Volume 18, Number 2 2020

Kidney Cancer JOURNAL

Official Journal of The Kidney Cancer Association

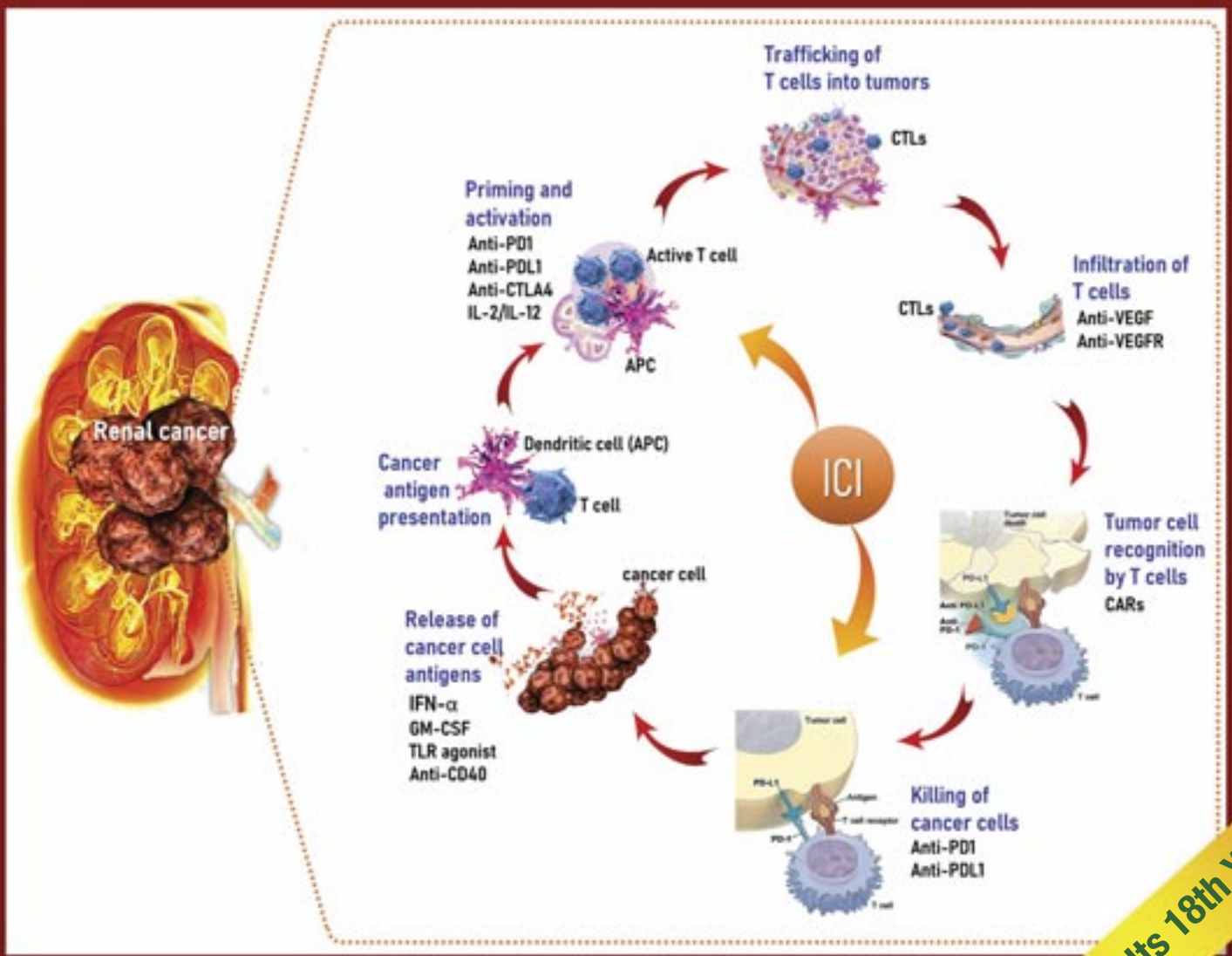
www.kidney-cancer-journal.com

ASCO 2020 Highlights: What Are the 'Take-Home' Messages?

Oligometastases: Mapping Strategies For a New Paradigm, Integrating SBRT

Redefining the IO Landscape & Harnessing Immune-checkpoint Inhibitor for RCC Therapy

Cytoreductive Nephrectomy: Guidelines for Upfront Systemic Therapy vs Surgery



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

Now in Its 18th Year

Editorial Mission
The purpose of Kidney Cancer Journal is to serve as a comprehensive resource of information for physicians regarding advances in the diagnosis and treatment of renal cell carcinoma. Content of the journal focuses on the impact of translational research in oncology and urology and also provides a forum for cancer patient advocacy. Kidney Cancer Journal is circulated to medical oncologists, hematologist-oncologists, and urologists.

Editorial Offices
517 Belle Gate Pl, Cary, NC 27519

About the Cover
This figure illustrates the complement interaction between immune-checkpoint inhibitors and anti-angiogenics that is essential to harness synergistic potential of immune-checkpoint blockade based therapies in advanced RCC. In this, anti-PD-L1 or other ICI agents restore immune-supportive microenvironment, whereas anti-angiogenic drugs potentially suppress immune checkpoints expression and also block the negative immune signals. Such mutual regulation of immune microenvironment reprogramming and angiogenic blockade is crucial for overcoming immunotherapy resistance, and also offers a basis for development of ICI based novel and efficient immunotherapeutic strategies for advanced RCC. (See article on page 50).

Follow us on Twitter
@ KidneyCancerJ

KCJ TABLE OF CONTENTS

36 Medical Intelligence

38 Unpacking the Virtual ASCO20 Sessions: What Are The Latest Developments in the RCC Toolbox?

42 Current Guidelines for Treating Oligometastatic RCC: An Ever-changing Paradigm Integrates New Strategies

50 The Current and Evolving Landscape of Immunotherapies for Advanced Renal Cell Carcinoma

56 Sequencing of Cytoreductive Nephrectomy in Metastatic Renal Cell Carcinoma During the VEGF-TKI and Immunotherapy Era

61 Uveal Melanoma and RCC: More Similar than Meets the Eye

KCJ EDITOR'S MEMO

Blazing a Trail Through the Virtual World of ASCO and COVID-19


Robert A. Figlin, MD

Who could have predicted at last year's meeting of the American Society of Clinical Oncology (ASCO) that all content for the 2020 sessions would be virtual and only available online? How could that happen? Maybe a pandemic?

Fast-forward to the surreal world of Covid-19 and the virtual highlights from ASCO. It is astonishing to consider that in contrast to this year, in 2019 there were 42,500 registrants for the ASCO meeting, and nearly 20,000 attendees from the US alone gravitated to this global event. This year, approximately 2215 abstracts were accepted for presentation during this year's program and more than 3400 additional abstracts were accepted for online publication, according to ASCO.

Nevertheless, as relentless as the pandemic has been, ASCO meetings fortunately take on a momentum of their own, even when the sessions are virtual. Despite the absence of face-to-face discussion, this year's agenda did not disappoint in providing data with sharp impact on oncology and implications for managing renal cell carcinoma (RCC). Controversies and trends from previous poster sessions and abstract presentations re-emerged, yielding some new if not "milestone" types of insights. But the devil is in the details, and unpacking information from online posts provides much to review with potential applications.

If there is scant evidence of dramatic shifts in the paradigm, occasionally seen during previous annual sessions, incremental progress has been sustained on many investigative fronts. With new data emerging from the virtual meeting, we now have even more ammunition to support selected approaches such as combination therapies with immune checkpoint inhibitors (ICIs) and TKIs, efforts to address upstream targets with novel agents in VHL-associated clear cell RCC, strategies to mitigate disease progression following ICI therapy, and more reason to cheer efforts exploring the prognostic significance of such factors as angiogenic and myeloid expression profiles. With regard to the latter, there is new substantial evidence supporting the prognostic potential of biomarkers in certain settings.

ASCO has always provided a much needed update to the ongoing major clinical trials, and analyses of these studies are now available through a number of websites as well as the coverage in this issue of the *Kidney Cancer Journal*. As we gauge the impact of data from these trials, we suggest

(continued on page 62)

Kidney Cancer Journal Author Guidelines

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

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

Manuscript Submission
Authors are required to submit their manuscripts in an electronic format, 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.

All material reproduced from previously published, copyrighted material should contain a full credit line acknowledging the original source. The author is responsible for obtaining this permission.

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

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

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

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

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

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

Copyright

Open Access information and policy:
KCJ is an open access journal. Please refer to full information regarding Free Access information and Policy statement here - http://www.kidney-cancer-journal.com/about-us.html#openaccess

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

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

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

Newsworthy, late-breaking information from Web-based sources, professional societies, and government agencies

KCA accepting applications for investigator awards

HOUSTON—The Kidney Cancer Associations is accepting applications for their Young Investigator Awards (YIAs) through August 5, 2020. Four $75,000 YIAs are available. Recipients will be announced in fall 2020.

YIAs encourage promising researchers in urology and clinical oncology who are planning to pursue an investigative career in kidney cancer.

The priority research areas that emerged as a result of the KCA's Think Tank: Coalition for a Cure, held last fall in conjunction with the 18th International Kidney Cancer Symposium, included cure or durable therapeutic response, improved screening and surveillance, neoadjuvant and adjuvant treatment strategies, and non-clear cell renal cell carcinoma. All grant proposals will be evaluated by an independent panel of reviewers, who are recognized experts in the field. They will conduct a blinded, scored review of all applications received.

Complete details about the grant application process are available here: https://kidneycancer.submittable.com/submit All questions regarding the grant application process should be submitted to grants@kidneycancer.org.

FDA approves additional pembrolizumab dosing strategy, 400 mg per 6 weeks

The FDA has approved an additional recommended dosage of 400 mg every six weeks (Q6W) for pembrolizumab (Keytruda), the anti-PD-1 therapy, across all adult indications, including monotherapy and combination therapy. This indication is approved under accelerated approval based on pharmacokinetic data, the relationship of exposure to efficacy and the relationship of exposure to safety. Continued approval for this dosing may be contingent upon verification and description of clinical benefit in the confirmatory trials. This new dosage option will be available in addition to the current dose of 200 mg every three weeks (Q3W).

"The important social distancing measures for COVID-19 have created a number of challenges for people with cancer, including keeping to planned treatment schedules," said Dr. Roy Baynes, senior vice president and head of global clinical development, chief medical officer, Merck Research Laboratories. "Today's approval of an every six-week dosing schedule for Keytruda gives doctors an option to reduce how often patients are at the clinic for their treatment."

Regenerative Medicine Advanced Therapy Designation awarded to ilixadencel in kidney cancer

STOCKHOLM—Immunicum has received Regenerative Medicine Advanced Therapy (RMAT) designation from the FDA for the company's lead candidate, ilixadencel, a cell-based, off-the-shelf immune primer for the treatment of metastatic renal cell carcinoma (mRCC). The FDA's decision was made based on the previously communicated results from the Phase 2 MERECA clinical trial that evaluated the safety and efficacy of ilixadencel in combination with Sutent® (sunitinib) in patients with newly diagnosed mRCC. Advantages of the RMAT designation include all the benefits of the Fast Track and Breakthrough Therapy Designation programs, including guidance and early interactions with the FDA to discuss potential surrogate or intermediate endpoints to support accelerated approval as well as potential ways to satisfy post-approval requirements.

Established in 2017 under the 21st Century Cures Act in the US, RMAT designation is an expedited program designed to facilitate the development and review of regenerative medicine therapies intended to address an unmet medical need in patients with serious conditions. An investigational regenerative medicine therapy (e.g. cell or gene therapy) is eligible for RMAT designation if it is intended to treat, modify, reverse or cure a serious condition and preliminary clinical evidence indicates that the drug or therapy has the potential to address unmet medical needs for such a disease or condition. As a cell therapy medicinal product, ilixadencel falls within the definition of a regenerative medicine therapy.

The latest results of the Phase 2 MERECA trial were presented in February at the ASCO-SITC Clinical Immuno-Oncology Symposium 2020 in Orlando, Florida. As of December 2019, the patient follow up data indicated a separation in Kaplan-Meier survival curves in favor of the ilixadencel treatment group in line with the projected separation based on the data from July 2019. The median OS value could not be calculated yet in either group as the data are not mature. The confirmed ORR for the ilixadencel treatment group was 42.2% (19/45) versus 24.0% (6/25) for the sunitinib control group.

KCA initiative brings personalized nutrition support to patients and caregivers

HOUSTON – The Kidney Cancer Association (KCA) is partnering with Savor Health® to bring Ina®, The Intelligent Nutrition Assistant to the kidney cancer community. Ina® provides personalized, evidence-based nutrition support "on demand" to help people living with cancer stay well-nourished and manage symptoms.

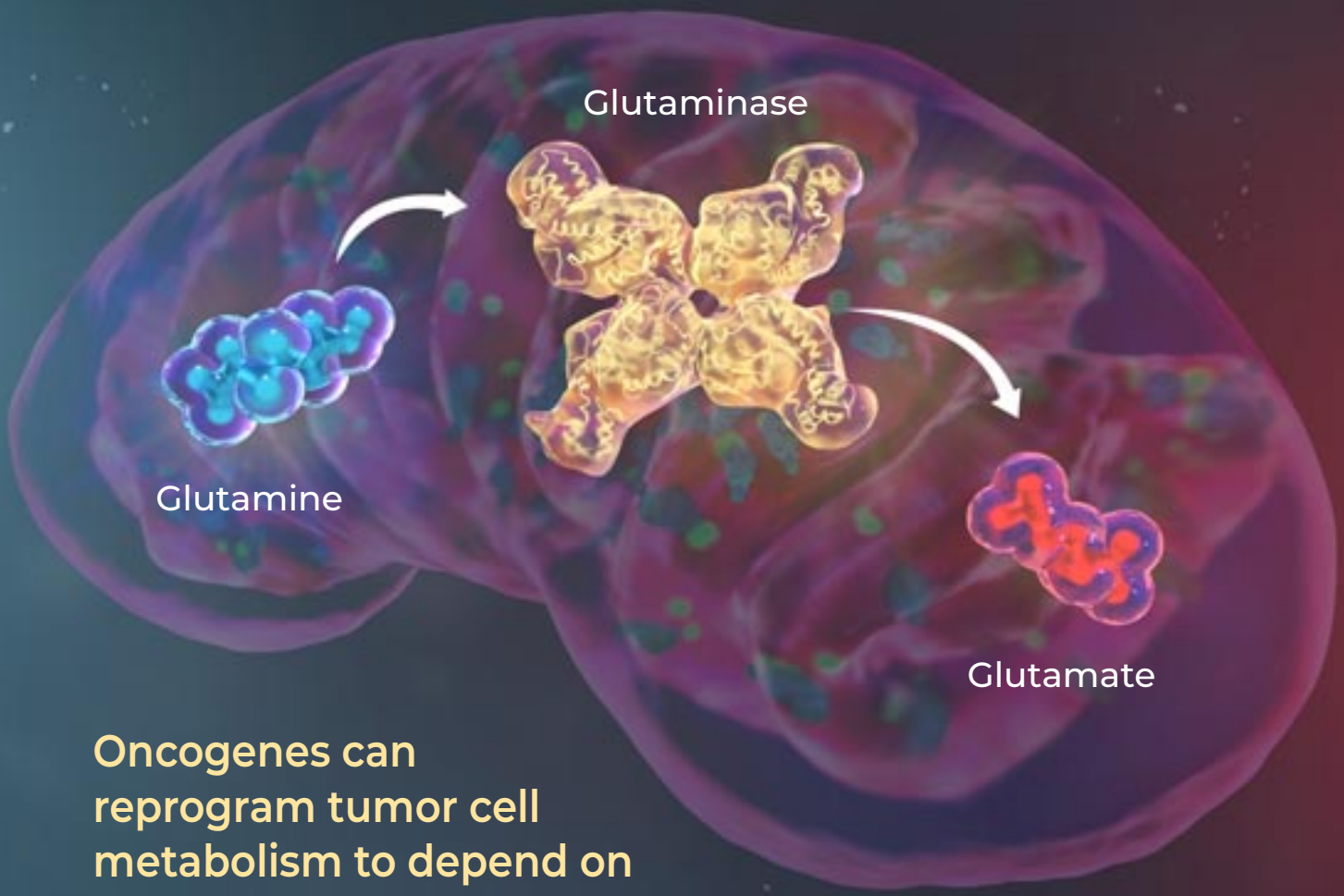
Developed by oncology-credentialed medical experts, Ina® is available 24/7 via SMS text. Patients and caregivers can text their questions on nutrition and symptom management from their cell phone and Ina® will respond with personalized nutrition tips, recipes, and answers – no phone calls or appointments necessary. All knowledge and advice is based on scientific evidence and the training of oncology-credentialed registered dietitians, nurses, and physicians who are experts in the needs of cancer patients.

(continued on page 62)

GLUTAMINASE

A PILLAR OF ONCO-METABOLISM

Go to **www.oncometabolism.com** to learn more.



Oncogenes can reprogram tumor cell metabolism to depend on glutamine for proliferation and survival.[1]

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

CALITHERA

www.Calithera.com

[1]Wong CC, et al. *Oncogene*. 2017;36:3359-3374.

Unpacking the Virtual ASCO20 Sessions: What Are The Latest Developments in the RCC Toolbox?

Senthil Pazhanisamy, PhD
Executive editor, *Kidney Cancer Journal*

Despite the unprecedented virtual nature of its program, this year's American Society of Clinical Oncology (ASCO) fulfilled its promise of offering a "diverse program, a multidisciplinary perspective, and a wealth of new research, and limitless opportunities for discovery" as thousands of oncologists around the world gather virtually to learn about the latest research in cancer. In ASCO20 meeting alone, the impactful results from several major trials have once again changed the landscape of front-line treatment that may provide a paradigm shift in how renal cancers are managed and/or treated in the future.

A review of highlights from the sessions suggests how latest breakthrough results could:

- Open up an avenue of a new class therapy: HIF-2 inhibitor MK-6428 owing to its promising efficacy and tolerability in patients with advanced RCC.
- Further clarify multiple choices in frontline ther apy, including the immune checkpoint inhibitor (ICI) therapy alone or combination with tyrosine kinase inhibitor (TKI).
- Address whether it is appropriate to sequence PD-1 inhibitor vs using them in combination.
- Help us assess the association of gene expression signatures and DNA alterations with response or resistance to immunotherapy.
- Provide important clues about angiogenic and myeloid expression markers to stratify patients based on transcriptomic profile as well as its prog nostic significance.

The abstracts included in this report have been selected by Robert A. Figlin, MD, Editor-in-Chief of the *Kidney Cancer Journal* and appear in an abbreviated format due to space constraints. These chosen abstracts highlight the most important trends in ongoing clinical studies and also reflect the breakthrough research from latest trials that impact the current standard of care in renal cancer. The full abstracts can be viewed on our KCJ website, please check out: https://kidney-cancer-journal.com/asco.html.

Abstract 5001: Pembrolizumab plus axitinib versus sunitinib as first-line therapy for advanced renal cell carcinoma (RCC): Updated analysis of KEYNOTE-426. *Elizabeth R. Plimack, Brian I. Rini, Viktor Stus et al.*

Results: 861 pts were randomly assigned (pembro + axi, n = 432; sunitinib, n = 429). Median (range) duration of follow-up for all pts was 27.0 mo (0.1-38.4). Pembro + axi improved OS (HR, 0.68 [95% CI, 0.55-0.85]; P< 0.001; 24-mo OS rate, 74% vs 66%) vs sunitinib. Median (95% CI) OS was not reached with pembro + axi and was 35.7 mo (33.3-NR) with sunitinib. Pembro + axi improved PFS (HR, 0.71 [95% CI, 0.60-0.84]; P< 0.001; 24-mo PFS rate, 38% vs 27%) vs sunitinib. For pembro +axi vs sunitinib respectively, median (95% CI) PFS was 15.4 (12.7-18.9) vs 11.1 mo (9.1-12.5); ORR was 60% vs 40% (P< 0.0001); CR rate was 9% vs 3%; and median DOR was 23.5 mo (range 1.4+ to 34.5+) vs 15.9 mo (range 2.3-31.8+). In general, the pembro + axi benefit was observed in all subgroups tested, including IMDC risk and PD-L1 expression subgroups. Post-hoc landmark analysis at 6-mo showed that pts on pembro + axi with ≥80% target lesion reduction had OS similar to that of pts with CR per RECIST v1.1 based on Kaplan-Meier curves and HR [95% CI] estimates (0.20 [0.05-0.84] vs. 0.10 [0.01-0.76], respectively) vs pts with 0-30% target lesion reduction. No new safety signals were observed.
Conclusions: Pembro + axi continued to demonstrate superior and durable antitumor activity vs sunitinib in pts with first-line aRCC with a 27-mo median follow up; no new safety signals were observed. Clinical trial information: NCT02853331.
Research Funding: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA

Abstract 5003: Phase II study of the oral HIF-2 inhibitor MK-6482 for Von Hippel-Lindau disease–associated renal cell carcinoma. *Eric Jonasch, Frede Donskov, Othon Iliopoulos et al.*

Results: As of December 6, 2019, 61 pts were enrolled; median (range) age was 41 years (19-66) and most pts

were male (52.5%) and had ECOG PS of 0 (82.0%). The most common lesions outside the kidney (non-RCC tumors) were CNS hemangioblastomas (80.3%) and pancreatic lesions (50.8%). Median (range) duration of treatment was 9.9 mo (1.9-18.2) and 95.1% of pts remain on therapy. Three pts discontinued (AE, n = 1; death [fentanyl toxicity], n = 1; pt decision, n = 1). There were 17 confirmed responses (ORR, 27.9% [95% CI, 17.1-40.8%]) and 8 (13.1%) unconfirmed (documented at 1 timepoint and to be confirmed at subsequent timepoint) responses; all responses were PRs. Of 61 pts, 53 (86.9%) had decrease in size of target lesions. In 17 pts with confirmed response, median (range) DOR was not reached (2.1-9.0 mo) and median (range) TTR was 5.5 mo (2.7-14.0). Responses were also observed in CNS, retinal, and pancreatic lesions. Median PFS was not reached; 12-mo PFS rate was 98.3%. Treatment-related AEs (TRAEs) occurred in 96.7% of pts, mostly grade 1 (44.3%) or grade 2 (42.6%) and primarily (≥20%) anemia (83.6%; considered an on-target-toxicity), fatigue (49.2%), and dizziness (21.3%). Grade 3 TRAEs occurred in 9.8% of pts, primarily fatigue (4.9%) and anemia (3.3%). There were no grade 4 or 5 TRAEs. One pt discontinued because of a TRAE (dizziness).

Conclusions: MK-6482 showed promising efficacy and tolerability in pts with VHL-associated ccRCC and responses in other VHL-related lesions. These data support further investigation of MK-6482 in VHL disease. Clinical trial information: NCT03401788.

Research Funding: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA

■ Abstract 5006: Phase II study of nivolumab and salvage nivolumab + ipilimumab in treatment-naïve patients (pts) with advanced renal cell carcinoma (RCC) (HCRN GU16-260). *Michael B. Atkins, Opeyemi Jegede, Naomi B. Haas et al.*

Results: 123 pts with clear cell(cc) RCC were enrolled between 5/2017 and 12/2019 at 12 participating HCRN sites. Median age 65 (range 32-86 years); 72% male. IMDC favorable 30 (25%), intermediate 79 (65%) and poor risk 12 (10%). 22 (18%) had a component of sarcomatoid histology (SARC). 117 pts are currently evaluable for response. RECIST defined ORR was: 34 (29.3%)[CR 5 (4.3%), PR 29 (24.8%)], SD 47 (40.2%), PD 36 (30.7%). ORR by irRECIST was 35%. ORR by IMDC was: favorable 12/29 (41.4%), interme-diate/poor 22/87 (25.3%) and for SARC 6/22 (27.3%). Median DOR is 13.8 (10.9, NA) mo. Median PFS is 7.4 (5.5, 10.9) mo. 110 pts remain alive. 60 pts (54 PD, 6 pSD) to date were potentially eligible for salvage nivo/ipi (Part B), but 28 did not enroll due to symptomatic PD (17), grade 3-4 toxicity on nivo (8), other (3). 27 of 32 Part B pts are currently evaluable for efficacy and 30 for toxicity. Best response to nivo/ipi was PR (11%), SD (30%), PD (59%). ORR by irRECIST was 19%. Grade 3-5 Treatment-related AEs (TrAE) were seen in 35/123 (28)% on nivo with 1 death due to respiratory failure. Grade 3-4 TrAE were seen in 10/30 (33%) on nivo/ipi with 0 deaths. Correlative studies are pending.

Conclusions: Nivo monotherapy is active in treatment naïve ccRCC across all IMDC groups. Toxicity is consistent with prior nivo studies. Salvage treatment with nivo/ipi after nivo monotherapy was feasible in 53% of pts with PD/pSD, with 11% responding. Clinical trial information: NCT03117309.

Research Funding: Bristol Meyers Squibb

■ Abstract 5007: FRACTION-RCC: Innovative, high-throughput assessment of nivolumab + ipilimumab for treatment-refractory advanced renal cell. *Toni K. Choueiri, Harriet M. Kluger, Saby George et al*

Results: 46 pts were randomized to NIVO+IPI. Pts had 0 (n = 1), 1 (n = 10), 2 (n = 12), 3 (n = 10), or ≥4 (n = 13) prior lines of therapy. All pretreated pts had prior anti-PD-(L)1-, none had prior anti-CTLA-4- therapy, and 37 had prior TKI-based therapy; 45 pts progressed on anti-PD-(L)1 as the most recent therapy. Most pts had clear cell aRCC (n = 44). After a median study follow-up of 8.9 months, ORR was 15.2%; no pts achieved complete response and 7 achieved partial response. DOR ranged from 2–19+ months (n = 7); 5 pts had ongoing response. Six of 7 responders had received ≥2 prior lines of therapy. Any-grade treatment-related adverse events (AEs) were reported in 36 pts (78.3%; fatigue, rash [both 19.6%], and diarrhea [17.4%] were most common). Grade 3–4 treatment-related AEs were reported in 13 pts (28.3%; diarrhea [8.7%], amylase and lipase [both 6.5%] were most common). Treatment-related immune-mediated AEs of any grade were reported in 22 pts (47.8%; rash [19.6%], diarrhea [17.4%], and alanine aminotransferase [8.7%]). No treatment-related deaths were reported. Updated and expanded results with an additional 3 months of follow-up will be presented.

Conclusions: These results suggest that NIVO+IPI may provide durable partial response in some pts with prior progression on checkpoint inhibitors, including some heavily pretreated pts. The safety profile of NIVO+IPI in FRACTION pts was similar to historic data in aRCC with this combination. Clinical trial information: NCT0299 6110.

Research Funding: Bristol-Myers Squibb

■ Abstract 5008: Phase II trial of lenvatinib (LEN) plus pembrolizumab (PEMBRO) for disease progression after PD-1/PD-L1 immune checkpoint inhibitor (ICI) in metastatic clear cell renal cell carcinoma (mccRCC). *Chung-Han Lee, Amishi Yogesh Shah, James J Hsieh et al.*

Results: 104 pts were enrolled. At data cutoff (January 12, 2020), 71 (69%) pts were still on study treatment. Most pts had ≥2 prior anticancer regimens (58%). 91 of 104 pts were evaluable for response at Week 12 (13 pts NE at Week 12); 46 of 91 pts achieved a confirmed partial response for an ORR of 51% (Table). Median progression-free survival (PFS) was 11.7 months and median duration of response (DOR) was 9.9 months. The most common treatment-related adverse events (TRAEs) were fatigue (49%), diarrhea (44%), proteinuria (37%), hypertension (31%), nausea (31%), dysphonia (29%), stomatitis (29%), and arthralgia (27%). There was 1 grade 5 TRAE (upper gastrointestinal hemorrhage). 43% of pts required dose reduction and 12% of pts discontinued treatment due to TRAEs. Response and safety data will be updated to include all pts evaluable at an April 9, 2020 cut-off.

Conclusions: LEN + PEMBRO demonstrated promising antitumor activity in pts with mccRCC with disease progression following ICI therapy. No new safety signals were detected. Efficacy outcomes by investigator review per irRECIST. Clinical trial information: NCT02501096.
Research Funding: Eisai Inc., Woodcliff Lake, NJ, USA, and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co. Inc., Kenilworth, NJ, USA

■ Abstract 5020: Biomarker analysis and updated clinical follow-up of preoperative ipilimumab (ipi) plus nivolumab (nivo) in stage III urothelial cancer (NABUCCO). *Nick Van Dijk, Alberto Gil Jimenez, Karina Silina et al.*

Results: After a median FU of 15.6 months, 2 pts relapsed (both non-pCR); 1 of these 2 pts died of metastatic disease. Tumors showing complete response (CR, for biomarker analysis defined as pCR, CIS or pTa) had a significantly higher tumor mutational burden than non-CR tumors. CR to ipi+nivo was independent of baseline CD8 T-cell presence. There was no difference between CR and non-CR tumors in baseline immune gene signatures, such as interferon gamma and T-effector signatures. Surprisingly, exploratory gene expression analysis revealed that non-CR was associated with a baseline B cell immune signature, particularly immunoglobulins and genes involved in B cell receptor signaling. CD20 positive cells (by mIF) and presence of tertiary lymphoid structures (TLS) at baseline were also associated with non-CR. Upon treatment with ipi+nivo, early and mature TLS increased significantly in responding tumors. A subset of pts showed CR in the bladder, but non-CR in a local LN tumor focus. WES revealed that these LN metastases were genetically different from the primary tumor bulk.
Conclusions: At 15.6 months follow-up, recurrence after pre-operative ipi+nivo was low. Pathological complete response was not restricted to tumors exhibiting preexisting T cell immunity. Clinical trial information: NCT03387761.
Research Funding: Bristol Meyers Squibb

■ Abstract 5024: Association of gene expression with clinical outcomes in patients with renal cell carcinoma treated with pembrolizumab in KEYNOTE-427. *David F. McDermott, Jae-Lyun Lee, Frede Donskov et al.*

Results: Patient characteristics for this analysis were comparable to the overall population. In cohort A, T-cell–inflamed GEP (n = 78) was statistically significantly associated with a better ORR (P = 0.021; AUROC = 0.65) but not PFS (P = 0.116). No other TME canonical signatures showed a correlation with ORR or PFS. ORR was estimated for mutations (**Table**).
Conclusions: RNA-sequencing–based, T-cell–inflamed GEP was associated with ORR in patients with clear cell renal cell carcinoma receiving first-line pembrolizumab. Precision was limited by sample size for estimating ORR by specific gene mutation status. Evaluation of tissue-based biomarkers in larger studies are planned. Biomarker analyses from patients in cohort B will also be presented. Clinical trial information: NCT02853344.
Research Funding: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA

■ Abstract 5061: Association of neutrophil to lymphocyte ratio (NLR) with efficacy from JAVELIN Renal 101. *Mehmet Asim Bilen, Brian I. Rini, Robert J. Motzer et al.*

Results: In the avelumab + axitinib arm, patients with < median NLR (N = 217) had longer observed PFS (stratified HR, 0.85; 95% CI, 0.634, 1.153) and longer observed OS (stratified HR, 0.51; 95% CI, 0.300, 0.871) than patients with ≥ median NLR (N = 217). The ORR was 57.1% in patients with < median NLR vs 47.5% in patients with ≥ median NLR, with complete response in 5.5% vs 1.4%. Multivariate analysis showed that low NLR was associated with longer PFS and OS by treating baseline NLR as either a continuous variable or a binary variable (dichotomized by median).
Conclusions: Low NLR was associated with better observed treatment outcomes in patients with aRCC who received avelumab + axitinib. Clinical trial information: NCT02684006.
Research Funding: This study was funded by Pfizer, as part of an alliance between Pfizer and Merck KGaA, Darmstadt, Germany.

■ Abstract 5080: Axitinib plus pembrolizumab in patients with advanced renal cell carcinoma: Long-term efficacy and safety from a phase Ib study. *Michael B. Atkins, Igor Puzanov, Elizabeth R. Plimack et al.*

Results: At data cut-off date (July 3, 2019), median OS was not reached; 38 (73.1%) patients were alive. 14 (26.9%) patients had died, none were related to treatment. The probability of being alive was 96.1% (95% CI 85.2–99.0) at 1 year, 88.2% (95% CI 75.7– 94.5) at 2 years, 82.2 % (95% CI 68.5– 90.3) at 3 years, and 66.8 % (95% CI 49.1–79.5) at 4 years. Median PFS was 23.5 (95% CI 15.4–30.4) months. Median duration of response was 22.1 (95% CI 15.1–not evaluable) months. Median time on treatment with the combination AXI/pembro was 14.5 months (n=52), median time on pembro after AXI discontinuation was 9.0 months (n=10), and median time on AXI after pembro discontinuation was 7.5 months (n=11). After stopping study treatment, 22 patients received subsequent systemic therapy, including nivolumab and cabozantinib (n=6 each). Grade 3/4 AEs were reported in 38 (73.1%) patients. 20 (38.5%) patients discontinued either drug due to AEs: 17 (32.7%) patients discontinued AXI, and 13 (25.0%) patients discontinued pembro with 10 (19.2%) discontinuing both drugs. Dose reduction of AXI due to AEs was reported in 16 (30.8%) patients. The most common AEs reported were diarrhea (84.6%), fatigue (80.8%), hypertension (53.8%), cough (48.1%), and dysphonia (48.1%). Increased alanine aminotransferase and aspartate aminotransferase occurred in 44.2% and 36.5% of patients, respectively. With this longer follow-up, there were no cumulative AEs or new AEs. OS by IMDC risk group will be presented.
Conclusions: In patients with advanced RCC with almost 5 years of follow-up, the combination of AXI/pembro continues to demonstrate clinical benefit with no

new safety signals. Clinical trial information: NCT02133742.
Research Funding: Pfizer

■ **Abstract 5082: Immune infiltration and angiogenesis as markers of outcome in the post-nephrectomy setting: Transcriptomic data from patients receiving placebo on a randomized phase III trial (PROTECT).** *A. Ari Hakimi, Martin H Voss, Fengshen Kuo et al.*
Results: Tumors from 236 patients were available for analysis. Overall, 37% developed metastatic recurrence and 81% were alive at last follow up. On univariate analysis increasing tumor stage, higher UISS score, and angiogenesis/myeloid subgroups (high – H and low – L) were associated with worse DFS and OS (all p values <0.05). On multivariate analysis TME subgroups remained significant for worse DFS and OS (Table).
Conclusions: Microenvironmental subgroups stratified into angiogenic and myeloid expression profiles carry independent prognostic significance and should be further explored to guide future biomarker-directed adjuvant trials. Clinical trial information: NCT01235962.
Research Funding: Novartis, Philantropic KCJ

Current Guidelines for Treating Oligometastatic RCC: An Ever-changing Paradigm Integrates New Strategies

Alexandra Drakaki, MD, PhD
Assistant Professor of Medicine
(Hematology/Oncology) and Urology
Medical Director of the GU Oncology
Program at the Institute of Urologic
Oncology at UCLA
Los Angeles, California

Albert J. Chang, MD
Associate Professor, Vice Chair of Surgical Services
and Brachytherapy Service Chief
Department of Radiation Oncology
David Geffen School of Medicine at UCLA
and UCLA Institute for Urologic Oncology
Los Angeles, California

Allan J. Pantuck, MD, MS, FACS
Professor and Vice Chair for Academic Affairs
Department of Urology
UCLA Institute for Urologic Oncology
Los Angeles, California

This review provides an update on emerging data from current literature on the treatment of oligometastatic renal cell carcinoma. A rapidly evolving paradigm of treatment reflects multimodal approaches ranging from active surveillance to combinations of stereotactic radiotherapy and systemic therapies. Guidelines for determining optimal choices are presented.

Oligometastatic disease can be conceptualized as an intermediate state between limited, organ-confined primary cancer and diffuse, polymetastatic disease. Oligo, which means few or scanty, is derived from the Greek "oligos." For clinicians, the term refers to a limited tumor burden potentially amenable to local treatment approaches, and a number of studies have redefined this definition over 25 years.[1-3] When first used, the term referred to a state of limited metastatic burden, where some patients may be amenable to cure if all known metastatic deposits can be extirpated or ablated, and further distant progression delayed or avoided altogether.[1] A more quantitative definition of the oligometastatic state suggests up to three or up to five lesions, by various accounts. Oligometastases may be present at the initial time of diagnosis of the primary tumor (called synchronous), or separated by an interval of time for recurrence since the initial diagnosis or treatment of the primary tumor (called metachronous). Metachronous oligometastases, particularly those with a long delay in the time to recurrence, are generally thought to have a better prognosis than tumors with metastatic disease at the time of presentation.

Keywords: oligometastases, renal cell carcinoma, ablation, radiotherapy, metastasectomy, nephrectomy, active surveillance, SBRT, IMDC risk factors, systemic therapy.

Corresponding Author: Allan J. Pantuck, MD, University of California, Los Angeles, 200, Medical Plaza Driveway Suite 140, Los Angeles, CA 90095; Phone: (310) 794-7700. Email: APantuck@mednet.ucla.edu

Clear cell renal cell carcinoma (ccRCC) is capable of both lymphatic and hematogenous spread, and has been noted to have the ability to spread to nearly every possible site in the body. Historically, it was noted that a small subset of patients presented with an indolent form of advanced disease in which surgical resection of small volume metastatic deposits led to serial, protracted disease free intervals, lending early support to the concept of metastasectomy. These early clinical observations have recently been supported by modern, large-scale genomic sequencing initiatives that have defined the genetic underpinnings for the diversity of metastatic phenotypes. These patterns of spread range from rapid and simultaneous metastatic dissemination to multiple tissue sites, to a highly attenuated pattern characterized by slower progression to solitary or oligometastatic disease. The most extreme such presentation being described comprises a protracted latency of up to two decades as a feature of tumors that metastasize to the pancreas.[4] While the hallmark genomic drivers of ccRCC metastases appear to be loss of chromosomes 9p and 14q,[4-6] cases that are multi-site rapid progressors are characterized by VHL wildtype and BAP1 driven evolutionary subtypes.[4] On the other hand, tumors that display a more attenuated phenotype of spread appear to harbor clones with PBRM1 mutations.[4]

The treatment paradigm for oligometastatic renal cell carcinoma (RCC) has moved in multiple directions beyond just surgery, especially in the post-cytokine era, as new treatments have vastly expanded the armamentarium and debunked earlier concepts of how outcomes can be improved. One of the concepts discarded from earlier studies was that oligometastatic RCC represents a radiation-resistant malignancy, showing a high degree of resistance to conventionally fractionated radiation therapy. Stereotactic body radiotherapy (SBRT) has been increasingly utilized for treatment of metastatic sites with high local control rates and low toxicity.

Metastatic RCC accounts for up to 25-30% of patients at diagnosis and leads to death in most cases.[7] Additional studies from that period pointed toward a poor prognosis for patients with oligometastatic RCC, with a 5-year survival rate of <10%.[8] As part of their identifying the challenges in the pre-cytokine era, these reports also examined other issues, for example, whether the number of metastatic sites rather than location dictated overall survival in oligometastatic RCC. One of these reports by Han et al,[9] found that oligometastatic RCC confined to only one organ site had a better prognosis than RCC in multiple organs. Survival in patients with disease limited to the lung was similar to that of patients whose disease was limited to bone.

This early pivotal retrospective study is important for other reasons, offering a benchmark for how much more information was needed at the time (2003) on the treatment of oligometastatic RCC and suggesting how future reports would explore more precisely emerging data. For example, Han et al[9] urged physicians to consider enrolling patients with multiple organ involvement into clinical trials because these patients appear to have a lower response rate to immunotherapy. It would be years after this published study that immunotherapy would begin to have a much more robust influence on the treatment of oligometastatic RCC in patients with multiple organ involvement and it is intriguing to consider how much the treatment algorithm has changed in the post-cytokine environment and the advent of checkpoint inhibitors.

Since then new concepts about treatment have ushered in a dramatically different era, albeit with its own set of new challenges. But unlike the challenges of decades ago when oligometastatic RCC was perceived as largely radioresistant, new challenges have emerged. These challenges are driven by advances in targeted therapies, the use of immune checkpoint inhibitors, and perhaps most significantly, the application of stereotactic body radiation therapy (SBRT) for oligometastatic RCC, thus improving outcomes in an otherwise radioresistant malignancy.

Challenging Choices in Treatment

These new challenges, however, are more related to our ability to sort through and resolve many issues and questions related to an abundance of data affecting our choices—whether to treat the tumors as metastatic or local disease, should it be removed, radiated, or observed? In evaluating our choices, we need to determine criteria for selection of appropriate candidates for surgical metastasectomy, understand the safety of combining SBRT with TKI agents and checkpoint inhibitors, assess the extent to which patients can undergo active surveillance as opposed to upfront systemic therapy, determine what time between nephrectomy and recurrence of RCC could be an indicator for observation, and consider how unique metastatic site influences the symptoms, deterioration of general condition and activities of daily living.

In addressing these issues, this review will focus on the most recent papers in the field and how emerging data could reshape treatment rationale. One of the controversies addressed extensively has been the role of complete surgical metastasectomy of RCC in the post-cytokine era. This is important in view of the fact that data supporting complete metastasectomy (CM) were derived primarily from the era of cytokine therapy.[10] Studies like those of Lyon et al addressed whether complete metastasectomy remains beneficial in patients who receive more recently approved systemic therapies. In doing so, they examined survival outcomes among patients treated with CM in the era of targeted therapy and checkpoint blockade availability.

Lyon et al identified 586 patients who underwent partial or radical nephrectomy of unilateral, sporadic renal cell carcinoma with a first occurrence of metastasis between 2006 and 2017. Of these patients 158 were treated with complete metastasectomy. The authors observed that CM was associated with improved CSS and OS compared to incomplete or no CM in the era of targeted therapy and checkpoint blockade availability. This association persisted after adjusting for the timing, location and number of metastases and it was observed in the context of 93% of patients who underwent CM but did not receive systemic treatment of the index metastasis.[10]

These data suggest that CM should continue to have a role in the management of oligometastatic RCC despite the improved efficacy of targeted therapies and checkpoint inhibitors relative to previously available systemic agents. Careful patient selection for this approach remains key. In this series most patients chosen for CM had a solitary metastasis and a prolonged disease-free interval between nephrectomy and metastasis development, consistent with known prognostic features of CM. Moreover, a strategy of CM followed by observation has the potential advantage of sparing patients the additional morbidity of systemic agents while preserving the efficacy of these agents for use later in the disease process.

Emphasizing that careful patient selection for SM is essential, Kato et al.[11] analyzed a host of factors all of which should be considered when determining which patients are candidates for surgery. Reviewing the literature in an editorial commentary, Kata et al cited numerous articles pointing toward a general consensus on clinical and pathological factors, including: performance status, disease-free interval, abnormal laboratory data, and sites of metastases, Fuhrman grade, and risk category in prognostic models. Acknowledging reports that complications and in-hospital mortality rates are not negligible in patients treated with targeted therapy who undergo surgical resection.[12, 13] Kato et al identified patients with a good indication for SM of RCC. These patients should have the following features:

- Solitary or oligometastatic lesions.
- Symptomatic metastases deteriorating activities of daily living and/or quality of life.
- Resistance to radiotherapy and/or recently developed systemic therapies.
- Easy surgical accessibility and resectability with a lower rate of complications.

Surgical Metastasectomy: Site-specific Clinical Factors

Treatment strategies may be influenced by site-specific clinical factors with prognostic value for local treatment

of metastases.[11] The four most common metastatic sites for RCC are lung, bone, non-regional lymph nodes, and liver.

Pulmonary metastases. SM is most commonly performed for patients having a limited number of unilateral pulmonary metastases. Patients with disease limited to the lung are the best responders to cytokine or targeted therapy.[14] Although many studies have reported clinical benefit for pulmonary lesions, a poor prognosis is more likely to be observed in patients with a higher number of lesions, concomitant mediastinal nodal metastases, and incomplete resection.

Bone metastases. As the second most common metastatic site in mRCC, lesions to the spine are the most affected bone site. Excisional surgery of bone metastases is an extraordinary and technically demanding procedure because the metastases are hypervascular and destructive, with reconstruction further complicating the likelihood for a successful outcome. In view of the negative impact of complication after SM in bone and brain metastases, SBRT may represent an alternative option to improve treatment options in these patients.

Lymph nodes, liver and pancreatic metastases. The data are sparse on these metastatic sites, particularly for isolated lymph nodes. The guideline from Kato et al is that SM for these lesions should be carefully considered in patients with good performance status and completely resectable solitary metastases.[15] RCC tumors spread rarely to the pancreas, but when they do, they represent solitary metastatic involvement in up to half of these cases.[16] This fact, combined with the often attenuated and delayed pattern of spread noted above, supports surgical resection as an option with durable long term survival in surgically amenable cases.

The controversy surrounding the benefit of SM is largely due to the lack of high-level evidence on its role in terms of improving survival in the era of systemic therapy. No randomized trials have evaluated the role of complete SM, although many observational studies have suggested a survival benefit of an aggressive surgical approach.[17] A systematic review of the literature derived from 56 retrospective studies in Embase and Medline databases offers valuable insights, however, with regard to prognostic factors to consider in clinical decision making when patients may be candidates for SM. Median overall survival in this review by Ouzaid et al[17] ranged from 36 to 1432 months for those undergoing SM vs 8 to 27 months when SM was not performed. The most important prognostic factor for OS was complete resection of metastases. Other prognostic factors included disease-free survival from nephrectomy, primary tumor features (T stage 3 or more, high grade, sarcomatoid features, and pathological status), the number of metastases, and performance status. Survival benefit was most apparent with lung metastasectomy.

Concluding that only a small subgroup of patients may benefit from SM, Ouzaid[17] nevertheless suggest it is a worthwhile option to consider, reiterating the conventional wisdom that the best candidates are those with good performance status, a long time interval with no evidence of disease, a relatively limited burden of disease (ideally a solitary metastasis), and achievable metastases-free status. Confirming what almost every series in the literature has observed, the review suggests that patients with synchronous metastases have worse prognosis. Some sites—such as brain and liver—are also associated with a poor prognosis and SM in this subset may not provide potential benefit.

An intriguing question raised by the literature is to what extent outcomes may be influenced by more specific secondary analyses following cytoreductive nephrectomy for oligometastatic RCC. A case in point: a study by Pierorazio et al[18] who examined whether outcomes could be predicted based on the fractional percentage of tumor removed (FPTV). Few studies have followed up on the hypothesis raised by this report, but the authors suggest some significant results: 55 patients had their FPTV calculated; 45 had >90% FPTV. The median disease-specific survival times were 11.6 and 2.9 months for patients with >90% and <90% FPTV removed (P=0.002).

The value of this provocative study also lies in its hypothesis-generating aspects. Although FPTV may not be the primary explanation for the discrepancy in survival, this measure could be an easy-to-calculate surrogate for complex factors driving the survival benefit in patients who had higher results for FPTV. Thus, the FPTV criteria could allow surgeons to easily identify patients who will benefit from cytoreductive surgery without using complex performance scales or nomograms.

Active Surveillance: When Can Immediate Aggressive Treatment be Delayed?

With the publication of a pivotal, prospective, Phase 2 trial by Rini et al[19] in 2016, the concept of active surveillance began to undergo more consideration as a viable approach. This study encouraged further investigations that also undercut the widely held perception that tumors needed to be treated immediately and aggressively. Since the publication of the Rini paper, a significant shift in thinking, including guidelines issued by the European Society for Medical Oncology, have had a sharp impact on treatment approaches.[20]

Among the salient factors accounting for this change in rationale is the paradigm of risk stratification from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC). Rini et al[19] relied on tis classification scheme to propose that AS may be an acceptable option. Patients can be classified into good, intermediate, or poor prognosis according to:

- Time from diagnosis to treatment (<1 year).
- Karnofsky performance status (<80%).
- Anemia
- Hypercalcemia
- Thrombophilia
- Neutrophilia

The absence of all previous parameters identifies patients in a favorable risk group; the presence of one or two, and at least 3 prognostic factors classifies patients into intermediate and poor-risk categories, respectively. The ESMO guidelines introduced the possibility of managing selected patients with favorable disease using AS. The Rini study has been touted as the study with the best available evidence; 48 patients with treatment-naïve,

NOW ENROLLING

The **COSMIC-313** study investigates cabozantinib with nivolumab and ipilimumab vs nivolumab and ipilimumab alone, in advanced, treatment-naive renal cell carcinoma. This study is part of the COSMIC Trials program evaluating cabozantinib, alone or in combination with immune checkpoint inhibitors, for the treatment of solid tumors. **Learn more at COSMIC313.com**

Eligibility

This study is currently enrolling patients who have not received prior systemic therapy for unresectable locally advanced or metastatic renal cell carcinoma with a clear cell component. Patients must meet additional inclusion and exclusion criteria to be eligible for enrollment.

Learn more at ClinicalTrials.gov or contact Exelixis Medical Information at 1-888-EXELIXIS (1-888-393-5494). NCT03937219.

THE COMBINATION OF CABOZANTINIB WITH NIVOLUMAB AND IPILIMUMAB IS NOT APPROVED FOR THE USE UNDER INVESTIGATION

EXELIXIS®

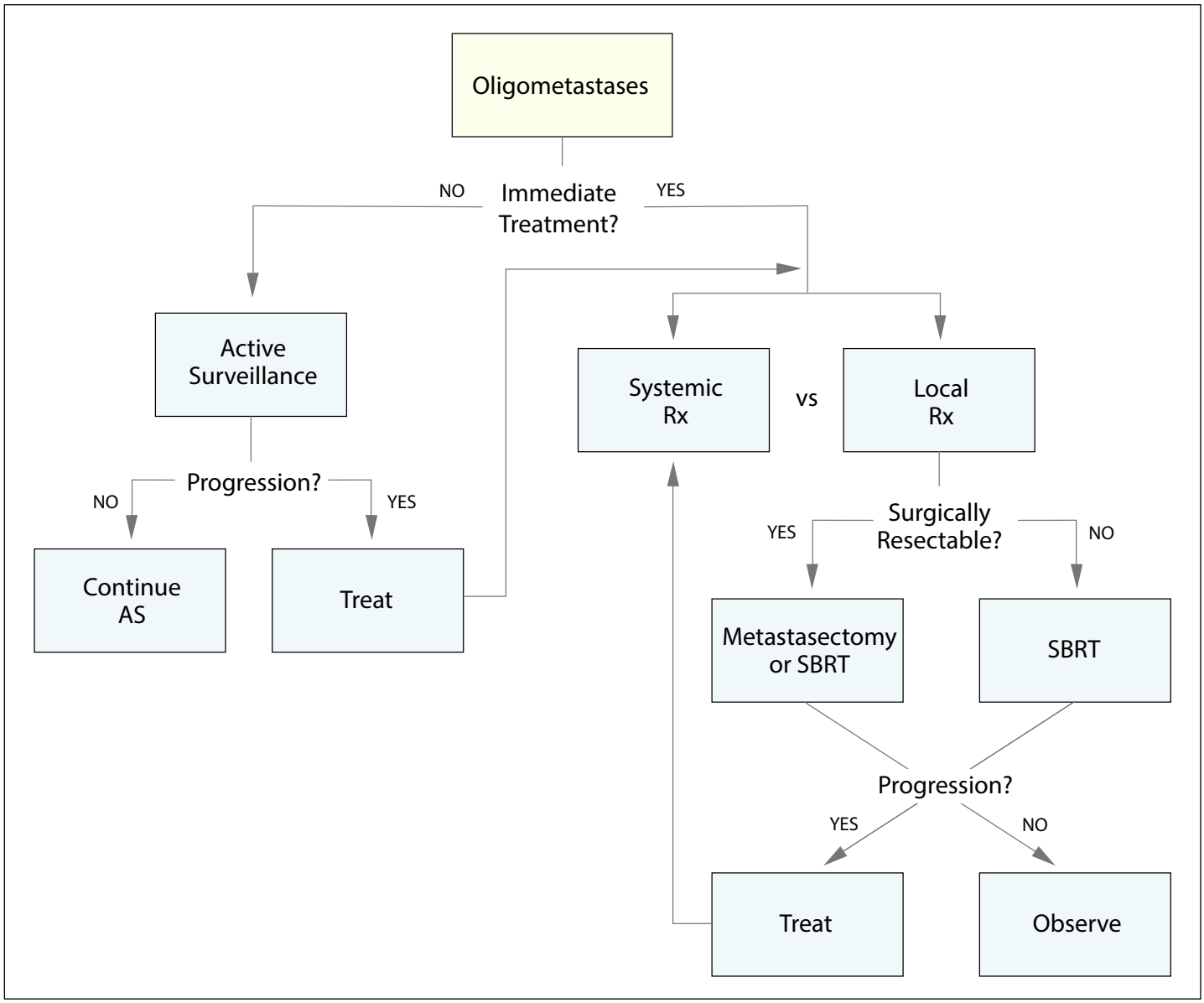


Figure 1. Treatment algorithm for oligometastases. Factors to be considered in managing oligometastases related to the primary tumor are indicated in this treatment algorithm. Active surveillance can be an option when immediate aggressive treatment can be delayed. In surgically resectable cases, stereotactic body radiation therapy (SBRT) is an option in selected patients. High local control rates have been observed with SBRT in RCC tumors once thought to be radioresistant, and is increasingly utilized for treatment of oligometastatic disease.

asymptomatic RCC were followed with AS for a median of 14.9 months. The key findings from the Rini report:

- A greater number of IMDC adverse risk factors and a greater number of metastatic sites were associated with a shorter surveillance period.
- In the favorable-prognosis group, (29 or 0% of patients) with ≤1 IMDC risk factor and 2 or fewer organs with metastatic disease, estimated median surveillance duration was 22.2 months.
- In an unfavorable prognosis group, estimated median surveillance duration was 8.4 months. Overall, 46% of patients died during the study from mRCC.

Although hypothesis-generating at this point, Rini et al postulated an immunogenic basis for the good outcome in patients who had a better prognosis with AS. The report raises a tantalizing biologic basis for the outcomes by observing that patients on AS had significantly fewer immunosuppressive cells and a higher number of interferon-gamma-producing T cells than the cohort of patients who began systemic therapy immediately. If this were true, then such a phenotype could be associated with an anti-tumor response, perhaps accounting for the relatively indolent nature of tumor growth reported in patients on AS.

Following the Rini report, additional studies have further delineated factors possibly accounting for the variation in benefit related to AS. Two retrospective analyses picked up on the direction from Rini et al. One of these by Woldu et al,[21] derived from 4 years of the National Cancer Data Base, looked at the timing of targeted therapy after cytoreductive nephrectomy—early within 2 months), moderately delayed (2- months), and delayed (6- months). The analysis, based on data from 2716 pa-

tients, found that delay in initiation of therapy was not independently associated with overall survival. The conclusion: in carefully selected patients, outcomes might not be compromised with initial observation.

A retrospective analysis by Bimbatti et al,[22] studying 52 patients with RCC over 9 years, examined whether IMDC risk class, number of metastatic sites, and tumor burden (TB) changed over time, whether these factors affected survival and how using such data could influence the decision about when it is appropriate to initiate systemic therapy. TB was defined as the sum in millimeters of the longest tumor diameter of each lesion.

Seen through the lens of IMDC prognostic classes, the median time on AS was 20.4 months in the favorable risk group, 17.8 months in the intermediate-risk group, and 5 months in the poor-risk group. Baseline IMDC class was the only factor to independently predict time on AS. An increased number of metastatic sites during AS and an increase in TB adversely affected overall survival. The "take-home" messages from Bimbatti et al are:

- AS could be considered a safe option in managing selected patients with asymptomatic good- or intermediate-risk status in oligometastatic RCC.
- An increase in TB during the AS time reflects a need to consider initiating fist-line systemic therapy, based on the post-surveillance overall survival results.

Do the results from Rini et al, Bimbatti et al and similar findings suggest that AS is underutilized and should be integrated more widely in the treatment algorithm? An Editorial Commentary by Ficarra et al[23] suggests not necessarily. For these authors, AS is a cautionary tale, of value in a well-selected subset of patients with indolent, asymptomatic, and good-risk. They conclude that delaying systemic treatment does not seem to have negative consequences on overall survival but questions persist. They suggest that there is a dilemma as to whether cancer control in patients managed with an initial AS protocol vs immediate systemic therapy is compromised, and to what extent initial debulking is also critical. They leave open the question whether AS in oligometastatic RCC should be considered an option or an exception until further studies clarify the risks and benefits.

SBRT: Widening the Net for Local Control of Oligometastatic RCC

Advances in imaging and precision of modern radiation delivery has enabled the development and adoption of SBRT for the treatment of both primary tumors and metastatic sites.[24] High local control rates have been observed with SBRT in RCC tumors once thought to be radioresistant, and is increasingly utilized for treatment of oligometastatic disease. In select de novo oligometastatic and oligorecurrent patients, SBRT offers the potential to delay the onset of a new line of systemic therapy that may be associated with adverse side effects.[24] Recent studies have demonstrated the advancement of SBRT in comparison to earlier studies of conventional fractionated radiotherapy (CF-EBRT). Reports have suggested that SBRT leads to greater and more durable radiographic responses and improved local control compared to CF-EBRT with minimal toxicity.

In addition to the editorial commentary by Beckham et al, recent reports have illustrated the integration of SBRT into the treatment algorithm[25-29] and have addressed a broad spectrum of issues related to its use to improve outcomes for enlarging or anatomically problematic masses.[28] In 2019, the National Comprehensive Cancer Network (NCCN) included the use of SBRT for recurrent and metastatic RCC into its guidelines.[25] In their meta-analysis of 28 studies, Zaorsky *et al*. found that SBRT is safe and effective for RCC oligometastases, with local control at 90% and any significant toxicity at 1%. One of the caveats to emerge from this meta-analysis—and confirmed by other studies—concerns the worse survival rates observed among patients with intracranial RCC oligometastases vs those with extracranial disease.

SBRT has the potential to promote an anti-tumor immune response through multiple mechanisms, including the promotion of neoantigen expression and activation of cytotoxic CD8+ T cells. This effect has been explained as dependent on type 1 interferon induction in the irradiated tumor .[25] Although hypothesis generating, the concept that SBRT appears to be immunostimulatory for historically radioresistant tumors argues for a plausible biological rationale to combine stereotactic ablative radiotherapy with immunotherapy. This point was enlarged upon in the report by Dengina et al[26] who also explored the immunogenic aspects of RCC. In their report on the use of extracranial SBRT with TKI or checkpoint inhibitors, they offered further insights on the mechanisms of action of stereotactic radiotherapy. The clinical response in lesions outside of the radiation field—known as abscopal effect—is worthy of further study and has been previously noted. Overall, Dengina et al suggest that SBRT can safely be administered to patients concomitantly receiving TKI or checkpoint inhibitors. The addition of SBRT to systemic therapy led to a rapid regression of the target lesions in 13 of 177 subjects, thus offering further proof of the benefit of such localized therapy.

As SBRT continues to evolve and its use better delineated, one of the underlying questions concerns its relationship to cytoreductive nephrectomy. Singhet al[30] pursued this issue in a single-arm feasibility study in patients who underwent CN 4 weeks after SBRT. They found that SBRT followed by nephrectomy was safe and patients benefited from significant changes to their immune status. Patient tumors had increased expression of the immunomodulatory molecule calreticulin, tumor, tumor-associated antigen, and a higher percentage of proliferating T cells compared with archived RCC tumors.

Two phase II trials have been presented evaluating the combination of SBRT and checkpoint inhibition. The Nivolumab Plus SBRT in 2nd and 3rd Line Patients with Metastatic Renal Cell Carcinoma (NIVES) Study suggested the safety and tolerability of SBRT with the nivolumab, an anti-PD-1 checkpoint inhibitor, with an objective response rate (ORR) of 17.4%, a complete response rate (CRR) of 1.4%, and disease control rate (DCR) of 58%. Of note, the ORR and DCR were 26.9% and 82% in irradiated sites of disease. However, the primary endpoint, improvement in ORR from 25% to 40%, was not

met, and the median PFS was 4.1 months, which was not improved from a prior study, CheckMate 025, in which patients receiving nivolumab alone (without SBRT) experienced a median PFS of 4.6 months.[31] Given that approximately half of the patients harbored 3 or more sites of metastatic disease and that the dose of radiation (30 Gy in 3 fractions) was on the conservative side of that in the aforementioned studies, improved clinical outcomes may be observed in a study population with a more limited volume of disease (≤3 sites) with a more aggressive radiation regimen was utilized. The RADVAX trial evaluated the combination nivolumab and ipilimumab with SBRT at a higher dose (50 Gy in 5 fractions) than that used in NIVES. The ORR of 56%, median PFS of 8.21 months, and the acceptable safety profile of the treatment combination are promising.[32] Further studies are necessary to understand how to optimize immunotherapy with SBRT to improve clinical outcomes.

In addition irradiation of metastatic sites, the utilization of SBRT to the primary site of disease is growing. Multiple studies have suggested high local control rates (90-100%) with acceptable toxicity (grade 3 toxicity <5%).[33-36] The largest study published from the International Radiosurgery Oncology Consortium for Kidney (IROCK) included 223 patients who underwent SBRT to the primary site only. 2- and 4y local control rates were 97.8%. A small decrease in kidney function was observed with a mean decrease in GFR of 5.5 +/- 13.3 ml/min.[36] A major limitation of these studies is the limited follow-up time.

Conclusion

Treatment of oligometastatic RCC has evolved rapidly and new treatment paradigms have emerged. In appropriately selected patients, the use of SBRT has gained support and has been integrated into widely accepted guidelines for the treatment of oligometastases, such as those by the National Comprehensive Cancer Network. Nevertheless decisions need to be individualized to achieve optimal local control based on consideration of IMDC risk factors and an approach reflecting multimodal treatments. Careful patient selection for surgical metastasectomy is essential. Patients with a good indication for surgical metastasectomy include those with solitary or oligometastatic lesions, symptomatic metastases deteriorating quality of life, resistance to radiotherapy and/or systemic therapies, and easy surgical accessibility and resectability with a lower rate of complications. There is growing evidence supporting the use of active surveillance in a well-selected subset of patients with indolent, asymptomatic, and good-risk mRCC, thus mitigating the need in some cases for immediate aggressive treatment.

References

1. Palma DA, Louie AV, Rodrigues B. New strategies in stereotactic radiotherapy for oligometastases. *Clin Can Res*. 20155;21:5198-5204.
2. Huang F, *Wu G, Yang K. Oligometastasis and oligo-recurrence: more than a mirage. Radiat Oncol.* 2014;9:230.
3. Weichselbaum RR, Hellman. Oligometastasis revisited. *Nat reviews Clinical Oncology.* 2011;8:3788-382.
4. Turajlic, Xu, Litchfield et al: Tracking Cancer Evolution Reveals Constrained Routes to Metastases: TRACERx Renal. *Cell*, 173:581-594, 2018.
5. La Rochelle J, Klatte T, Dastane A, Rao PN, Seligson D, Said J, Shuch B, Zomorodian N, Kabbinavar F, Belldegrun A, Pantuck AJ: Chromosome 9p deletions identify an aggressive phenotype of localized clear cell renal cell carcinoma: implications for pre-operative biopsy and active surveillance of small renal tumors. Cancer, 116:4696-702, 2010.
6. Kroeger N, Klatte T, Chamie K, Rao PN, Birkhäuser FD, Sonn GA, Riss J, Kabbinavar FF, Belldegrun AS, Pantuck AJ. Deletions of chromosomes 3p and 14q molecularly subclassify clear cell renal cell carcinoma. Cancer. 2013 Apr 15;119(8):1547-54
7. Zisman A, Pantuck AJ, Wieder J, et al. Risk group assessment and clinical outcome algorithm to predict the natural history off patients with surgically resected renal cell carcinoma. *J Clin Oncol*. 202;20:4559-4566.
8. Pantuck A, Zisman A, Belldegrun AS. The changing natural history of renal cell carcinoma. *J Urol*. 2001;166:1611-123.
9. Han K-R, Pantuck AJ, Bui MHT, et al. Number of metastatic sites rather than location dictates overall survival of patients with node-negative metastatic renal cell carcinoma. *Urol*. 61:314-319.
10. Lyon TD, Thompson RH, Shah PH, et al. Complete surgical metastatectomy of renal cell carcinoma in the post-cytokine era. *J Urol*. 2020;203:275-282.
11. Kato S, Demura S, Murakami H, et al. Surgical metastasectomy for renal cell carcinoma: which patients are the real candidates for surgery? *Ann Translational Med*. 2019;(Suppl 8):S273.
12. Palumbo C, Pecoraro A, Knipper S, et al. Survival and complication rates of metastasectomy in patients with metastatic renal cell carcinoma treated exclusively with targeted therapy: a combined population-based analysis. *Anticancer Res*. 2019;39:357-4361.
13. Meyer CP, Sun M, Karam JA, et al. Complicati0ons after metastasectomy for renal cell carcinoma—a population-based assessment. *Eur Urol*. 2017;772:1771-174.
14. Beuselinck B, Oudard S, Rixe O, et al. Negative impact of bone metastasis on outcome in clear-cell renal cell carcinoma treated with sunitinib. *Ann Oncol*. 2011;22:794-800.
15. Leibovich BC, Cheville JC, Lohse CM et al. A scoring algorithm to predict survival for patients with metastatic clear cell renal cell carcinoma: a stratification tool for prospective clinical trials. *J Urol*. 2005; 174:1759-1763.
16. Yuasa T, Inoshita N, Saiura A, et al: Clinical Outcomes of patients with pancreatic metastases from renal cell carcinoma. BMC *Cancer*, 15:46, 2015.
17. Ouzaid I, Capitanio U, Staehler M, et al. Surgical metastasectomy in renal cell carcinoma: a systematic review. *Eur Urol Oncol*. 2019;2:141-149.
18. Pierorazio PM, McKiernan JM, McCann TR, et al. Outcome after cytoreductive nephrectomy for metastatic renal cell carcinoma is predicted by fractional percentage of tumour volume removed. *BJU Int*. 2007;100:755-759.
19. Rini BI, Dorff TB, Elson P, et al. Active surveillance in metastatic renal-cell carcinoma: a prospective, phase 2 trial. *Lancet Oncol*. 2016; 17:13177-1324.
20. Escudier B, Porta C, Schmidinger M, et al. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2019;30:706-720.
21. Woldu SL, Matulay JT, Clinton TN, et al. Incidence and outcomes of delayed targeted therapy after cytoreductive nephrectomy for metastatic renal-cell carcinoma: a nationwide cancer registry study. *Clin Genitourin Cancer.* 2018;1:1221-1235.
22. Bimbatti D, Ciccarese C, Fantinel E, et al. Predictive role of changes in the tumor burden and International Metastatic Renal Cell Carinoma Data Base Consortium class during active surveillance for metastatic renal cell carcinoma. *Urol. Oncol*. 2018;3:526.
23. Ficarra V, Mosca A, Rossanese M, et al. Is active surveillance an option for metachronous metastatic renal cell carcinoma. *Ann Transl Med.* 2019;7: 84.
24. Beckham TH, Imber BS, Simone CB. Stereotactic body radiation therapy for oligometastatic renal cell carcinoma: improving outcomes in an otherwise radioresistant malignancy. *Ann Transl Med*. 2019; 7(Suppl):S98.
25. Zaorsky NG, Lehrer E, Kothan G, et al. Stereotactic ablative radiation therapy for oligometastatic renal cell carcinoma (SABR ORCA): a meta-analysis of 28 studies. *Eur Urol Oncol*. 2019;2:515-523.
26. Dengina N, Mitin T, Gamayunov S, et al. Stereotactic body radiation therapy in combination with systemic therapy for metastatic renal cell carcinoma: a prospective multicenter study. *ESMO Open*. 2019; 4:e000535.
27. Hoerner-Riber, Duma M, Blanck O, et al. Stereotactic body radiotherapy (SBRT) for pulmonary metastases from renal cell carcinoma—a multicenter analysis of the German working group "Stereotactic Radiotherapy." *Journal of Thoracic Disease*. 2017;9:4512-4522.

(continued on page 62)

IKCS 2020

NOV 6–7, 2020 | MIAMI, FLORIDA | #IKCS2020

Save the Date

For more information about the Kidney Cancer Association and about the Nineteenth International Kidney Cancer Sympoisum in Miami, visit **KidneyCancer.org**

STRONG ALONE. UNSTOPPABLE TOGETHER.

KidneyCancerAssociation™

The Current and Evolving Landscape of Immunotherapies for Advanced Renal Cell Carcinoma


Allen Jacob, MD


Jaret Shook


Thomas E. Hutson, DO, PharmD, FACP

Allen Jacob, MD[1], Jaret Shook[2], and Thomas E Hutson, DO, PharmD, FACP[3]
[1]Texas A&M College of Medicine, Bryan TX;
[2]Ohio Northern University College of Pharmacy, Ada, OH;
and Urologic Oncology Program,
[3]Texas Oncology, Baylor Sammons Cancer Center, Dallas, TX

Abstract
There has been tremendous progress in the treatment landscape of metastatic renal cell carcinoma over the last decade with new, more efficacious strategies emerging and the incorporation of several of these therapies into combinations with even greater benefit to patients. Novel immune checkpoint inhibitors (ICI) have emerged as a primary backbone to many of the most active regimens. However, drawbacks of ICI remain such as lower long-term response rates and the absence of potential biomarkers that will facilitate patient selection. In addition, current data regarding the outcomes of patients including optimal management of patients who progress after ICI are fairly limited. Owing to such limitations, there is an urgent need to identify more reliable biomarkers of immunotherapies for better prediction of treatment response and more efficient stratification of patients. In this review, we provide the current status of the immunotherapy landscape for advanced renal cell carcinoma as well as discuss future directions.

Introduction
Renal cell carcinoma (RCC) is one of the top ten most frequently diagnosed cancers with an incidence of around 400,000 cases worldwide.[1] In United States alone, RCC accounts for 73,820 new cases and 14,770 deaths in 2019. In patients with RCC, about 30% of patients who present with metastatic disease at the time of initial diagnosis typically require systemic therapy and almost 30% of patients who are treated for localized RCC develop recurrent disease during the follow-up.[2] RCC is typically known for its resistance to conventional forms of therapies as hormonal and cytotoxic chemotherapeutics have considerably failed to produce remissions and improve overall survival. For the past several years, ongoing clinical trial efforts were aimed at developing *targeted* therapeutic agents for the management and treatment of metastatic renal cell cancer (mRCC). Until 2005, medical therapies for mRCC were limited to interferon alpha or interleukin 2 as cytokine-based therapies which provided only a modest survival benefit of approximately 1 year.[3,4] Based on the preliminary data indicating 15% overall response rate (ORR) and a 5% complete response (CR), the high-dose intravenous IL-2 was approved by the US Food and Drug Administration (FDA) for the treatment of RCC in 1992. High-dose IL-2 used in selective patients with metastatic renal cell carcinoma had led to rare complete and durable responses.[3] In a follow-up study, CR was 7% and median duration of response was at least 80 months. The scope of IL-2 based therapy is, however, limited by substantial incidence of high-grade adverse events as well as the inability to predict response.

In recent years, multiple targeted therapies predominantly focusing on two major molecular pathways, namely angiogenesis and intracellular signal transduction pathways, have gained increasing attention in RCC landscape. Since 2005, there has been remarkable progress in the treatment of RCC with VEGF inhibitors (sunitinib, sorafenib, axitinib, pazopanib, cabozantinib, bevacizumab, lenvatinib), as well as mammalian target of rapamycin (mTOR) pathway inhibitors (everolimus, temsirolimus). These agents provided considerable survival benefits in pivotal trials as well as gained regulatory approval to become the *defacto* choice of first-line systemic therapy.[5] More recently, key insights obtained in regard to the VHL pathway have profoundly shaped the evolving mutational landscape of mRCC and also provided the basis for the development of the VHL-hypoxia pathway-based therapeutic landscape in renal cancers.[6] Despite the significant progress over the past 15 years, there is still room for improvement for targeted therapies as current drug interventions for mRCC have yet to demonstrate the ability to circumvent recurrence and several therapies are accompanied by severe adverse events.[3,4] In this review, we summarize recent breakthroughs in the immunotherapy space that remodeled

Keywords: immune-checkpoint inhibitors, ICI, anti-angiogenics, immunotherapy landscape, immune microenvironment reprogramming, TKI, RCC.

Corresponding Author: Thomas E Hutson@usoncology.com

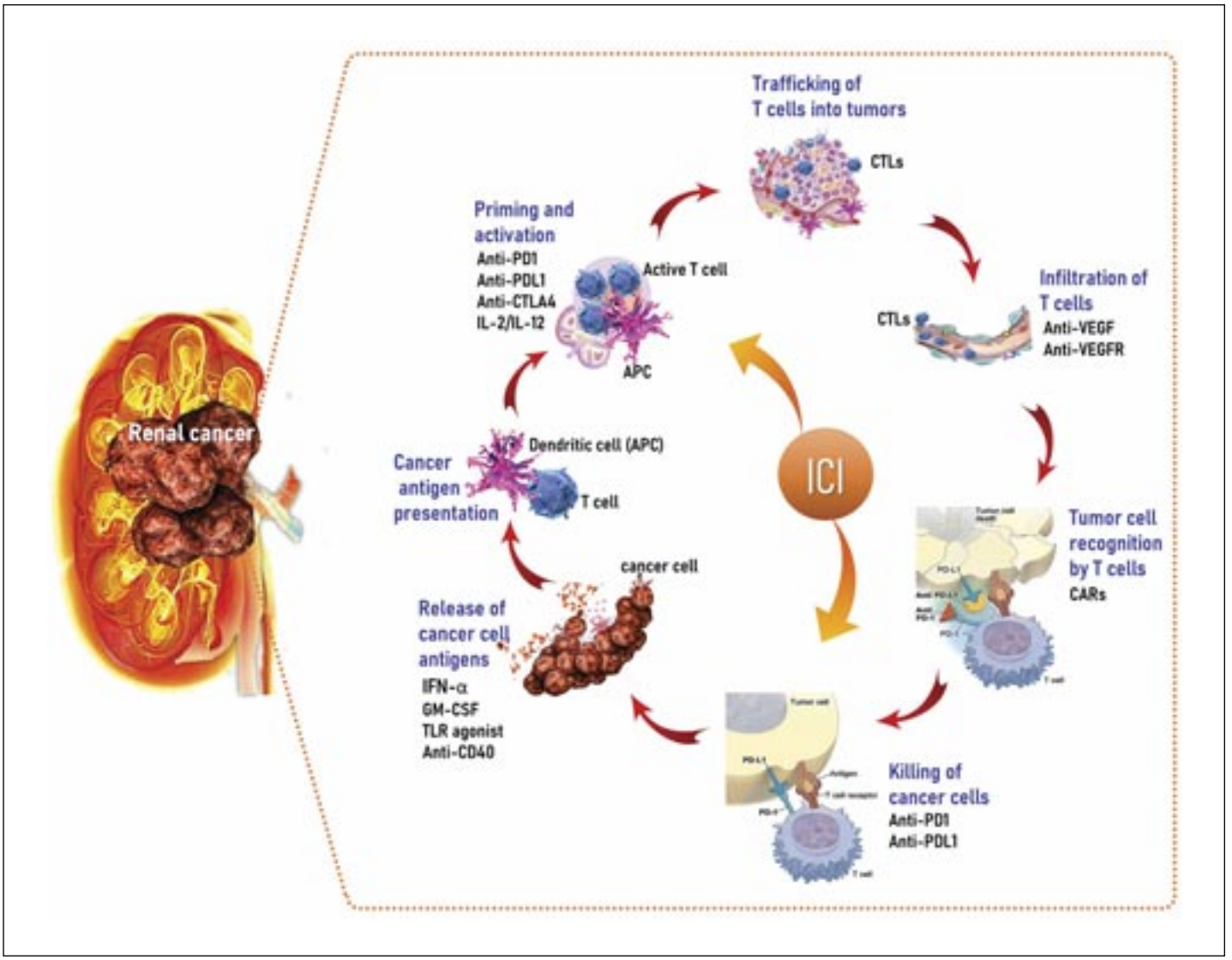


Figure 1. Synergistic effect of immune checkpoint blockade and anti-angiogenesis as a rational for improved targeted therapies. The resistance towards ICI could be alleviated by combination therapy with anti-angiogenesis treatment that not only prunes blood vessel but also reprograms the tumor immune microenvironment. In this sequential and iterative immunity-angiogenesis cycle, the complement interaction between ICI and anti-angiogenics transforms the immunosuppressive tumor microenvironment into immunosupportive microenvironment. PD-1: anti-programmed death receptor 1; PD-L1: anti-programmed death receptor ligand 1; CTLA-4: anti-cytotoxic T lymphocytes antigen-4; APC: antigen-presenting cell; VEGF: vascular endothelial growth factor; CAR: Chimeric antigen receptor; TLR: toll-like receptors.

the RCC treatment algorithm and also highlight the novel approaches being evaluated in ongoing clinical trials.

Rationale for Selection of Immunotherapy

Given that RCC is considered immune-responsive in nature with high numbers of immune cells present in the tumor microenvironment, targeted immunotherapy was explored as a potential therapy in RCC patients who were non-responsive to conventional targeted therapies.[7] One immune strategy involved the use of immune checkpoint inhibitors (ICI).[8] In particular, the use of sophisticated ICIs, including anti-programmed death receptor 1 (PD-1), anti-programmed death receptor ligand 1 (PD-L1), and anti-cytotoxic T lymphocytes antigen 4 (CTLA-4), have been developed and studied in large international phase III trials demonstrating significant and clinically relevant improvements in efficacy. As such, these new therapies have quickly been integrated into the RCC landscape. PD-1 and PD-L1 antibody- based novel ICIs have been approved by the FDA as the standard second-line treatment for mRCC as well as in the first-line for moderate to high-risk mRCC.[9] Notably, the footprints of ICI, expanded across the landscape of oncology with the approval of nivolumab and ipilimumab combination, especially in patients with intermediate to poor-risk renal cell carcinoma (RCC).

Underlying Mechanisms of Action

In-depth understanding of T cell function and associated immunosuppressive molecules have highlighted the central role of the tumor micro-environment. During tumorigenesis, a tumor may trigger certain immune- resistant mechanisms including systemic dysfunction in T

Table 1. Frontline Phase III Clinical Trials Involving ICIs Vs Antiangiogenics in Advanced RCC

Clinical Trial	CheckMate-214[9] (NCT02231749)	Keynote-426[16] (NCT02853331)	Javelin Renal 101[17] (NCT02684006)	IMmotion151[20] (NCT02420821)
Treatment Arms	Ipilimumab + Nivolumab followed by Nivolumab maintenance	Pembrolizumab + axitinub	Avelumab + axitinib	Atezolizumab + Bevacizumab
Comparator	Sunitinib	Sunitinuib	Sunitinib	Sunitinib
Primary endpoint	Co-primary endpoint of OS, PFS, and ORR in intermediate risk	Co-primary endpoint of OS and PFS	Co-primary endpoint of OS and PFS in patients with PD-L1 ≥1%	PFS and OS
Number of Patients recruited	1,096	861	886	915
Median OS, months	NR vs. 37.9	NR vs NR	Not reported	24-mo: 63% vs. 83%
Median PFA, months	9.7 vs 9.7	15.1 vs 11.1	13.8 vs 7.2	12-mo: 86% vs 83%
Overall response rate, %	41 vs 34	59.3 vs 35.7	51.4 vs 25.7	37% vs 33%

cell signaling and exploitation of immune checkpoints.[6-11] By employing such anti-immune mechanisms, tumors can evade specific immune responses.[12] Further insights regarding such immune evasive mechanisms in the host-tumor immune environment have led to the development of novel antibody based agents directed against immune checkpoints in tumors.[13,14] In many tumors, upregulated programmed death-ligand 1 PD-L1 expression can either be constitutive or induced to evade immune surveillance. PD-1 expressed on activated T cells can bind to its ligand PD-L1 on tumor cells, leads to T cell exhaustion and downregulated immune defense against tumors.[10] By blocking or counteracting the tumor mediated inhibition of T cell receptor activated IL 2 production and T cell proliferation, ICIs can potentially suppress the events that otherwise downregulate a cellular immune response. This counteraction results in a successful anti tumor T cell mediated immune activity and antibodies raised against such PD-1 and PD-L1 inhibitory axis can unleash activated tumor-reactive T cells to promote durable anti-tumor responses in many tumors. Thus, this biological rationale encouraged the synergistic association of CTLA-4 inhibition, which facilitates active immune response at the level of T-cell proliferation, with PD-1 suppression, which modulates the immune response at the level of the tumor micro-environment. Since the disruption of PD-1–PD-L1 signaling mediated by nivolumab can lead to restored antitumor immunity, PD-L1 expression is associated with improved overall survival in response to nivolumab therapy.[11] This anti-PD-1 antibody nivolumab, selectively blocks the interaction of PD-1 (expressed on activated T cells) with its ligands PD-L1 and PD-L2 (expressed on immune cells and tumor cells) and thus counteracting the cellular immune response pathways.[12] Such discoveries led to the approval of anti-PD1 antibodies (for example: pembrolizumab and nivolumab) and anti-PD-L1 antibodies (for example: atezolimumab) for the treatment of advanced melanoma, NSCLC, RCC, head and neck squamous carcinoma, Hodgkin's lymphoma, and bladder cancer.[13]

Monotherapy or Combinatorial Therapy of Immune Checkpoint Inhibitors

The ICI field is evolving rapidly with many clinical trials already completed studying several checkpoint inhibitors alone, in combination, or with other targeted therapies. Since the approval of the CTLA-4 antibody ipilimumab in patients with melanoma in 2011, several PD-1/PD-L1 inhibitors including nivolumab, pembrolizumab, atezolizumab, durvalumab, and avelumab as well as the CTLA-4 inhibitor ipilimumab were investigated for their anti-tumor efficacy.[23] Nivolumab, a fully humanized IgG4 anti-PD-1 that was developed in the form of a monoclonal antibody directed at PD-1, became the first ICI approved by FDA in 2015 for the treatment of refractory mRCC. In a randomized, open-label, phase III study CheckMate-025 (NCT01668784), a total of 821 advanced ccRCC patients who had received previous treatment with one or two regimens of antiangiogenic therapy were randomly assigned either nivolumab or everolimus.[8] The primary end point was overall survival and the secondary end points included the objective response rate and safety. Results showed that the objective response rate (ORR) was greater with nivolumab than with everolimus (25% vs. 5%; $p<0.001$) and median PFS was better with nivolumab than with everolimus (4.6 months vs 4.4 months; $p = 0.11$).[8] Results indicated that the nivolumab arm had 25.0 months median overall survival (95% CI, 21.8 to not estimable), longer as compared to only 19.6 months (95% CI, 17.6 to 23.1) in the everolimus arm. Nivolumab's overall survival benefit was evident across prespecified subgroups, including subgroups defined per region, MSKCC prognostic score, and number of previous regimens of antiangiogenic therapy. Only 19% of the patients receiving nivolumab experienced grade 3 or 4 treatment-related adverse events as compared to 37% of the patients receiving everolimus, and only 8% requiring treatment discontinuation because of

Table 2. Ongoing Clinical Trials Assessing the Role of Immune Checkpoint Inhibitors in Advanced RCC

Clinical Trial	CheckMate-9ER (NCT03141177)	Cosmic-313 (NCT03937219)	Pdigree (NCT0393166)	Clear (NCT02811861)	Titan-RCC (NCT02917772)	Omnivore (NCT03203473)
Treatment Arm	Cabozantinib + nivolumab	Cabozantinib + nivolumab + ipilimumab followed by cabozantinib + nivolumab maintenance	Ipilimumab nivolumab followed by cabozantinib + nivolumab maintenance	Lenvatinib + everolimus	Nivolumab (adaptive); nivolumab + ipilimumab if progresion	Nivolumab (adaptive); nivolumab + ipilimumab if progression
Comparator	Sunitinib	Ipilimumab + nivolumab followed by nivolumab maintenance	Ipilimumab + nivolumab followed by nivolumab maintenance	Sunitinib	NA	NA
Primary	PFS	PFS	OS	PFS	ORR	Number of subjects with persistent PR/CR after nivolumab discontinuation (arm A)

toxicity. Altogether, this pivotal clinical trial demonstrated that nivolumab delivers better PFS, overall response rate and overall survival, paving the way for the use of nivolumab as a preferred second line monotherapy option after progression on anti-VEGF therapies in international guidelines.[8] Interestingly, although overexpression of PD-L1 has been shown to be associated with poor prognosis and pathological features in RCC, its expression pattern in primary tumors failed to predict whether inhibition of PD-1/PD-L1 axis can provide survival benefit in patients in clinical trials.[19] Overall, PD-L1 status is not clinically useful for making treatment decisions in mRCC.

Studies indicate that anti-CTLA4 and anti-PD1 antibodies possess non-overlapping mechanisms, and combination of these two classes of ICIs in a double-blind, phase III study showed improved clinical response (up to 60%) in melanoma at the expense of significantly increased frequency of toxicities.[14] The dual ICI of nivolumab/ipilimumab is one of the preferred first-line therapies in poor-risk and intermediate-risk patients. In RCC, CheckMate-214 (NCT02231749) was the first trial to evaluate the CTLA-4 and PD-1 inhibitor combination with the co-primary endpoints included ORR, progression free survival (PFS), and OS in the IMDC intermediate or high risk population.[9] Results from CheckMate 214 validated the concept that combination therapy using a PD-1 inhibitor (nivolumab) and a CTLA-4 blocker (ipilimumab) can deliver at least additive benefit versus the anti-VEGF TKI sunitinib in first line metastatic RCC. Results show that the addition of ipilimumab to nivolumab resulted in significantly better overall survival (HR, 0.63; $P<0.001$) and improved objective response rate (42% vs. 27%; $p<0.001$) as compared to sunitinib in intermediate and poor-risk patients. In addition, the safety of nivolumab and ipilimumab was reasonable and secured this combination regimen within the first-line treatment algorithm in intermediate- and poor-risk patients with RCC.[15]

Given such encouraging efficacy of ICIs in the metastatic setting, there is huge interest in exploring their potential role in the adjuvant/neo-adjuvant setting to reduce or prevent recurrence. Currently, a number of phase III trials evaluating the efficacy of ICI treatment in the adjuvant setting are ongoing. In phase III CheckMate-914 multinational study (NCT03138512) the efficacy of adjuvant nivolumab plus ipilimumab vs placebo was evaluated in patients with localized RCC with a high risk of RCC relapse after nephrectomy. Similarly, other agents such as pembrolizumab (Keynote 564; NCT03142334), and atezolizumab (IMmotion010; NCT03024996), nivolumab (Prosper RCC; NCT03055013) are also currently being evaluated.

Combining Immune Checkpoint Inhibitors and Tyrosine Kinase Inhibitors

Given the recent discoveries of the effectiveness of immune resistance blockade in tumors, ICI agents in combination with either multikinase inhibitors or other monoclonal antibodies (CTLA4 and PD-1) have been or are currently being studied in previously untreated patients with advanced RCC. Recently reported and FDA approved combinations of ICI or ICI with TKI therapy have been rapidly integrated into the first line treatment setting based upon international phase III trials. The recently completed and ongoing trials proposed antiangiogenics be used in association with targeted immunotherapy to overcome resistance by emphasizing the role of the tumor microenvironment (TME).[16,17] Moreover, inhibition of the VEGF pathway has been shown to facilitate access of T-cell population into the TME and also decreases the activity of T-regulatory cells and myeloid-derived suppressor cells, thereby enhancing responsiveness to immunotherapy.[18]

Similar clinical trials in mRCC are currently ongoing. In another randomized phase II trial (NCT03075423), the combination of axitinib and pembrolizumab was evaluated versus sunitinib in untreated advanced or metastatic RCC. Results revealed that the combination of axitinib and pembrolizumab significantly reduced the risk of death (HR for death, 0.53; $p<0.0001$) and disease progression (HR for disease progression or death, 0.69; $p<0.001$). In the combination arm, the ORR was 59.3% ($p<0.001$) compared to 35.7% in the sunitinib group. These favorable outcomes were observed across all risk groups and regardless of PD-L1 expression.[16] Similarly, pembrolizumab is also being evaluated in the cohort B of the KEYNOTE 427 phase II trial. In pRCC, durvalumab is being evaluated in combination with savolitinib, a highly selective MET tyrosine kinase inhibitor, in the CALYPSO phase II trial (NCT02819596).

The Phase III trial IMmotion 151 (NCT02420821) used the combination of PD-L1/PD-1 pathway inhibitor with an anti-VEGF agent in untreated mRCC.[20] This study investigated the combination of atezolizumab, an anti-PD-L1 antibody, with bevacizumab, as compared to sunitinib monotherapy in mRCC. Based on PD-L1 expression level on tumor-infiltrating immune cells, patients were stratified by PD-L1 status. Results indicated longer PFS (11.2 months) in the combination arm vs. 7.7 months in the sunitinib arm (HR, 0.74; $p=0.02$) in the PD-L1+ patients. Improved PFS was also observed in ITT patients. The ORR in the PD-L1+ patients was 43% in the combination arm as compared to 35% in the sunitinib arm. The CR rate in the PD-L1+ patients was 9% in the combination arm as compared to 4% in the sunitinib arm. In the bevacizumab–atezolizumab arm, grade 3 or 4 toxicities occurred in 40% of patients group and in 54% of patients in the sunitinib group.[20]

In another randomized phase III trial known as JAVELIN Renal 101 (NCT02684006), Motzer et al investigated the combination of axitinib and avelumab in treatment-naive RCC patients with metastatic or advanced disease.[17] In the axitinib and avelumab combination arm, median PFS in the combination arm was 13.8 months versus 8.4 months in sunitinib arm (HR, 0.69; $p<0.001$). The ORR and CR rate were 55% and 4% were in the combination arm as compared to 26% and 2% in the sunitinib arm. When PD-L1+ patients were assessed, the median PFS was 13.8 months in axitinib and avelumab combination arm, versus 7.2 months in the sunitinib arm (HR, 0.61; $p<0.001$).[17] This study demonstrated that patients who received a combination of avelumab plus axitinib had longer PFS and a higher objective response rate than those who received sunitinib monotherapy. KEYNOTE 426 phase III trial (NCT02853331) evaluated the efficacy and safety of pembrolizumab (MK-3475) in combination with axitinib versus sunitinib monotherapy as a first-line treatment for 861 participants with advanced or metastatic renal cell carcinoma.[16] The combination therapy arm of pembrolizumab plus axitinib showed a longer median PFS of 15.1 months compared to 11.1 months of the axitinib arm (HR = 0.69; $p < 0.001$). The safety profile was comparable to the results of the JAVELIN Renal 101 trial. Interestingly, the benefit of pembrolizumab plus axitinib for OS, PFS, and ORR was observed in the entire population irrespective of the prognostic group and PD-L1 tumor expression. In the KEYNOTE-427 (NCT02853344) trial, pembrolizumab monotherapy for treatment naïve patients has also demonstrated promising efficacy and acceptable tolerability in patients with accRCC. Results indicated that ORR was 38.2 % and CR 2.7% in all treated patients. In PD-L1 negative patients, ORR was found to be 50.0 % as compared with 26.4% and the median PFS was 8.7.

Although the combination of ICI and antiangiogenics has shown encouraging preliminary antitumor activity for advanced or mRCC, clinical trials indicate that toxicity and tolerability may be difficult in some patients. For instance, in the phase I study CheckMate 016 (NCT01472081), the efficacy and safety of nivolumab in combination with antiangiogenic tyrosine kinase inhibitors or ipilimumab for the treatment of mRCC.[21] In this study, addition of sunitinib or pazopanib to nivolumab resulted in a high incidence of high-grade toxicities, limiting its scope in future trials.

Future Directions

The remarkable advancement of immunotherapy into the landscape of mRCC has improved the outlook for many patients. In the coming years, emerging targeted and immune therapies, or their combinations, may not only deliver the improved efficacy achieved with overriding immune resistance but also profoundly shape the therapeutic landscape. There remains unmet need for prospective ICI-based immunotherapy data in regard to their ability to be appropriately sequenced as well as selected after ICI. Evidently, successful outcome from ICI plus antiangiogenic combinatorial regimens may be dependent on prudent selection of the specific agents tailored with optimal dose. Most importantly, appropriate therapeutic sequence of combinatorial regimen along with their dosage optimization will need to be ascertained to avoid treatment discontinuation based on intolerable toxicity and also ensure that the remarkable therapeutic outcome will be achieved. The dosage optimization for ICI monotherapy or the combination of ICI with VEGF inhibitor in conjunction with optimal modulation of TME is essential to facilitate the efficacy of ICI. Besides, in the rapidly evolving renal cancer landscape with the prospective of future ICI plus antiangiogenics, efforts should be directed at obtaining consensus from various immunotherapy agents as appropriate control arm. Likewise, since complex immune modulatory responses can be elicited by continuous exposure to ICI combination, the irreversible T cell exhaustion, immune-editing, and antigenic drift like complication should be take into account while considering new therapeutic combination. Currently available trials involving heterogeneous patient populations making cross trial comparisons impossible. Further emphasis is needed on potential biomarkers and prospective validation of biomarkers combinations. The treatment associated toxicities remain a major roadblock hindering the widespread use and applicability of these treatments. Therefore, evidence-based and algorithmic approaches in stratification, treatment sequence, and treatment selection need

to be standardized in the management of immune-related toxicities. In addition, due consideration should be given for effective protocol design including endpoint choice, and methods used for treatment response to avoid some pitfalls.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin.* 2019;69(1):7-34.
2. Czarnecka AM, Kornakiewicz A, Kukwa W, Szczylik C. Frontiers in clinical and molecular diagnostics and staging of metastatic clear cell renal cell carcinoma. *Future Oncol.* 2014;10(6):1095-1111.
3. Fyfe G, Fisher RI, Rosenberg SA, Sznol M, Parkinson DR, Louie AC. Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. *J Clin Oncol.* 1995;13(3):688-696.
4. McDermott DF, Regan MM, Clark JI, et al. Randomized phase III trial of high-dose interleukin-2 versus subcutaneous interleukin-2 and interferon in patients with metastatic renal cell carcinoma. *J Clin Oncol.* 2005;23(1):133-141.
5. Wang J, Li X, Wu X, et al. Role of immune checkpoint inhibitor-based therapies for metastatic renal cell carcinoma in the first-line setting: A Bayesian network analysis. *EBioMedicine.* 2019;47:78-88.
6. Jonasch E. Implications of VHL-HIF pathway dysregulation in renal cell carcinoma: current therapeutic strategies and challenges. *Kidney Cancer Journal.* 2020;18(1):6-10.
7. Leite KR, Reis ST, Junior JP, et al. PD-L1 expression in renal cell carcinoma clear cell type is related to unfavorable prognosis. *Diagn Pathol.* 2015;10:189.
8. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med.* 2015;373(19):1803-1813.
9. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. *N Engl J Med.* 2018;378(14):1277-1290.
10. Chen DS, Irving BA, Hodi FS. Molecular pathways: next-generation immunotherapy—inhibiting programmed death-ligand 1 and programmed death-1. *Clin Cancer Res.* 2012;18(24):6580-6587.
11. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. *N Engl J Med.* 2017;377(19):1824-1835.
12. Choueiri TK, Fishman MN, Escudier B, et al. Immunomodulatory Activity of Nivolumab in Metastatic Renal Cell Carcinoma. *Clin Cancer Res.* 2016;22(22):5461-5471.
13. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. *Science.* 2018;359(6382):1350-1355.
14. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *N Engl J Med.* 2015;373(1):23-34.
15. Jonasch E. NCCN Guidelines Updates: Management of Metastatic Kidney Cancer. *J Natl Compr Canc Netw.* 2019;17(5.5):587-589.
16. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med.* 2019;380(12):1116-1127.
17. Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med.* 2019;380(12):1103-1115.
18. Kwilas AR, Donahue RN, Tsang KY, Hodge JW. Immune consequences of tyrosine kinase inhibitors that synergize with cancer immunotherapy. *Cancer Cell Microenviron.* 2015;2(1).
19. Motzer RJ, Rini BI, McDermott DF, et al. Nivolumab for Metastatic Renal Cell Carcinoma: Results of a Randomized Phase II Trial. *J Clin Oncol.* 2015;33(13):1430-1437.
20. Rini BI, Powles T, Atkins MB, et al. Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): a multicentre, open-label, phase 3, randomised controlled trial. *Lancet.* 2019;393(10189):2404-2415.
21.Amin A, Plimack ER, Ernstoff MS, et al. Safety and efficacy of nivolumab in combination with sunitinib or pazopanib in advanced or metastatic renal cell carcinoma: the CheckMate 016 study. *J Immunother Cancer.* 2018;6(1):109. KCJ

COVID-19 and Cancer Resources

Kidney Cancer Journal

KCJ is committed to provide the latest information and resources to its readers and the larger oncology community to ensure that cancer patients receive high-quality care. In line with this, we have compiled various resources that provide information to support patients with cancer, clinicians, and researchers within the cancer care delivery team. As we update the KCJ webpage on a regular basis, please continue to check back for the most current information here: kidney-cancer-journal.com/covid-19.html

Sequencing of Cytoreductive Nephrectomy in Metastatic Renal Cell Carcinoma During the VEGF-TKI and Immunotherapy Era

Jun Gong, MD
Department of Medicine
Division of Hematology and Oncology
Cedars-Sinai Medical Center
Los Angeles, California

Abstract
The survival benefit of cytoreductive nephrectomy (CN) was demonstrated in patients with metastatic renal cell carcinoma (mRCC) in randomized control trials of interferon alfa. Since 2005, the development of targeted therapies with vascular endothelial growth factor tyrosine kinase inhibitors (VEGF-TKIs) has prompted investigations into the benefit of CN in patients treated with these standard agents in mRCC. With the advent of immune checkpoint inhibitors (ICIs) that have now been approved as new first-line treatments in mRCC, the role of CN in this population remains even more undefined. In this review, we highlight seminal studies of CN in mRCC patients treated with VEGF-TKIs. We also discuss early evidence on the impact of CN in patients with mRCC in the immunotherapy era. We end with a discussion on factors that could potentially aid the selection of mRCC candidates for CN.

Introduction
Renal cell carcinoma (RCC) is among the top 10 most frequently diagnosed cancers in men and women worldwide with >140,000 RCC-related deaths yearly.[1] Although the majority of RCC cases are diagnosed at a localized stage, nearly one third of cases present with regional or distant metastases where the 5-year survival is 53% for patients with locoregional (stage III) disease and a dismal 8% for metastatic disease.[2] Two randomized control trials demonstrated the survival benefit of cytoreductive nephrectomy (CN) followed by interferon alfa over interferon alfa alone in patients with metastatic RCC (mRCC) in the cytokine era.[3,4] In a pooled analysis of these studies including a total of 331 patients with mRCC and primary tumors deemed resectable, the median overall survival (OS) was 13.6 months for CN plus interferon vs. 7.8 months for interferon alone (31% reduced risk of death, P=0.002).[5]

Keywords: Cytoreductive nephrectomy, metastatic renal cell carcinoma, VEGF therapy, TKI therapy, CARMENA trial, SURTIME trial, IMDC risk criteria, ADAPT trial, immunotherapy.

Corresponding Author: Jun Gong, MD, Samuel Oschin Cancer Center, 8700 Beverly Blvd., Los Angeles, CA 90048.
Email address: jun.gong@cshs.org

Since 2005, the advent of targeted therapies involving vascular endothelial growth factor (VEGF) tyrosine kinase inhibitors (TKIs) and mammalian target of rapamycin (mTOR) inhibitors led to a paradigm shift in the systemic treatment of mRCC with improvements in OS to nearly 40 months for targeted therapy in the contemporary era compared to a median OS of 10 months in the cytokine era.[6,7] To provide level 1 evidence on the role of CN for mRCC in the targeted therapy era, 2 randomized controlled trials CARMENA and SURTIME were conducted.[8,9]

CARMENA
The CARMENA (Cancer du Rein Metastatique Nephrectomie et Antiangiogéniques) trial was a randomized, multicenter, open-label phase III trial randomizing (1:1 fashion) 450 treatment-naïve patients with metastatic clear-cell RCC to receive CN within 28 days of randomization followed by sunitinib treatment (3-6 weeks after nephrectomy) or sunitinib alone (50 mg daily for 4 weeks on, 2 weeks off) within 21 days of randomization.[9] The primary endpoint was OS and 226 patients were randomized to the CN plus sunitinib arm and 224 to the sunitinib alone arm. At a median follow-up of 50.9 months (95% confidence interval or CI 44.0-56.9), the sunitinib-alone group had a longer median OS (18.4 months, 95% CI 14.7-23.0) than those in the CN-sunitinib group (13.9 months, 95% CI 11.8-18.3) in the intention-to-treat (ITT) population with a hazard ratio (HR) for death of 0.89 (95% CI 0.71-1.10). Given that the upper boundary of the 95% CI for the HR did not exceed the fixed noninferiority limit of 1.20, sunitinib alone was deemed not inferior to CN followed by sunitinib. In the CN-sunitinib group, 55.6% and 44.4% were in the Memorial Sloan Kettering Cancer Center (MSKCC) intermediate-risk and poor-risk groups, respectively, while in the sunitinib-alone group, the corresponding values were 58.5% and 41.5%. In both intermediate-risk and poor-risk groups, the median OS was longer in the sunitinib-alone group than in the CN-sunitinib group (23.4 vs. 19.0 months in the intermediate-risk subgroup and 13.3 vs. 10.2 months in the poor-risk group). Notably, 16 patients (7.1%) did not undergo nephrectomy and 40

(17.7%) never received sunitinib. In the sunitinib-alone group, 11 patients (4.9%) never received sunitinib and 38 (17.0%) underwent subsequent nephrectomy a median of 11.1 months after randomization for the control of symptoms.

SURTIME

The SURTIME (Immediate Surgery or Surgery After Sunitinib Malate in Treating Patients With Metastatic Kidney Cancer) was originally a randomized, multicenter, open-label phase III trial conducted during a similar time period as CARMENA that randomized (1:1 fashion) a total of 99 patients with untreated, clear-cell mRCC to immediate CN followed by sunitinib (50 mg daily 4 weeks on, 2 weeks off) or 3 cycles of sunitinib followed by CN (sunitinib was stopped day before nephrectomy) and resumption of sunitinib (delayed CN arm) (8). Sunitinib was started in both arms 4 weeks after surgery, and in the case of systemic progressive disease (PD) in the deferred CN arm, CN was not recommended and left to the discretion of the investigator. The primary endpoint was the 28-week progression-free rate (PFR). Of note, the trial was originally powered for 458 patients, but suffered from poor accrual resulting in a downsizing to 98 patients. At a median follow-up of 3.3 years (range 0-6.2 years), a total of 87 (88%) met MSKCC intermediate risk criteria, and the 28-week PFR in the ITT population was 42% (90% CI 30-55%) in the immediate CN arm vs. 43% (90% CI 31-56%) in the deferred CN arm (1-sided Fisher test p=0.61). The PFS HR for deferred vs. immediate CN was 0.88 (95% CI 0.56-1.37, *P*=0.57), while for OS the HR for deferred vs. immediate CN was 0.57 (95% CI 0.34-0.95, *P*=0.03). The median OS was 32.4 months (95% CI 14.5-65.3 months) in the deferred CN arm vs. 15.0 months (95% CI 9.3-29.5 months) in the immediate CN arm. In the per-protocol population, OS was higher in the deferred CN arm than the immediate CN group (HR 0.71, 95% CI 0.40-1.24), but the difference was not statistically significant (*P*=0.23).

Delayed Cytoreductive Nephrectomy

The results of SURTIME, when placed in the context of CARMENA, appear to support that upfront CN does not result in additional survival benefit with potential to even be harmful in patients with primary clear cell mRCC who require treatment with sunitinib. Instead, there was evidence to suggest that deferred CN conferred a greater survival benefit than immediate CN, particularly in those who are MSKCC intermediate risk. SURTIME, however, suffered from poor accrual and was ultimately grossly underpowered and therefore its results should be considered exploratory. To further provide evidence in support of deferred CN in mRCC, 2 large studies, albeit retrospective, using prospectively collected data were recently conducted.[10,11]

The first was a retrospective pooled analysis of 3 single-arm prospective phase II studies (12-14) and n=20 patients from the deferred CN experimental arm of SURTIME.[11] The goal was to compare patients with MSKCC intermediate-risk primary clear cell mRCC receiving presurgical VEGF-TKIs (sunitinib or pazopanib) followed by delayed CN in the absence of systemic PD vs. upfront CN followed by VEGF-TKIs where treatment-naïve patients received VEGF-TKIs 12-18 weeks prior to planned CN. This deferred CN cohort was compared to a European upfront CN cohort from 4 centers planned to receive VEGF-TKI after surgery between 2006-2016. The pooled deferred CN included 189 patients (57% received sunitinib and 43% pazopanib) where 144 (76%) patients were MSKCC intermediate risk and 42 (22%) poor risk. From 244 patients who received upfront CN, a final 149 patients were included after excluding favorable-risk and non-clear cell mRCC. Of these, 131 patients (88%) were intermediate risk and 18 (12%) were poor risk, while the majority (76%) of patients received sunitinib. For intermediate-risk patients, OS in the deferred CN cohort was 33.0 months (95% CI 25.0-51.0) vs. 22.8 months (95% CI 17.9-30.6) in the upfront CN cohort (HR for death 0.72, 95% CI 0.52-0.996, *P*=0.047). In the overall cohort, OS was 24.3 months (95% CI 20.8-34.8) vs. 18.4 months (95% CI 14.4-26.9, *P*=0.09) in the deferred CN and upfront CN arms, respectively. Notably, 66 (35%) patients in the deferred CN cohort did not undergo CN (24% in the intermediate-risk and 52% in the poor-risk group), while following nephrectomy in the upfront CN group, 34 MSKCC intermediate-risk patients (25.9%) had a short cancer-specific survival of <6 months with 10 (7%) never going on to receive a VEGF-TKI, 8 due to rapid PD.

To further evaluate the benefit of deferred CN in mRCC using International mRCC Database Consortium (IMDC) risk criteria, a retrospective analysis of the prospectively maintained IMDC database was conducted for patients with mRCC diagnosed between 2006-2018 across 33 international centers (10). Patients with mRCC whose first systemic therapy was sunitinib were included whereas patients were excluded if first treatment (sunitinib or upfront CN) occurred >12 months after diagnosis, patients were on surveillance for >6 months after upfront CN (i.e., sunitinib given >6 months after upfront CN), and timing of deferred CN was unknown. Patients were stratified by receipt of upfront CN followed by sunitinib, sunitinib alone, or deferred CN (defined as any CN after receipt of upfront sunitinib) with primary outcome being OS. A final 1541 patients with newly diagnosed mRCC were included, 805 received upfront CN followed by sunitinib, 651 received sunitinib alone, and 85 received sunitinib followed by delayed CN at a median of 7.8 months (interquartile range or IQR 4.8-12.6) from the date of initiation of sunitinib. A majority 85% were clear-cell with 40% of cases being IMDC poor-risk.

With a median follow-up from first treatment initiation of 25 months (IQR 10-49), the median OS for patients treated with sunitinib alone, CN followed by sunitinib, and sunitinib followed by CN were 10 (IQR 4–20), 19 (IQR 9–46), and 46 (IQR 25–67) months, respectively. On multivariable analysis, upfront CN followed by sunitinib was significantly associated with improved OS vs. sunitinib alone (HR 0.60, 95% CI 0.53-0.68, *P*<0.001), as did deferred CN vs. sunitinib alone (HR 0.45, 95% CI 0.33-0.60, *P*<0.001. Among CN-treated patients, deferred CN was associated with improved OS vs. upfront CN followed by sunitinib (HR 0.52, 95% CI 0.39-0.70, *P*<0.001). Similar findings were seen with time to

treatment failure (TTF) in favor of deferred CN. On sensitivity analyses excluding patients with PD and among patients receiving upfront sunitinib, median *OS without and with deferred CN were 16 (IQR 9-32) and 46 (IQR 25-67) months, respectively (P*<0.001), while median TTF without and with deferred CN were 8 (IQR 5-16) and 14 (IQR 9-27) months, respectively (*P*<0.001). On multivariable analysis adjusted for responses, deferred CN remained significantly associated with OS (HR 0.58, 95% CI 0.40-0.84, *P*=0.004).

Candidates for Cytoreductive Nephrectomy

The evidence thus far including data from CARMENA and SURTIME has tempered enthusiasm towards initial CN, particularly in unselected patients, with growing evidence to support a deferred CN approach in those with intermediate risk mRCC who require systemic therapies for VEGF-TKIs. It is worthwhile to note that in CARMENA, there was an element of deferred CN in the sunitinib-alone arm whereby 38 patients (17%) underwent secondary CN for acute symptoms or near-complete response at a median of 11.1 months from randomization to CN (9). In an update and post hoc analysis of CARMENA, 40 patients in the sunitinib-only arm had a secondary nephrectomy with a median OS of 48.5 months (95% CI 27.9-64.4) vs. 15.7 months (95% CI 13.3-20.5) in patients who did not have nephrectomy.[15] Although this finding was likely a reflection of patient selection bias towards those with more favorable disease course, this updated analysis of CARMENA reclassified patients based on IMDC risk groups instead of MSKCC risk groups[15] and highlights: 1) the role for CN after sunitinib with an OS achieved in intermediate-risk patients that should not be underestimated and 2) the importance of selection given that the secondary nephrectomy rate was even higher (25%-30%) among patients who survived long enough.

Deferred CN is a favorable approach for other reasons as well. As described in SURTIME, a deferred CN approach allows a greater proportion of patients who are otherwise in need of systemic therapy to receive such therapy as all patients in the ITT deferred CN arm received systemic therapy compared to 87% in immediate CN arm.[8] Safety was reassuring as the surgical complication rate was similar in patients who underwent CN after 3 months of pretreatment with sunitinib compared with those who underwent immediate surgery. A deferred CN route also allows a selecting out of patients with aggressive biology or inherent resistance to VEGF-TKIs, i.e., individuals who would have been unlikely to benefit from CN in the first place. For example, an exploratory landmark analysis in SURTIME at week 16 of OS according to treatment arm and progression status suggested that patients who had PD in the deferred CN arm before planned surgery or ≤16 weeks of immediate CN had similar poor survival prognosis.[8] In the deferred CN group, 8 of 48 (16.7%) experienced PD by 3 cycles of sunitinib. At the 4-week post-CN restaging assessment, 9 of 46 patients (20%, 95% CI 9-33%) had PD in the immediate CN arm vs. 8 of 34 patients (24%, 95% CI 11-41%) in the deferred CN arm.[8]

With this evidence in mind, it may be practical and logical to initiate all patients with mRCC in need of VEGF-TKIs on a delayed CN pathway to select for the best candidates for CN and avoid unnecessary surgery in those who are unlikely to benefit from CN. However, as many groups have contended, the optimal selection of candidates for CN is difficult to generalize to all mRCC patients.[16,17] There are still mRCC patients in need of immediate CN even if CN was not initially planned (e.g., palliation for symptoms). Others have argued that upfront CN still may have a role in those with good performance status and limited metastatic burden amenable to surveillance or metastectomy.[16] Many agree that initial treatment with systemic therapy is preferred in those with MSKCC/IMDC poor risk disease, poor performance status, and/or large-volume metastatic burden.[16,17] It has been noted that current risk stratification criteria for mRCC invariably classify all CN candidates into intermediate- or poor-risk categories, and given that those who would benefit from CN are likely to have 3 or less adverse prognostic factors, we are essentially focusing our debate on optimal selection of CN candidates within the MSKCC or IMDC intermediate-risk disease category.[17] In the context for guiding the selection of CN in mRCC at presentation, there is certainly a clinical need to redefine low-risk patients.

Lastly, it should be noted that these landmark studies of CN in mRCC were conducted in the era of VEGF-TKIs. The current treatment landscape of mRCC has again shifted in the past 2 years with the advent of immune checkpoint inhibitors (ICIs) whereby dual ICI combinations (ie, nivolumab and ipilimumab) and VEGF-TKI and ICI combinations (ie, axitinib with pembrolizumab or avelumab) have become Food and Drug Administration (FDA) approved for the first-line treatment of mRCC.[18-20] With immunotherapy-based regimens now widely recognized as the preferred first-line standards for mRCC, it would be prudent to investigate the role of CN in this population.

Role of CN in the Immunotherapy Era

Data is still fairly limited on the role of CN in the current immunotherapy era. A retrospective analysis of the National Cancer Data Base (NCDB) involving patients with predominantly clear cell mRCC who received modern immunotherapy between 2015 and 2016 was recently conducted to analyze survival after CN in this population.[21]A total of 96,329 cases were screened but those preceding 2015 were excluded given that the first ICI approval was granted in 2015. The final cohort consisted of 391 mRCC patients (183 diagnosed in 2015, 208 diagnosed in 2016), including 221 (56.5%) who received CN plus immunotherapy and 170 (43.5%) who received immunotherapy only. After a median follow-up of 14.7 months in 183 patients with outcomes data, there were 75 deaths (41%) overall. Patients who received CN had younger age and a larger median primary tumor size, but baseline demographics and Charlson/Deyo comorbidity scores were otherwise similar across groups. In the immunotherapy-only group, the frequency of clinically positive nodes and hepatic metastasis was higher, but the rate of bone, brain, and pulmonary metastases was comparable between groups with no significant difference in

Table. Designs of Select Phase III Trials of Immunotherapy and Deferred CN in mRCC

Trial	Design	Primary Endpoint Sample Size
SWOG 1931	Induction ICI-based combination therapy and if PR or SD, 1:1 randomization to continue systemic therapy or CN within 8 weeks of randomization followed by systemic therapy; systemic therapy to be held 12 weeks in perioperative period	OS, n=302 (all histologies except collecting duct)
NORDIC-SUN	Induction nivolumab/ipilimumab for 4 cycles (3 months) and if deemed suitable for CN with ≤ 3 IMDC risk factors, randomization to deferred CN followed by maintenance nivolumab or maintenance nivolumab alone. Those deemed not suitable for surgery or have >3 IMDC risk factors at first 3-month evaluation to continue systemic therapy for another 3 months. If deemed suitable for CN and ≤3 IMDC risk factors at 6-month evaluation, randomization to deferred CN or maintenance nivolumab alone. Those not deemed suitable for CN or >3 IMDC risk factors continue systemic therapy	OS, n=400 (all histologies)

CN, cytoreductive nephrectomy; mRCC, metastatic renal cell carcinoma; ICI, immune checkpoint inhibitor; PR, partial response; SD, stable disease; OS, overall survival; IMDC, International mRCC Database Consortium

the number of known metastatic sites. Sarcomatoid features were seen in 22 cases (5.6%) but this was similarly distributed between groups.

Patients who underwent CN and immunotherapy had significantly improved OS than those who received immunotherapy only (median not reached vs. 11.6 months, HR 0.23, p<0.001). Of the 221 patients who received CN and immunotherapy, 197 underwent upfront CN, while 24 received immunotherapy before CN (including 9 who had continuation of immunotherapy following CN). In a comparison of upfront and delayed CN groups, patients who received immunotherapy first tended to be older and more likely to have bone metastases, but they tended to have lower Fuhrman grade, smaller tumor size, lower pathologic T stage, and lower likelihood of lymphovascular invasion. In contrast, patients who underwent upfront CN were more likely to have pulmonary metastases. The rates of brain, liver, and pathologically positive lymph node (pN1) metastases were similar between groups. Notably, this study was limited by its observational nature with potential for unaccounted confounders. There are also limitations in the data captured by the NCDB including the inability to account for risk stratification that could have affected decisions to offer CN, type of immunotherapy regimen, number of cycles, and duration between last immunotherapy treatment and surgery. With that said, the median OS for the delayed CN group was not reached, compared with 30 months for the upfront CN group (HR 0.25, *P*=0.139).

Recently, the phase III ADAPT trial investigated the efficacy of Rocapuldencel-T, an autologous dendritic cell-based immunotherapy designed to capture and present host tumor-specific antigens to elicit antitumor immune responses.[22] In this open-labeled, multicenter, randomized trial, a total of 462 patients with IMDC intermediate- or poor-risk, untreated mRCC with a primary tumor in place and predominant clear cell histology were randomized (2:1 fashion) to receive Rocapuldencel-T and sunitinib or sunitinib alone (the standard of care at that time). Rocapuldencel-T was manufactured by isolating autologous tumor total RNA from partial nephrectomy or CN and administered into a single lymph node basin as 3 intradermal injections of 0.2 mL each after completion of at least one 6-week sunitinib cycle followed by 1 dose every 3 weeks for a total of 5 doses (induction phase). This was followed by 1 dose every 3 months until withdrawal study criteria were met with doses administered through 48 weeks irrespective of PD unless unacceptable toxicity occurred, per patient/physician discretion, or ≥2 progression events occurred.

In the ITT population, median OS in the combination arm was 27.7 months (95% CI 23.0-35.9) and 32.4 months (95% CI 22.5-not reached) in the sunitinib arm with an unadjusted HR of 1.10 (95% CI 0.83-1.46). There were 307 subjects enrolled into the Rocapuldencel-T and sunitinib arm and 155 subjects to the sunitinib alone arm in the overall ITT population but 450 patients with clear cell mRCC were randomized to combination therapy or sunitinib alone with or without nephrectomy. Notably, the median OS was 18.4 months for those who did not receive nephrectomy, which was numerically higher but declared noninferior to the median OS of 13.9 months in patients who received nephrectomy. A key takeaway point from this prospective, phase III ADAPT study was that in a population where the majority of patients received immunotherapy-based therapy and were of intermediate-risk classification (>75%), the median OS of those who received nephrectomy (essentially upfront nephrectomy in those receiving experimental immunotherapy given the nature of autologous tumor RNA isolation) was comparably worse than the median OS of

the upfront CN group of intermediate-risk mRCC patients of CARMENA.[9] Instead, the median OS of those receiving nephrectomies in ADAPT was more comparable to the poor-risk group of patients receiving upfront CN in CARMENA. It is important to note that this would be a cross-study comparison with inherent limitations and that Rocapuldencel-T is different from conventional ICIs that have been established in the first-line treatment of mRCC. Nevertheless, ADAPT provides initial glimpses into the outcomes of mRCC patients receiving nephrectomies and immunotherapy-based regimens in the more current era.

Although evidence seeking to address the role of CN in mRCC in the immunotherapy era is starting to be published, further investigation in ideally large, prospective settings are certainly warranted. It is worthwhile to mention that ongoing phase III studies of CN and ICI-based regimens in mRCC are evaluating the impact of deferred CN (**Table**), whereby induction with standard ICI-based therapies are performed and if there is absence of PD, then randomization to CN takes place. In NORDIC-SUN, having >3 IMDC risk factors at the time of assessment is deemed not suitable for CN. The study designs of SWOG-1931 and NORDIC-SUN are likely reflective of growing acknowledgement that deferred CN is becoming the preferred approach allowing for a period of assessment of disease response and biology to systemic therapy prior to advancing to CN even in the contemporary immunotherapy era in mRCC.

Conclusion

In patients with mRCC deemed candidates for CN, the initial treatment approach and optimal sequencing of CN and systemic therapy has yet to be definitively established. However, a growing consensus is that nonselective use of CN to treat clear cell mRCC is unlikely to provide a meaningful survival benefit. Selection of candidates for CN should be performed in a multidisciplinary team-based setting incorporating conventional risk or prognostic stratification systems. Based on recent seminal studies of CN in mRCC patients treated with VEGF-TKIs, there is evidence to support that response to presurgical systemic therapy and upfront systemic therapy should be prioritized over surgery. This is reflected in modern phase III study designs whereby the impact of deferred CN is being evaluated in mRCC patients treated with current immunotherapy-based combinations. Results from these ongoing studies are eagerly anticipated as the role of CN in the immunotherapy era remains undefined.

References

1. Capitanio U, Bensalah K, Bex A, Boorjian SA, Bray F, Coleman J, et al. Epidemiology of Renal Cell Carcinoma. *Eur Urol*. 2019;75(1):74-84.
2. Choueiri TK, Motzer RJ. Systemic Therapy for Metastatic Renal-Cell Carcinoma. *N Engl J Med*. 2017;376(4):354-66.
3. Flanigan RC, Salmon SE, Blumenstein BA, Bearman SI, Roy V, McGrath PC, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *N Engl J Med*. 2001;345(23):1655-9.
4. Mickisch GH, Garin A, van Poppel H, de Prijck L, Sylvester R. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. *Lancet*. 2001;358(9286):966-70.
5. Flanigan RC, Mickisch G, Sylvester R, Tangen C, Van Poppel H, Crawford ED. Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. *J Urol*. 2004;171(3):1071-6.
6. Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara J. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *J Clin Oncol*. 1999;17(8):2530-40.
7. Motzer RJ, Rini BI, McDermott DF, Aren Frontera O, Hammers HJ, Carducci MA, et al. Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2019;20(10):1370-85.
8. Bex A, Mulders P, Jewett M, Wagstaff J, van Thienen JV, Blank CU, et al. Comparison of Immediate vs Deferred Cytoreductive Nephrectomy in Patients With Synchronous Metastatic Renal Cell Carcinoma Receiving Sunitinib: The SURTIME Randomized Clinical Trial. *JAMA Oncol*. 2019; 5(2):164-70.
9. Mejean A, Ravaud A, Thezenas S, Colas S, Beauval JB, Bensalah K, et al. Sunitinib Alone or after Nephrectomy in Metastatic Renal-Cell Carcinoma. *N Engl J Med*. 2018;379(5):417-27.
10. Bhindi B, Graham J, Wells JC, Bakouny Z, Donskov F, Fraccon A, et al. Deferred Cytoreductive Nephrectomy in Patients with Newly Diagnosed Meta-static Renal Cell Carcinoma. *Eur Urol*. 2020.
11. de Bruijn R, Wimalasingham A, Szabados B, Stewart GD, Welsh SJ, Kuusk T, et al. Deferred Cytoreductive Neph-rectomy Following Presurgical Vascular Endothelial Growth Factor Receptor-targeted Therapy in Patients with Primary Metastatic Clear Cell Renal Cell Carcinoma: A Pooled Analysis of Prospective Trial Data. *Eur Urol Oncol*. 2020;3(2):168-73.
12. Bex A, Blank C, Meinhardt W, van Tinteren H, Horenblas S, Haanen J. A phase II study of presurgical sunitinib in patients with metastatic clear-cell renal carcinoma and the primary tumor in situ. *Urology*. 2011;78(4):832-7.
13. Powles T, Blank C, Chowdhury S, Horenblas S, Peters J, Shamash J, et al. The outcome of patients treated with sunitinib prior to planned nephrectomy in metastatic clear cell renal cancer. *Eur Urol*. 2011;60(3):448-54.
14. Powles T, Sarwar N, Stockdale A, Sarker SJ, Boleti E, Protheroe A, et al. Safety and Efficacy of Pazopanib Therapy Prior to Planned Nephrectomy in Metastatic Clear Cell Renal Cancer. *JAMA Oncol*. 2016;2(10):1303-9.
15. Mejean A, Thezenas S, Chevreau C, Bensalah K, Geoffrois L, Thiery-Vuil-lemin A, et al. Cytoreductive nephrectomy (CN) in metastatic renal cancer (mRCC): Update on Carmena trial with focus on intermediate IMDC-risk population. *J Clin Oncol*. 2019;37 (15_suppl):4508-.
16. Bhindi B, Abel EJ, Albiges L, Bensalah K, Boorjian SA, Daneshmand S, et al. Systematic Review of the Role of Cytoreductive Nephrectomy in the Targeted Therapy Era and Beyond: An Individualized Approach to Metastatic Renal Cell Carcinoma. *Eur Urol*. 2019;75(1):111-28.
17. Larcher A, Wallis CJD, Bex A, Blute ML, Ficarra V, Mejean A, et al. Individualised Indications for Cytoreductive Nephrectomy: Which Criteria Define the Optimal Candidates? *Eur Urol Oncol*. 2019;2(4):365-78.
18. Motzer RJ, Penkov K, Haanen J, Rini B, Albiges L, Campbell MT, et al. Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2019;380(12):1103-15.
19. Motzer RJ, Tannir NM, McDermott DF, Aren Frontera O, Melichar B, Choueiri TK, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2018;378(14):1277-90.
20. Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2019;380(12):1116-27.
21. Singla N, Hutchinson RC, Ghandour RA, Freifeld Y, Fang D, Sagalowsky AI, et al. Improved survival after cytoreductive nephrectomy for metastatic renal cell carcinoma in the contemporary immunotherapy era: An analysis of the National Cancer Database. *Urol Oncol*. 2020.
22. Figlin RA, Tannir NM, Uzzo RG, Tykodi SS, Chen DYT, Master V, et al. Results of the ADAPT Phase 3 Study of Rocapuldencel-T in Combination with Sunitinib as First-Line Therapy in Patients with Metastatic Renal Cell Carcinoma. *Clin Cancer Res*. 2020. KCJ

Uveal Melanoma and Kidney Cancer: More Similar than Meets the Eye

Nirmish Singla, MD, MSCS
Urology Service, Department of Surgery
Memorial Sloan Kettering Cancer Center
New York, NY

Discoveries in one cancer type may hold clues to understanding seemingly unrelated cancers of other types as well. In the case of uveal melanoma (UM), Rodrigues et al. used comparative genomic hybridization assays to demonstrate that partial deletion of chromosome 3 encompassing the *BAP1* locus was associated with strikingly worse 5-year metastasis-free and overall survival.[1] Their findings resonate with the seminal study by Harbour et al., which originally implicated BAP1 loss in UM metastasis.[2]

Notably, chromosome 3 plays an integral role in the pathogenesis of the most common type of kidney cancer as well, clear cell renal cell carcinoma (ccRCC). In particular, loss of chromosome 3p occurs in the majority of ccRCC cases, leaving the alleles on the remaining short arm of chromosome 3 susceptible to genetic alterations.[3] In line with Knudson's two-hit hypothesis, the most common driver mutations found in ccRCC involve the tumor suppressor genes found within a short stretch on chromosome 3p, including the histone deubiquitinase gene *BAP1* in up to 15% of sporadic cases. As in the case of UM, loss of the BAP1 protein has been consistently associated with more aggressive forms of disease and worse prognostic outcomes in ccRCC patients, leading further to the development of distinct molecular subclassifications of ccRCC. In a similar manner, Rodrigues et al. speculate on different prognostic subtypes of UM defined by the presence of *BAP1* alterations and/or chromosome 8q gains.[1]

This unique genomic similarity between ccRCC and UM—which also extends to include mesothelioma among other malignancies within the spectrum of the *BAP1* tumor predisposition syndrome—leads one to question whether there may be a targetable role for *BAP1* that can be useful in designing therapeutic basket trials. A possible predictive role for *BAP1* in informing response to immune checkpoint inhibitors has been postulated in both ccRCC via human endogenous retroviral expression[4] and in malignant mesothelioma.[5] Although response to systemic immunotherapy has been traditionally less robust for metastatic UM compared to its cutaneous counterpart, perhaps the molecular landscape may guide a more precise approach to treatment and improve outcomes for these patients.

Keywords: uveal melanoma, clear cell renal cell carcinoma, *BAP1*, chromosome 3, prognosis, treatment

Corresponding Author: JNirmish Singla, MD, MSCS, 1275 York Ave. New York, NY 10065 Phone: (248) 761-2452.
Email: nirmish@gmail.com

References

1. Rodrigues M, Ait Rais K, Salviat F, et al. Association of Partial Chromosome 3 Deletion in Uveal Melanomas With Metastasis-Free Survival. *JAMA Ophthalmol*. 2020.
2. Harbour JW, Onken MD, Roberson ED, et al. Frequent mutation of BAP1 in metastasizing uveal melanomas. *Science*. 2010;330(6009): 1410-1413.
3. Brugarolas J. Molecular genetics of clear-cell renal cell carcinoma. *J Clin Oncol*. 2014;32(18):1968-1976.
4. Panda A, de Cubas AA, Stein M, et al. Endogenous retrovirus expression is associated with response to immune checkpoint blockade in clear cell renal cell carcinoma. *JCI Insight*. 2018;3(16).
5. Ladanyi M, Sanchez Vega F, Zauderer M. Loss of BAP1 as a candidate predictive biomarker for immunotherapy of mesothelioma. *Genome Med*. 2019;11(1):18. KCJ

EDITOR'S MEMO

(continued from inside front cover)

that you track the new information from KEYNOTE 426 and KEYNOTE 427, the OMNIVORE study, JAVELIN Renal 101 and PROTECT, to name just a few. For example, if you were looking for confirmatory evidence underlying the rationale for using pembrolizumab and axitinib in the frontline setting, then review the findings from KEYNOTE 426.

Similarly, in the frontline setting, what are your prognostic criteria when another combination, avelumab and axitinib, is being considered? If we had a reliable biomarker with prognostic significance, treatment choices could be further clarified. There has been much interest in the neutrophil to lymphocyte ratio in this regard and an abstract from this year's meeting offers data from a Phase 3 trial to potentially improve clinical decision making.

Hopefully, by this time in 2021, we can gather again at a "live" event to meet with our colleagues and reminisce about a time when the vast halls of the convention center were eerily empty and silent.

Robert A. Figlin, MD
Editor-in-Chief

MEDICAL INTELLIGENCE

(continued from page 36)

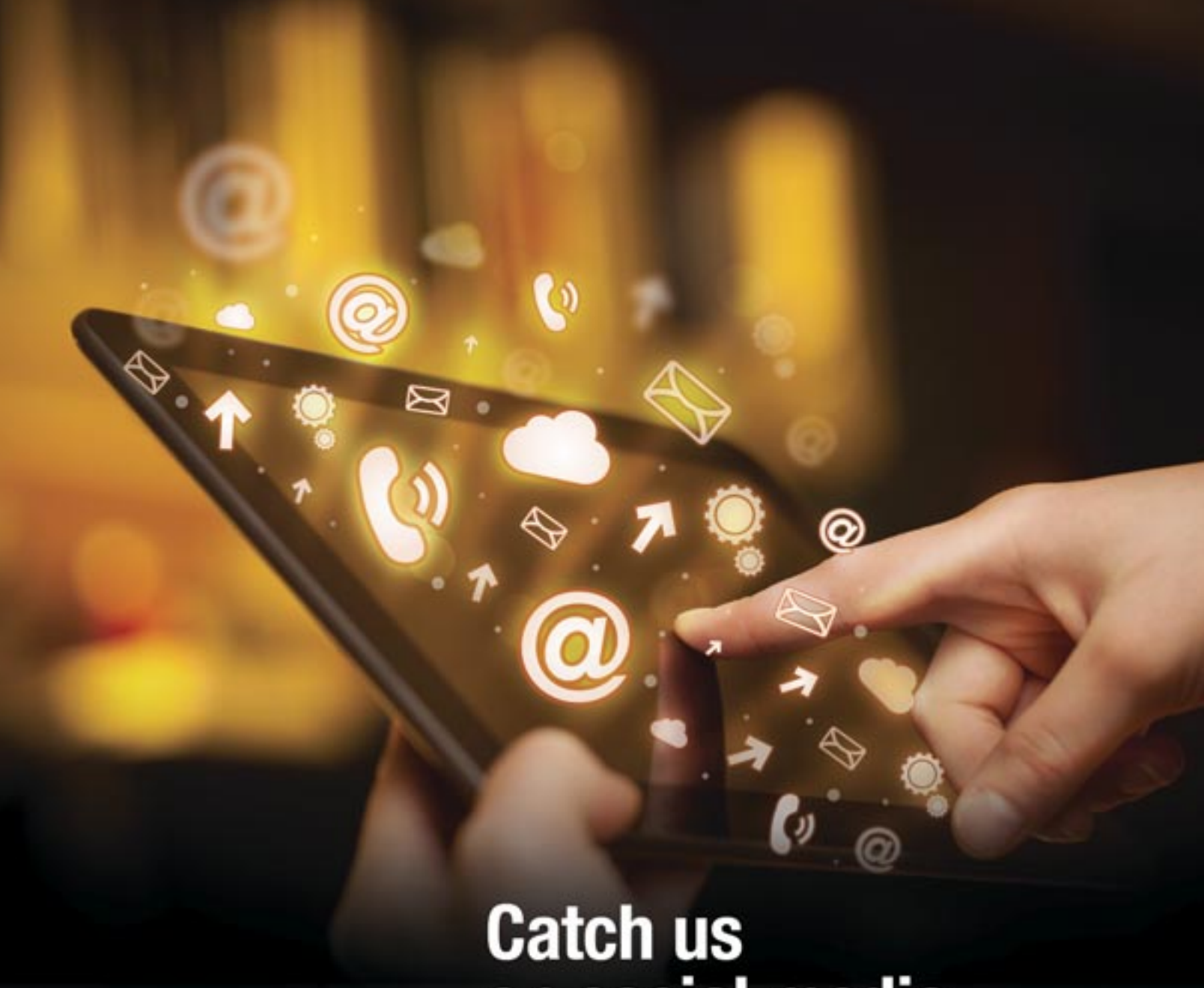
Ina® is compliant with the Health Insurance Portability and Accountability Act (HIPAA). It brings a much-needed cancer-specific nutrition resource to the kidney cancer community. A 2015 study in the *Journal of Cachexia, Sarcopenia and Muscle* showed that 31.7% of metastatic renal cell carcinoma (mRCC) patients were classified as being at risk of malnutrition. Poor nutrition status and low body mass index (BMI) scores were predictors of decreased survival and poor quality of life among kidney cancer patients.

"The Kidney Cancer Association is delighted to share this innovative new resource with the kidney cancer community," said Gretchen E. Vaughan, President and CEO of the KCA. "Nutrition is a major concern for people living with cancer and easy, quick, and relevant advice is crucial. Especially now, when other aspects of life may feel outside of their control, we hope that anyone impacted by kidney cancer can feel empowered by the knowledge Ina provides."

This partnership supports the KCA's mission to provide support and resources that empower people to make informed decisions about their health. For more information on how to use Ina®, please visit the KCA's website at https://www.kidneycancer.org/ina-by-savor-health. KCJ

(continued from page 48)

28. Altoos B, Amini A, Yacoub M, et al. Local control rates of metastatic renal cell carcinoma (RCC) to thoracic, abdominal, and soft tissue lesions using stereotactic body radiotherapy (SBRT).*Radiat Oncol*. 2015; 10:218.
29. Buti S, Bersanelli M, Viansone A, et al. Treatment outcome of metastatic lesions from renal cell carcinoma undergoing extra-cranial stereotactic body radiotherapy: the together retrospective study. *Cancer Treat Res Commun*. 2020;22:10061.
30. Singh AK, Winslow TB, Kermany MH, et al. A pilot study of stereotactic radiation therapy combined with cytoreductive nephrectomy for metastatic renal cell carcinoma. *Clin Can Res*. 2017;23:5055-505.
31. Masini C, Iotti C, De Giorgi U, et al: Nivolumab in combination with stereotactic body radiotherapy in pretreated patients with metastatic renal cell carcinoma: First results of the phase II NIVES study. 2020 Genitourinary Cancers Symposium. Abstract 613. Presented February 15, 2020.
32. Hammers HJ, Vonmerveldt D, Ahn C, et al: Combination of dual immune checkpoint inhibition with stereotactic radiation in metastatic renal cell carcinoma. 2020 Genitourinary Cancers Symposium. Abstract 614. Presented February 15, 2020.
33. Chang et al. 2016 Clinical Oncology September 2016 Vol. 28, Issue 9, e109-e114 PMID 27131756
34. Staehler et al. 2015 PMID 25132240
35. Siva et al. 2017 BJUI 2017 PMID 28188682
36. Siva et al. 2018 Cancer PMID 29266183 KCJ



Catch us on social media.

Facebook - @KidneyCancerJournal

LinkedIn - #Kidney-Cancer-Journal

Twitter - @KidneyCancerJ

Instagram - @KidneyCancerJournal

Kidney Cancer JOURNAL