown by other studies to be of prognostic significance).\textsuperscript{10,11} In addition, other prognostic factors, including serum hemoglobin, lactate dehydrogenase (LDH), calcium and albumin were also unavailable from their dataset and could have varied between the groups receiving CN or not.

Another study reported on a large and robust sample cohort from the National Cancer Data Base reviewed between 2006 and 2013. The report by Hanna et al\textsuperscript{12} also found an OS benefit when CN was combined with targeted therapy: the median OS of CN vs non-CN patients was 17.1 months vs 7.7 months respectively. CN was also found to be associated with (Figures 3, 4) a lower risk of any death (HR, 0.45, P<.001).

Two Pivotal Randomized Trials (the SURTIME and CARMENA trials): Are They a Turning Point in Debate Regarding CN?

The CARMENA Trial This phase 3, randomized study attempted to delineate the value of CN and systemic therapy in the era of targeted therapy – specifically sunitinib. In this study, the median OS was 18.4 months in the sunitinib only arm versus 13.9 months in the CN/ sunitinib arm. Thus, the CARMENA trial did not support the conclusions of previously reported retrospective and database studies of CN as it failed to show an overall OS benefit with CN in patients treated with sunitinib therapy. However, over the last two years, the validity and application of CARMENA’s results have been questioned based on widely ranging criticisms. One of the criticisms is related to this trial’s slow and likely incomplete recruitment, as noted in a report by Arora et al.\textsuperscript{13} During 8 years of accrual to this study, 450 patients were enrolled at 79 centers, considerably short of the target of 576 patients. This fact raised questions about whether the recruitment process was biased, especially since patients with a lower metastatic burden were “selectively treated outside the trial.” The extent to which the results from CARMENA can be generalized to all patients with metastatic RCC has also been scrutinized. For example, the 18.4-month OS in the sunitinib arm is lower than in other recently published studies.\textsuperscript{14} Arora et al further criticized CARMENA because the trial recruited patients with a higher number of metastatic sites than in the National Cancer Data Base trial. There is a strong suggestion that candidates for CARMENA (due to their lower metastatic burden) underwent a nephrectomy outside the trial.

Perhaps most importantly, there was a sizeable degree of crossover in the trial which utilized intention to treat criteria. Specifically, 17\% of patients who were randomized to sunitinib alone actually underwent CN and 7\% of the patients in the CN arm did not undergo CN. IN addition, he higher percentage of patients with advanced disease in the CN/sunitinib arm (70\% vs 51\%) could have also influenced outcomes.\textsuperscript{15}

The SURTIME Trial This randomized phase 3 trial attempted to evaluate whether a period of sunitinib therapy before CN might improve outcomes in patients with metastatic renal cancer compared with immediate CN followed by sunitinib therapy. The objective of the SURTIME trial was also to investigate whether pretreatment with sunitinib before planned surgery improves outcome by identifying patients with inherent resistance to VEGF-TKI therapy who are unlikely to benefit from CN. SURTIME also examined whether a deferred approach to CN could reduce cancer-related morbidity, primary tumor size, and neovascularization, which, in turn, may decrease surgical risk and morbidity. Very impor-
In patients with poor IMDC/MSKCC risk disease, poor an important part of determining survival outcomes? European Association of Urology and the AUA have furt provide a useful guide directed to the appropriate selection of candidates for CN after careful consideration of prognostic risk factors. Updated guidelines from the selection of candidates for CN after careful consideration of prognostic risk factors. Updated guidelines from the.

As stated above, numerous studies have addressed the implications of the SURTIME and CARMENA trials given the fact that both trials left a trail of unanswered questions regarding the role of CN in patients treated with sunitinib. Subsequent papers have also attempted to provide a useful guide directed to the appropriate selection of candidates for CN after careful consideration of prognostic risk factors. Updated guidelines from the European Association of Urology and the AUA have further clarified the role of CN.

To what extent are prognostic and predictive factors an important part of determining survival outcomes? Beyond SURTIME and CARMENA: A New Algorithm to Determine the Role of CN? As stated above, numerous studies have addressed the.

Fig 3. Kaplan-Meier survival analyses of patients with metastatic renal cell carcinoma treated with targeted therapy stratified according to cytoreductive nephrectomy (CN) status (yes or no), National Cancer Data Base, 2006 to 2012. Data were restricted to 12,995 patients with no missing information on vital status or follow-up time.

Fig 4. Kaplan-Meier survival analyses of patients with metastatic renal cell carcinoma treated with cytoreductive nephrectomy and targeted therapy (TT) stratified according to timing of surgery (before or after systemic therapy), National Cancer Data Base, 2006 to 2012. Data were restricted to 4,223 patients with available information on timing of surgery and targeted therapy.

Bindhi’s review of patients with metastatic RCC suggested the following:

- Poor performance status and poor IMDC/MSKCC risk classification is associated with a poor prognosis, and a lack of OS benefit with CN.
- Good performance status and good/intermediate IMDC/MSKCC risk classification is predictive of OS benefit with CN in patients without adverse IMDC/MSKCC risk factors, who demonstrate good performance status and low-volume metastatic burden and initial CN generally should be considered before systemic therapy.
- Metastectomy, when possible, markedly improves survival and may allow patients to remain off systemic therapy, thereby avoiding associated toxicities.
- In patients with poor IMDC/MSKCC risk disease, poor performance status, and large-volume metastatic burden, initial treatment with systemic therapy is generally advised. In patients with brain metastases, spinal metastases, and bone metastases with risk of fracture, systemic therapy combined with radiation of the lesions is preferred before considering CN.

Future Directions: How Will Checkpoint Inhibitors Be Integrated in the Paradigm? One of the key issues to be addressed by planned trials is the need to reassess the role of CN in the setting of checkpoint inhibitor therapies that have now attained first-line treatment status. An intriguing hypothesis is that cytoreduction and the resultant reduction of immunosuppressive signals may enhance the benefit of PD-L1 blockade. As trials like Checkmate-214 move forward, the sequencing of systemic therapy and/or CN will continue to be an essential focus of interest.

Conclusion
Although more level 1 evidence for the use of initial CN in the era of targeted therapy is still needed, a consensus is taking shape based on large analyses of population-
of care for earlier lines of therapy.

The Company plans to discuss the updated OS results with the FDA to identify the appropriate path forward for tivozanib in RCC in the fourth quarter, and to provide an update regarding the potential submission of a New Drug Application for tivozanib in RCC following these discussions.

“These are the first data to demonstrate durable improvements in this highly refractory advanced kidney cancer population, including the post-immunotherapy setting, a predefined subset of the TIVO-3 trial,” said Brian Rini, MD, Professor of Medicine, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Director, Cleveland Clinic Genitourinary Cancer Program, and principal investigator of the TIVO-3 trial. “The TIVO-3 study suggests the potential for tivozanib to serve as an important new treatment option for patients with advanced RCC. I look forward to seeing tivozanib studied further in the immunotherapy combination setting, and to continuing to explore its full potential in the evolving RCC treatment landscape.”

In this wide-ranging discussion, three opinion leaders address essential issues related to the use of immunotherapy combinations in the frontline space for RCC. As they compare the rationale for the use of these respective combinations, each participant offers a unique perspective, including key messages from the pivotal trials supporting IO treatment. The participants include Rana Mckay MD, Matthew Milowsky, MD, and Thomas Powles, FRCP. The discussion is chaired by Robert Figlin, MD, Editor-in-Chief of Kidney Cancer Journal.

**Combining Ipilimumab and Nivolumab**

**Dr Figlin:** In the ever-changing landscape for the management of RCCs, please summarize the key takeaways from the recent data on nivo/ipi in the frontline setting?

**Dr Mckay:** Data regarding nivo and ipi in patients with metastatic RCC have dramatically changed the way we approach newly diagnosed patients. For the first time, we are challenging the treatment paradigm of frontline TKI alone. The combination of nivo/ipi in a large randomized phase 3 trial, CheckMate-214, was actually shown to be superior to sunitinib and is one of the first studies to demonstrate superiority of non-VEGF agents in the frontline space. The big takeaway from this study—the primary endpoint of the study was actually to look at objective response, PFS, and overall survival in patients with intermediate and poor-risk disease. The study included about 51% of patients with intermediate risk disease and 17% of patients with poor-risk disease. The study was actually conducted to look at objective response, PFS, and overall survival in patients with intermediate and poor-risk disease. The study included about 51% of patients with intermediate risk disease and 17% of patients with poor-risk disease.

When we look at the breakdown of patients with intermediate and poor-risk disease, we see a statistically significant improvement in objective response rate with the combination of nivo/ipi. What’s striking is that the complete response rate was 9% in this patient population. Additionally, there was an improvement in PFS and an updated efficacy analysis showing it was statistically significant. Overall survival was also superior to sunitinib with a HR of 0.66 in the updated analysis which was statistically significant and practice changing. While the primary endpoint of the study did not evaluate favorable risk disease, it’s important to look at the favorable risk patients and try to understand what does the combination of nivo/ipi do with this patient population. While the objective response rate was higher with sunitinib compared to nivo/ipi, when we look at that complete response rate, we see that it is actually higher in the nivo/ipi patients. The CR rate in favorable risk patients in CheckMate-214 was around 6% in sunitinib-treated patients but 11% in the nivo/ipi patients, suggesting that there probably is a subset of patients with favorable risk disease who may derive benefit from the combination of nivo/ipi. Additionally, when looking at the intent to treat population, nivo/ipi showed improved ORR, PFS, and OS compared to sunitinib.

The other thing to point out is when we look at the favorable risk patients who were enrolled in the CheckMate-214 we see an overperformance of the controlled arm. The PFS of sunitinib-treated patients approaches 25.1 months, higher than frontline trials that used sunitinib as a comparator arm. Nivo/ipi has certainly changed the frontline space. It clearly has demonstrated improved responses and survival for patients with advanced disease, and for the first time we see patients entering durable remissions with IO combination therapy.

**Dr Figlin:** What populations of patients are best suited for this approach in your practice?

**Dr Mckay:** At the present time, most of our biomarkers to guide clinical decision making are based on clinical parameters. We have clinical risk stratification systems that help inform prognosis and they have been utilized in guiding treatment decisions, however these are not predictive. Unfortunately, we do not have any soluble, blood-based biomarkers that have proven to be validated across mRCC. The combination nivo/ipi has demonstrated efficacy for those with intermediate and poor-risk disease and those who are able to receive IO therapy and do not have significant autoimmune disease that would...
preclude therapy. While overall, patients with favorable risk disease did better with sunitinib in this study, the CR rate was higher with nivo/ipi frontline. I'm not automatically saying no to ipi/nivo in patients with favorable risk disease. I'm looking at their presentation, at co-morbidities, performance status. The number of patients in the current era who would receive a single agent TKI in the frontline space is limited. There is cabozan-
tinib as an option in this regard for those with bone me-
tastases based on the CABOSUN trial. But we need to question the use of VEGF TKIs in the frontline space. The current data support IO-IO combinations or IO-VEGF TKI in the frontline.

Dr Figlin: Do you use existing risk stratification systems (ie, IMDC, MSKCC) in making this assessment?

Dr Mckay: The MSKCC risk factors were validated in the cytokine era. Now the IMDC system has been validated in the TKI era. While it has not yet been validated with use of IO therapy, it is nonetheless a critical risk stratification to think about when you see a patient with metastatic disease. Where I see the risk stratification system coming in very handy is in thinking about the role of cy

toreductive nephrectomy in the context of patients with metastatic disease. We’re being a bit more prudent in de-
ciding which patients derive benefit from upfront CN as opposed to delayed CN. IMDC risk parameters really come into play when thinking about starting a patient on systemic therapy first or CN and system therapy later. Overall, risk stratification systems are really helpful when thinking about the integration of surgery with systemic therapy for patients with advanced disease.

Dr Figlin: Is PD-L1 scoring useful in deciding how best to use this regimen?

Dr Mckay: When reviewing the IO-IO and VEGF-IO trials, each of these studies used a totally different assay to de-
termine PD-L1 expression status. The percentages of PD-
L1 expression based on the assays that were used varied across the studies. For example, in CheckMate-214, PD-
L1 expression was seen in 24% of the total population and in KEYNOTE-426 and JAVELIN 101 there were dif-
ferent assays used, and the number was around 60% and 53%. We have a lot more to learn about the utility of PD-
L1. And the other thing to consider is that the bulk of these tests were done on archival nephrectomy speci-
mens as opposed to fresh biopsies at baseline. We know that PD-L1 status is very dynamic and there are temporal and spatial changes in this biomarker. PD-L1 is certainly prognostic in RCC. Those who have PD-L1 expression do worse than those without. However its role as a pre-
dictive biomarker in RCC is still evolving.

Dr Figlin: Are there specific sites of metastasis (ie, brain, bone, other) that would make you less likely to use this regimen?

Dr Mckay: We know that patients with bone metastases have historically done worse than those without bone metastases. We have great data from the CABOSUN study demonstrating efficacy of cabozantinib over sunitinib in the frontline phase. And while that’s a phase 2 study, I think there is rationale for using cabozantinib in the frontline for those who have bone metastases that may negatively impact their quality of life. Additional studies are investigating IO combinations with cabozantinib in the frontline. These studies will further inform manage-
ment of advanced RCC. Also, one more thing about pa-
tients with brain metastases: we can learn from the melanoma literature about the safety of IO therapies in patients who have brain metastases.

Dr Figlin: Are there specific co-morbidities that would make you less likely to use this regimen?

Dr Mckay: Patients who have underlying or concurrent autoimmune disease—that would be a red flag. Cur-
rently, a study is being conducted by the NCI looking at immunotherapy in patients who have autoimmune disease. We recently conducted a retrospective analysis of patients with RCC who have autoimmune disease who received IO therapy and we are reporting on their out-
comes. Management needs to be coordinated with rheu-
matologists and other consultants to make sure the risk/benefit ratio is sound.

Combining Avelumab and Axitinib

Dr Figlin: In the ever changing landscape for the manage-
ment of advanced RCCa, please summarize the key ta-
keaways from the recent data on avelumab/axitinib in the frontline setting?

Dr Milowsky: In terms of the landscape in the frontline setting for metastatic RCC, the benefit for avelumab/axiti-

nib was established in the JAVELIN Renal 101 Study. 886 patients were randomized to avelumab, a PD-L1 in-
hibitor plus axitinib, a VEGF receptor TKI compared to sunitinib, another VEGF receptor TKI. For the primary endpoint of the study, there was a significant improve-
ment in progression free survival (PFS) in the PD-L1-se-
lected (defined as greater than or equal to 1% of the immune cells staining positive) individuals. The PFS was 14 months for the combination vs 7 months for suniti-

nib with an HR of 0.61 for progression or death. The be-

efit was also seen in the overall population for ave-

lumab/axitinib over sunitinib. At this first pre-planned interim analysis with a median followup of 11.6 months, there was not a significant improvement in overall sur-
vival for the combination with an HR of 0.788 (P=0.14).

Also important in this study is the response rate which was substantially higher for patients who were treated with the combination in both the PD-L1 selected and overall population (55% in the PD-L1 selected ave-
lumab/axitinib group vs 25% for sunitinib). The tolera-
bility was similar to sunitinib including grade 3 adverse events.

Dr Figlin: What populations of patients are best suited for this approach in your practice?

Dr Milowsky: These are first-line patients, so they are pre-
viously untreated and have advanced RCC. The data
from this study showed that over 80% did have a prior nephrectomy. We do not know how that ultimately plays into things. In terms of the population, if you look at the the combination, the benefit was seen in all subgroups. The majority of subjects, over 60%, were intermediate risk. If you have patients who need a robust and relatively rapid response—the median time to response was 2.5 months—it represents a great option. With the Checkmate 214 data for ipi/nivo (ipilimumab/nivolumab) demonstrating a benefit in intermediate and poor risk patients, our standard for favorable risk patients remained sunitinib. Now, with the combination data for avelumab/axitinib we have benefit in favorable risk patients as well. This approach now represents a standard of care in the IMDC favorable risk group as well as in patients with intermediate and poor risk disease.

Dr Figlin: Do you use existing risk stratification systems (ie: IMDC, MSKCC, others) in making this assessment?

Dr Milowsky: We use the IMDC groups in the clinic for prognostication. With newer therapies, this is likely to change with the potential for additional variables to include within these models. In the context of IO therapies, the future is likely to include new predictive and prognostic models.

Dr Figlin: Is PD-L1 scoring useful in deciding how best to use this regimen?

Dr Milowsky: Initially the JAVELIN study was designed differently based on a phase 1b study that showed there was a higher percentage of patients with high PD-L1 expression benefiting from avelumab and axitinib. The primary endpoint of the JAVELIN Renal 101 Study was subsequently changed to look specifically in patients with high PD-L1 status. There was a benefit in the high PD-L1 group but there was also a benefit in the overall population. Based on JAVELIN 101, PD-L1 status should not be used to guide treatment decisions unless we see additional information such as more mature survival data that could change this interpretation. Dr. Choueiri et al presented an important biomarker analysis from JAVELIN 101 at the ASCO Annual Meeting 2019 looking at PD-L1 expression, tumor mutational burden, T-cell subsets, and immune gene expression signatures. This type of work will help guide us in the future.

Dr Figlin: Are there specific sites of metastasis (ie, brain, bone, other) that would make you less likely to use this regimen?

Dr Milowsky: Within the context of this study, there was no clear information to suggest that site of disease should guide therapy with the combination. Over 50% of patients had at least two sites of disease. The study excluded patients with active CNS metastases. We would use the combination in patients with treated CNS metastases. The study excluded active autoimmune disease and we need to be cautious in patients with autoimmune disease. The study does not speak to a particular patient population that should or shouldn’t be treated. The real question is: are there patients that benefit more from IO-IO therapy vs IO-TKI?

Dr Figlin: Are there specific co-morbidities that would make you less likely to use this regimen?

Dr Milowsky: In general, it is a regimen that is very usable. The study, however, excluded active autoimmune disease and again we need to be cautious about the use of IO in patients with active autoimmune disease or in the case of VEGFR TKI therapy, in patients with difficult to control hypertension as one example. Overall, the toxicity is manageable.

Combining Pembrolizumab and Axitinib

Dr Figlin: In the ever changing landscape for the management of advanced RCCA, please summarize the key takeaways from the recent Keynote-426 data on pembrolizumab/axitinib in the front line setting?

Dr Powles: The key messages are that this randomized, frontline, phase 3 trial, which enrolled all comers, was the first trial to show a response rate of progression-free survival and overall survival advantage. And it was associated with a 47% reduction in the risk of death and a PFS of just over 15 months. Putting that together is an exceptionally good result. The drugs seem to work in good, intermediate and poor-risk patients, in all risk groups.

Dr Figlin: What populations of patients are best suited for this approach in your practice?

Dr Powles: The regimen is suited for all risk groups or PD-L1 status. It is an all comers-type approach.

Dr Figlin: Do you use existing risk stratification systems (ie: IMDC, MSKCC, others) in making this assessment?

Dr Powles: We do not need to do that. It’s useful from a patient perspective to know which group they are in. Essentially, what we see from this trial is that the drugs (pembrolizumab and axitinib) seem to work whether across the board and seem to work particularly well in poor-risk patients.

Dr Figlin: Is PD-L1 scoring useful in deciding how best to use this regimen?

Dr Powles: No, not really. In the competitive arm it suggests that ipi/nivo is more suited to the intermediate and poor risk patients and as a biomarker it may be important.

Dr Figlin: Are there specific sites of metastasis (ie: brain, bone, other) that would make you less likely to use this regimen?

Dr Powles: There do not appear to be subgroups in which it is ineffective.

Dr Figlin: Are there specific co morbidities that would
Dr Powles: I think we have to look into questions with underlying immune diseases. Those patients were excluded from the trial. Overall, patients on immune suppressive drugs or patients with active infections—those patients were excluded from the trial. But the majority of patients appeared to have a relatively good rating.

Dr Figlin: Has the Keynote-426 trial changed your paradigm or approach?

Dr Powles: We’ve seen a change in European guidelines, the European Association of Urology guidelines, and the NCCN (National Comprehensive Cancer Network) American guidelines. But that changed very rapidly off the back of this trial. This is the best survival signal we’ve ever seen in a randomized perspective. And it’s the first time we’ve seen a survival signal for a VEGF-targeted therapy combined with an immune therapy. So there are many firsts with this trial, which is why it is so important. Axitinib and pembrolizumab should be considered as a standard of care for unselected patients and it appears to maximize survival outcomes, which is really exciting.
patients with cancer. A better understanding of how this HHLA2/KIR3DL3 pathway works and determining if disrupting it allows immune cells to target and destroy cancer cells could be particularly important for patients with metastatic renal cell carcinoma (RCC) who might not benefit from existing immunotherapies.

Research Team:
Eric Jonasch, MD - The University of Texas MD Anderson Cancer Center
Guang Peng, PhD - The University of Texas MD Anderson Cancer Center

S-phase DNA damage response links genomic instability mechanisms to anti-tumor immunity in renal cell carcinoma
This research team will investigate how the novel tumor suppressor gene NPRL2 functions. The team will study how NPRL2 triggers innate immune response in RCC through impairing S-phase DNA damage response (S-DDR). NPRL2 is frequently deleted from chromosomes in clear cell renal cell carcinoma (ccRCC) and the research team will also explore treatment strategies exploiting this deficiency.

Young Investigator Award (YIA) Recipients:
Scott M. Haake, MD - Vanderbilt University Medical Center
W. Kimryn Rathmell, MD, PhD (Mentor) - Vanderbilt University Medical Center

Endogenous retrovirus expression drives immunogenicity of papillary renal cell carcinoma
In prior published work, Dr Haake and colleagues established that endogenous retroviruses (ERVs) are a biomarker for immune response in ccRCC patients and a potential therapeutic target. This research project will shift focus to investigate ERV expression in papillary RCC (both type 1 and 2) to and how ERV impacts anti-tumor immune response in this understudied RCC subtype.

Akash Kumar Kaushik, PhD - University of Texas Southwestern Medical Center
Ralph J. DeBerardinis, MD, PhD (Mentor) - University of Texas Southwestern Medical Center

In vivo glutamine metabolism in VHL and FH mutant renal cell carcinoma
Dr Kaushik’s research project will take a closer look at the amino acid glutamine – a major source of energy and growth for some cancer cells – and its role in cellular activity. In particular, Dr Kaushik will investigate the efficacy of a glutaminase inhibitor in patient-derived mouse models with mutated versions of the VHL and FH tumor suppressor genes. He will also examine how effective specific inhibitors of a key energy-generating cellular process are in VHL- and FH-mutant tumors.

Ed Reznik, PhD - Memorial Sloan Kettering Cancer Center
A. Ari Hakimi, MD (Mentor) - Memorial Sloan Kettering Cancer Center

Metabolic determinants of the tumor microenvironment and sensitivity to immunotherapy in ccRCC
The tumor microenvironment (TME), which includes blood vessels, stroma, immune and other types of cells, and signaling molecules, plays an important part in the effectiveness of immunotherapy. Dr Reznik will closely examine tumor metabolism as it relates to the TME of ccRCC. A better understanding of the TME and its varied components might help indicate which therapies are more likely to be effective for patients with ccRCC, thereby avoiding potentially unnecessary treatment. The findings also have the potential to identify new therapeutic targets.

Tian Zhang, MD, MHS - Duke Cancer Institute
Daniel J. George, MD (Mentor) - Duke Cancer Institute

Immune correlates of immunotherapy responses in renal cell carcinoma
Patients with metastatic ccRCC have several options when it comes to first-line immunotherapy, including combination treatment with VEGF inhibitors that stop blood vessels from growing excessively. Choosing between options is still a challenge. Dr Zhang will analyze how the TME responds to immunotherapy. In addition, Dr Zhang will investigate a panel of five genes and its association with resistance to ipilimumab/nivolumab combination therapy.
placebo. Higher baseline CXCL10 was associated with worse DFS (HR 1.41 per log increase in CXCL10, Bonferroni-adjusted \(P = 0.003\)). This remained significant after adjustment for T-stage, Fuhrman grade, and ECOG performance status.

**Conclusion:** Among patients treated with adjuvant VEGFR TKIs for RCC, drug-host interactions mediate changes in circulating cytokines. Elevated baseline CXCL10 was associated with worse DFS. Studies to understand functional consequences of these changes are under way.


**Summary:** In metastatic renal-cell carcinoma (mRCC), recent data have shown efficacy of first-line ipilimumab and nivolumab (ipi-nivo) as well as immuno-oncology (IO)/vascular endothelial growth factor (VEGF) inhibitor combinations. Comparative data between these strategies are limited. This study compared the efficacy of ipi-nivo versus IO-VEGF (IOVE) combinations in mRCC, and described practice patterns and effectiveness of second-line therapies.

Using the International Metastatic Renal-cell Carcinoma Database Consortium (IMDC) dataset, patients treated with any first-line IOVE combination were compared with those treated with ipi-nivo. All patients received first-line IO combination therapy. A first- and second-line response rates, time to treatment failure (TTF), time to next treatment (TNT), and overall survival (OS) were analysed. Hazard ratios were adjusted for IMDC risk factors. In total, 113 patients received IOVE combinations and 75 received ipi-nivo. For IOVE combinations versus ipi-nivo, first-line response rates were 33% versus 40% (\(P = 0.4\)), TTF was 14.3 versus 10.2 mo (\(P = 0.2\)), TNT was 19.7 versus 17.9 mo (\(P = 0.4\)), and median OS was immature but not statistically different (\(P = 0.17\)). Adjusted hazard ratios for TTF, TNT, and OS were 0.71 (\(P = 0.14\)), 0.65 (\(P = 0.11\)), and 1.74 (\(P = 0.14\)), respectively. Sixty-four (34%) patients received second-line treatment. In patients receiving subsequent VEGF-based therapy, second-line response rates were lower in the IOVE cohort than in the ipi-nivo cohort (15% vs 45% (\(P = 0.04\); \(n = 40\)), though second-line TTF was not significantly different (3.7 vs 5.4 mo; \(P = 0.4\); \(n = 55\)). Limitations include the study’s retrospective design and sample size.

**Conclusion:** There were no significant differences in first-line outcomes between IOVE combinations and ipi-nivo. Most patients received VEGF-based therapy in the second line. In this group, second-line response rate was greater in patients who received ipi-nivo initially. 

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