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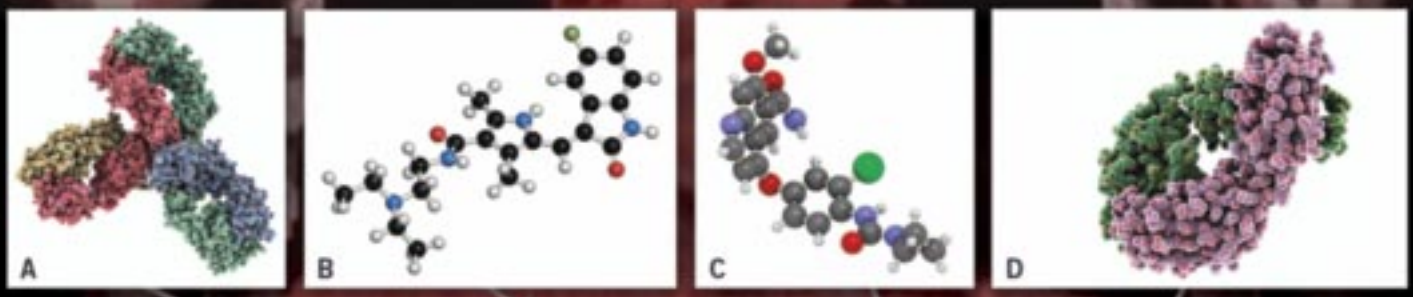

Quiz: Match each molecule with its drug

Drugs: Nivolumab (Opdivo), Pembrolizumab (Keytruda), Lenvatinib (Lenvima), Sunitinib (Sutent)

Answers on Table of Contents page, About the Cover.

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

Now in Its 17th 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.

Publishing Staff
Stu Chapman, *Executive Editor*
Jenny Chapman, *Director, Business Development*
Michael McClain, *Design Director*

Director of Advertising
Susan Hirschhaut
(847) 476-0588
susan@datamedica.org

Business and Administration Office
333 E. 75th Street, Suite 5D
New York, NY 10021

Editorial Offices
Genitourinary Publishing
333 E. 75th Street, Suite 5D
New York, NY 10021
Tel: (516) 356-5006

About the Cover
Answers to quiz on which drugs are represented by molecules: (A) Pembrolizumab (Keytruda), (B) Sunitinib (Sutent), (C) Lenvatinib (Lenvima), (D) Nivolumab (Opdivo). Larger image depicts a 66-year-old male with metastatic renal carcinoma. Fused Whole Body FDG PET CT Scan following intravenous administration of 9.7 mCi of 18-FDG reveals metabolically active tumor in right paratracheal lymph node chain and confluent adenopathy in the mid-abdomen, retroperitoneum in aortocaval chain.

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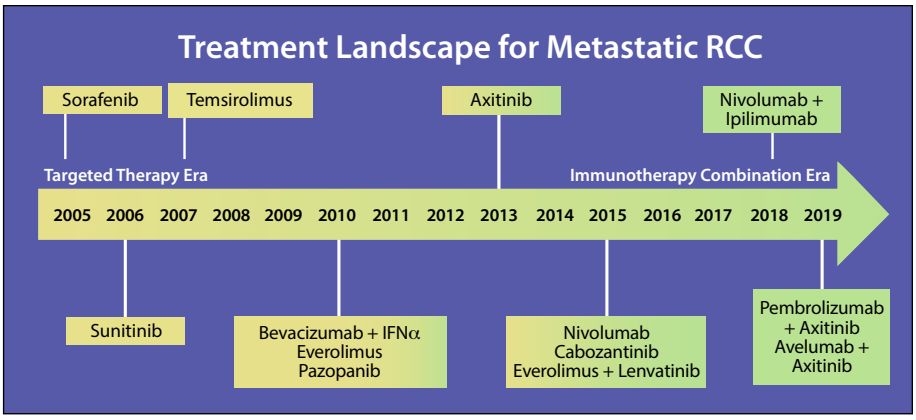
KCJ GUEST EDITOR'S MEMO

ASCO 2019 Postscript: Inflection Point? Pivotal Results? Hold On, Not So Fast


Sumanta (Monty) Pal, MD

With more than 2,400 abstracts accepted for presentation at the 2019 ASCO Annual Meeting, and more than 3,200 additional abstracts accepted for online publication, this year's scientific sessions offered clinicians an incredible selection of information from which to glean insights and consider potentially practice changing data. As always, it is tempting to review selected abstracts in renal cell carcinoma (RCC) and speculate to what extent the emerging results presented in kidney cancer could suggest an inflection point for treatment and whether some of the exciting abstracts could have significant impact on our management strategies.



In contrast to previous ASCO meetings, the consensus seemed to be that the 2019 sessions did not eclipse the pivotal information we have seen emerging from earlier symposia where one could sense that the "needle" was moving perceptibly on various issues. For example, compared to previous years, none of the information at this year's ASCO was selected for review during the Plenary sessions, a bellwether that suggests significant potential impact on clinical practice. Despite the absence of kidney cancer in the Plenary sessions, many abstracts in RCC merit attention and some of these are covered elsewhere in this issue of the *Kidney Cancer Journal*.

In commentaries, blogs, and interviews featuring ASCO-related analyses with key opinion leaders, these trends were among those attracting wide attention:

- Results demonstrated the safety and benefit of immune checkpoint

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Kidney Cancer Journal Author Guidelines

Scope of Manuscripts

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

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

Manuscript Submission

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

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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.

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Essential Peer-Reviewed Reading in Kidney Cancer

The peer-reviewed articles summarized in this section were selected by the Editor-in-Chief, Robert A. Figlin, MD, for their timeliness, importance, relevance, and potential impact on clinical practice or translational research.

Cabozantinib in Renal Cell Carcinoma **With Brain Metastases: Safety and Efficacy in a Real-World Population.** Peverelli G, Raimondi A, Ratta R, et al. *Clin Genitourin Cancer.* 2019. May 13. pii: S1558-7673(18)30652-9. doi: 10.1016/j.clgc.2019.05.002. [Epub ahead of print]

Summary: Cabozantinib showed efficacy and manageable toxicity in patients with metastatic renal cell carcinoma (mRCC). This study described the safety and efficacy of cabozantinib in mRCC patients with brain metastases (BM) in a real-world experience. It retrospectively collected data of patients treated with cabozantinib within the Italian Managed Access Program. Patients were selected for the presence of BM before the start of treatment and for at least 1 previous tyrosine kinase inhibitor (TKI) treatment regimen for metastatic disease. Safety data were reported, and overall response rate (ORR), brain-specific response, progression-free survival (PFS), and median overall survival (OS) were analyzed. Overall, 12 patients treated with cabozantinib were evaluated. Any grade adverse events (AEs) accounted for 92%, Grade 3/4 AEs rated at 36% with no major neurological side effects. The most common AEs included hypertension (33%), fatigue (24%), aminotransferase elevation (25%), hypothyroidism (16%), and gastrointestinal toxicity (16%). The ORR was 50% with a disease control rate of 75%. All 5 patients treated with a combined systemic and brain-directed approach obtained intracranial disease control, without increased toxicity. Median PFS and median OS were 5.8 and 8.8 months, respectively. Comparable safety and tolerability results for other TKI regimens were reported from the literature.

Conclusion: Cabozantinib showed safety, acceptable tolerability, and promising antitumor activity in a population of mRCC patients with BM from a real-world experience. A combined modality approach for renal cell carcinoma with BM, whenever feasible, could be recommended to improve oncological outcomes.

Morphologic subtyping as a prognostic predictor for survival in papillary renal cell carcinoma: Type 1 vs. type 2. Wong ECL, Di Lena R, Breau RH, et al. *Urol Oncol.* 2019 Jun 5. pii: S1078-1439(19)30195-4. doi: 10.1016/j.urolonc.2019.05.009. [Epub ahead of print]

Summary: This study evaluated outcomes of surgically treated patients with clinically localized papillary renal cell carcinoma (RCC) and determine if papillary RCC subtype is associated with recurrence and survival. This is a historical cohort study using the prospectively maintained Canadian Kidney Cancer Information System database between January 2011 and September 2018. All patients underwent partial or radical nephrectomy. Patient, tumor, treatment, and outcomes were compared between papillary RCC type 2 and type 1 cohorts. During the study period, 509 patients had clinically localized papillary RCC type 2 (n = 172) or type 1 (n = 337) histology. Sex, race, and comorbidities were similar between groups. Pathologic stage (pT3 or pT4), nuclear grade (3 or 4), and tumor diameter were higher in the type 2 papillary RCC cohort ($P < 0.0001$). A greater proportion of type 2 papillary RCC patients received radical nephrectomy (42.4% vs. 24.6%, $P< 0.0001$). More type 2 papillary RCC patients underwent lymph node dissection (19.6% vs. 5.5%, $P< 0.0001$) and had lymph node metastases removed during surgery (6.4% vs. 0.6%, $P= 0.103$). Overall, adjusting for age, grade, pathologic stage, positive nodes, and tumor size, type 2 papillary RCC had worse outcomes compared to type 1, as demonstrated by elevated all-cause mortality (hazard ratio = 7.7 [95% confidence interval: 2.0-28.9]), $P=0.0027$) and worse recurrence-free survival (hazard ratio = 8.2 [95% confidence interval: 3.6-19.0], $P< 0.0001$).

Conclusion: Patients with clinically localized type 2 papillary RCC present with higher risk disease and have worse prognosis compared to patients with clinically localized type 1 papillary RCC. This is reportedly the largest cohort study comparing papillary RCC subtypes.

Prospective Observational Study of Pazopanib in Patients with Advanced Renal Cell Carcinoma (PRINCIPAL Study). Schmidinger M, Bamias A, Procopio G, et al. *Oncologist.* 2019 Apr;24(4):491-497. doi: 10.1634/theoncologist.2018-0787.

Summary: Real-world data are essential to accurately assessing efficacy and toxicity of approved agents in everyday practice. PRINCIPAL, a prospective, observational study, was designed to confirm the real-world safety and efficacy of pazopanib in patients with advanced renal cell carcinoma (RCC). Patients with clear cell advanced/metastatic RCC and a clinical decision to initiate pazopanib treatment within 30 days of enrollment were eligible. Primary objectives included progression-free survival (PFS), overall survival (OS), objective response rate (ORR), relative dose intensity (RDI) and its effect on treatment outcomes, change in health-related quality of life (HRQoL), and safety. We also compared characteristics and outcomes of clinical-trial-eligible (CTE) patients, defined using COMPARZ trial eligibility criteria, with those of non-clinical-trial-eligible (NCTE) patients. Secondary study objectives were to evaluate clinical efficacy, safety, and RDI in patient subgroups.

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

Avelumab + Axitinib Approved for Treatment of RCC

Avelumab (Bavencio) was approved for first-line treatment of advanced renal cell carcinoma (RCC) in combination with Axitinib (Inlyta), the FDA has announced. The agency based the approval on data from the JAVELIN Renal 101 trial, a randomized, multicenter, open-label trial of avelumab combined with axitinib. The trial included 886 patients with previously untreated advanced RCC who were randomly assigned either to treatment with 10 mg/kg avelumab intravenous infusion every two weeks plus 5 mg oral axitinib twice daily or to treatment with 50 mg oral sunitinib once daily for four weeks followed by two weeks off.

Researchers found that median progression-free survival was 13.8 months for patients who received avelumab plus axitinib and 8.4 months for patients who received sunitinib. The FDA notes that the overall survival data were immature, and at 19 months, the death rate was 27% in the intent-to-treat population. Nine percent of patients experienced grade 3 to 4 toxicity, which led to permanent discontinuation in 7 percent. Seven percent of patients in the trial had major cardiac adverse events.

Recommended dosing of avelumab is an intravenous infusion of 800 mg every two weeks combined with 5 mg oral axitinib twice daily. Commonly reported adverse reactions with avelumab plus axitinib include diarrhea, fatigue, hypertension, musculoskeletal pain, nausea, mucositis, palmar-plantar erythrodysesthesia, dysphonia, decreased appetite, hypothyroidism, rash, hepatotoxicity, dyspnea, abdominal pain, and headache. The manufacturer's labeling information directs clinicians to inform patients of the risk for pneumonitis, hepatitis, colitis, endocrinopathies, nephritis, and renal dysfunction.

Epidemiology of RCC: New Snapshot of Rates vs Other Cancers

The American Cancer Society has updated findings on the epidemiology of all cancers, based on data from the National Cancer Institute. The average age at diagnosis of kidney cancer is 64. In 2019, it is estimated the US will see 73,820 new cases of kidney cancer (44,120 in men and 29,700 in women), and that nearly 14,700 individuals will die from this disease.

Table 8. Five-year Relative Survival Rates* (%) by Stage at Diagnosis, US, 2008-2014

	All stages	Local	Regional	Distant
Breast (female)	90	99	85	27
Oral cavity & pharynx	65	84	65	3
Colon & rectum	65	90	71	14
Ovary	47	92	75	29
Colon	64	90	71	14
Pancreas	9	34	12	3
Rectum	67	89	70	15
Prostate	98	>99	>99	30
Esophagus	19	45	24	5
Stomach	31	68	31	5
Kidney†	75	93	69	12
Testis	95	99	96	74
Larynx	61	78	46	34
Thyroid	98	>99	98	56
Liver‡	18	31	11	2
Urinary bladder§	77	69	35	5
Lung & bronchus	19	56	30	5
Uterine cervix	66	92	56	17
Melanoma of the skin	92	98	64	23
Uterine corpus	81	95	69	16

*Rates are adjusted for normal life expectancy and are based on cases diagnosed in the SEER 18 areas from 2008-2014, all followed through 2015. †Includes renal pelvis. ‡ Includes intrahepatic bile duct. § Rate for in situ cases is 95%. **Local:** an invasive malignant cancer confined entirely to the organ of origin. **Regional:** a malignant cancer that 1) has extended beyond the limits of the organ of origin directly into surrounding organs or tissues; 2) involves regional lymph nodes; or 3) has both regional extension and involvement of regional lymph nodes. **Distant:** a malignant cancer that has spread to parts of the body remote from the primary tumor either by direct extension or by discontinuous metastasis to distant organs, tissues, or via the lymphatic system to distant lymph nodes. **Source:** Noone AM, Howlader N, Krapcho M, et al. (eds). *SEER Cancer Statistics Review, 1975-2015, National Cancer Institute*, Bethesda, MD, http://seer.cancer.gov/csr/1975_2015/, based on November 2017 SEER data submission, posted to the SEER website April 2018.©2019 American Cancer Society, Inc., Surveillance Research

Hispanic origin is not mutually exclusive from Asian/Pacific Islander or American Indian/Alaska Native. *Rates are per 100,000 population and age adjusted to the 2000 US standard population and exclude data from Puerto Rico. †Data based on Indian Health Service Contract Health Service Delivery Areas. **Source:** Incidence – North American Association of Central Cancer Registries, 2018. Mortality – National Center for Health Statistics, Centers for Disease Control and Prevention, 2018. ©2019 American Cancer Society, Inc., Surveillance Research

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Gretchen Vaughan, New CEO at Kidney Cancer Association, Envisions A New Era in Patient Advocacy and Supportive Research Initiatives

Gretchen Vaughan

In this interview, Gretchen Vaughan, recently named the new CEO of the Kidney Cancer Association, offers insights on her role with the KCA and vision for the future of the organization. In relating her personal commitment to patients, caregivers and families, she discusses how the KCA will renew its commitment to finding a cure for kidney cancer and improve the quality of life of patients affected by the disease.

Q: Please review your background in health care management issues and how it relates to your appointment as CEO of the Kidney Cancer Association.

Ms Vaughan: In 2004, I made a career shift and joined MD Anderson Cancer Center after a twelve-year career in financial services. I began first by volunteering at MD Anderson, and soon thereafter, cancer research immediately became my life's passion. During my 13 years at MD Anderson, I had the opportunity to know and love patients through tough diagnoses, heart-wrenching scans and tests, and results that sometimes ended in heartbreak and sometimes in immense joy. Regardless of the outcome, one thing was constant through every story – a cure was waiting.

Then several years ago, I lost two friends to kidney cancer. They were both in their 30s and had so much life left to give. It was a life changing experience and a devastating example of how much work there is to do within kidney cancer research.

When I was given the opportunity to take this role, I knew it was a perfect match for me where I could take my financial and business acumen, my experience at MD Anderson, and my love for patients and their families to substantially move the needle to accelerate research in this field.

I see the potential for the KCA to do something phenomenal and game changing. I am eager to bring the organization into a new era and unite us under one goal and one mission: the elimination of death and suffering from renal cancers.

Q: What are several plans/strategies you have for introducing new initiatives with the Association? How do you balance its role as patient advocate vs its academic focus?

Ms Vaughan: It is a new day at the KCA. Moving forward, it is our goal, regardless of whether we are interacting with physicians, researchers, or patients, that all the outcomes are for the benefit of the patient. Previously, the KCA outlined three focus areas for its work: Education, Research, and Advocacy. We are currently in the process of developing a multi-year strategic plan that will lay the groundwork for the future of the organization. As we do so, we will be analyzing where we believe the KCA can create the greatest transformation to improve the lives of patients. How can we utilize the KCA resources to do something revolutionary for the cause? What research is necessary to change the game for the life of a patient? What resources can we provide that can truly make a difference for patients and their families as they begin making medical decisions? These are the types of questions we are asking as we move into the future.

We are continuing to implement programmatic initiatives to support our mission¾from the sponsorship of patient support groups to the giving of significant funds for research. The KCA recently announced $1 million in new research funding for two annual $500,000 grant applications, the Advanced Discovery Awards (ADA) ¾targeting the early detection and innovative treatments of kidney cancer. In addition, we have increased our Young Investigator Award (YIA) from two, $50,000 grants to four, $75,000 grants. Totaling over $1.3 million, these grants are just one way in which we are supporting those dedicated to identifying new treatments and ultimately a cure for the disease.

Q: Will the KCA launch any new initiatives on the legislative front to increase government funding of kidney cancer research? Why doesn't the federal government do more for kidney cancer research?

Ms Vaughan: Through thoughtful discussions with our board and committees during the strategic planning process, we are examining the options at the state and federal levels in the United States and across the globe that would make an honest impact in the lives of patients. In addition, we are making connections with other organizations to understand how we might complement their efforts and to identify any gaps we may be able to fill for the betterment of patients.

Q: Do you plan any changes in the format and focus of the International Symposia? Are you satisfied with the attendance?

Ms Vaughan: We are not currently planning to make

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MIAMI

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Original Contribution

Patients Perspectives on Adjuvant Therapy in Renal Cell Carcinoma

Michael Staehler[1], Dena Battle[2], Ithaar Derweesh[3], Dan George[4], Axel Bex[5], Hans Hammers[6], Börje Ljungberg[7], Eric Jonasch[8]

[1]Department of Urology, University Hospital Munich-Grosshadern, Ludwig Maximilian University, Munich, Germany
[2]KCCure, Alexandria, VA;
[3]Department of Urology, Moores UCSD Cancer Center, University of California, San Diego, San Diego, CA;
[4]Duke Cancer Institute, Duke University Medical Center, Durham, NC;
[5]The Netherlands Cancer Center, Division of Surgical Oncology, Department of Urology, Amsterdam, Netherlands;
[6]Harold C. Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, Dallas, TX;
[7]Department of Surgical and Perioperative Sciences, Urology and Andrology, Umeå University, Umeå, Sweden;
[8]Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX;

Abstract

Objectives:
Adjuvant therapy for renal cell carcinoma (RCC) is not an established standard of care. Three randomized studies show no median survival advantage for adjuvant treatment, and one study demonstrated prolonged disease-free survival, with OS data still maturing. With the recent approval of adjuvant sunitinib by the US Food and Drug Administration (FDA), it is important to assess the attitudes of patients at high-risk of recurrence from disease towards adjuvant therapy in RCC.

Methods:
We conducted a survey-monkey survey distributed electronically to patients with RCC. Twelve questions investigated self-reported patient characteristics, disease state, anxiety and attitude towards adjuvant therapy. Statistical analysis was performed using SPSS statistics 2.

Results:
A total of 450 patients participated. Median age was 55.6 years (17-82 years) and 56.4% of the patients were female. 73.6% of the patients did not have metastatic disease at initial diagnosis. Of patients with an initial M0 diagnosis, 39.1% reported recurrence, and 35.3% were receiving systemic therapy for metastatic RCC. 63.1% of the patients would use adjuvant therapy if it prolonged OS, 60.1% if it prolonged disease free survival, 42.7% if it showed acceptable toxicity, and 36.7% if they were guaranteed both insurance coverage as well as treatment efficacy. Experience with systemic therapy was correlated with a wish for a prolonged OS ($p<0.0001$). 28.0% of the patients were seeking more information prior to their decision. Patients on systemic therapy had a significant higher acceptance of toxicity ($p<0.0001$).

Conclusions:
Patients desire both DFS and OS when deciding on adjuvant therapy, and over 30 percent are willing to accept moderate to significant toxicity in return for clinical benefit. This should be considered in future counseling of patients contemplating adjuvant drug therapy.

Keywords: renal cell carcinoma, kidney cancer, adjuvant therapy, patient's perspective, patient survey, quality of live

Corresponding Author: Michael Staehler, MD PhD, Multidisciplinary Center on Renal Tumors, Department of Urology, University of Munich, Marchioninistr. 15 81377 Munich
michael.staehler@med.uni-muenchen.de

Introduction

The incidence of renal cell carcinoma (RCC) has increased worldwide by more than 30% from 1990–2013.[1] The rise in incidence is mainly due to increased imaging and earlier detection of smaller masses. Despite these advances, death rates in RCC continue to rise in some countries while stabilizing or declining in other countries.[2] The only curative treatment available for stage 1, 2 or 3 disease is surgery, followed by observation. Approximately 30 % patients undergoing curative surgery for non-metastatic RCC will have tumor recurrence within 5 years.[3]

Prior to the introduction of VEGF targeted agents for the treatment of metastatic RCC adjuvant trials with pre-VEGF era agents failed to meet their primary endpoints and until recently, there were no approved therapies available in the adjuvant setting.[4]

The S-TRAC trial comparing sunitinib versus placebo in high-risk patients with clear cell RCC met its primary endpoint of improving disease-free survival (DFS).[5] Together with the ASSURE trial (which did not meet its primary endpoint), and the recently presented PROTECT trial, these results have re-ignited the debate around the utility of adjuvant treatment.[5-7] Results on overall survival (OS) so far are immature in all trials, but so far there has been no clear trend towards an OS advantage for ad-

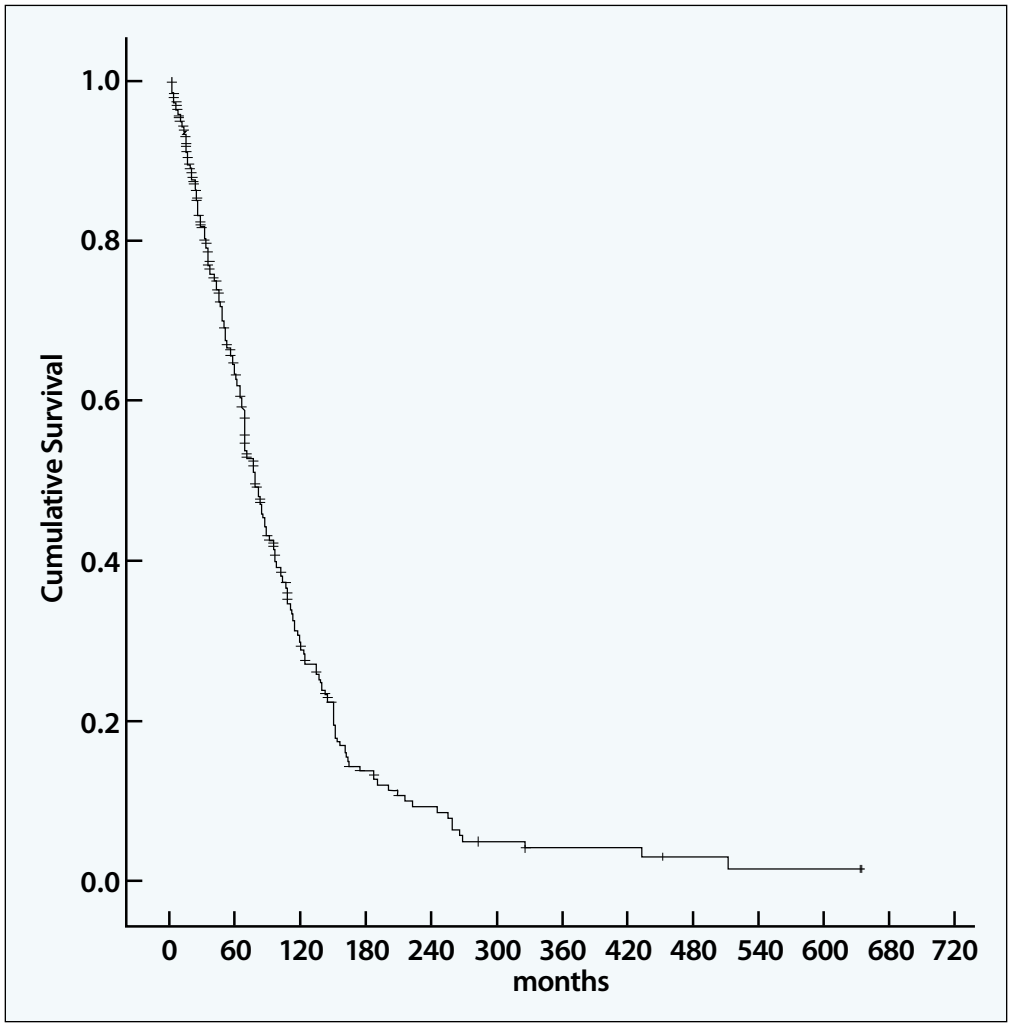

Figure 1. Median time from initial diagnosis to response (Kaplan-Meier) 78.7 months (CI 69.7 – 87.8)

juvant therapy. Given the conflicting data from multiple trials, significant controversy exists as to whether the clinical use of sunitinib in the adjuvant setting is justified. Critics of the S-TRAC data often cite concerns related to the short duration of DFS improvement, lack of OS trends and toxicity associated with treatment as reasons to question clinical use. However, a critically overlooked question is what factors and wishes drive patients when making treatment decisions.

Given the fact that adjuvant sunitinib has been recently approved by the US Food and Drug Administration (FDA), the purpose of our study was to investigate the patients perspective on adjuvant therapy in RCC.

Material and Methods

The patient survey was designed by members of the European Association of Urology (EAU) Renal Cell Carcinoma Guidelines Panel and KCCure, a U.S. based non-profit patient advocacy organization, specializing in research funding for kidney cancer. The survey included a total of 12 questions that addressed patient's concerns and considerations related to adjuvant therapy, as well as questions about their disease, surveillance regimes and overall anxiety related to their diagnosis (**Figure 1**). The questionnaire was hosted on KCCure's website and posted on international patient forums addressing approximately 800 patients between April 1st and June 15th, 2017. Duplicate responses were eliminated before the data were analyzed. The same questions were answered by 19 patient advocates during an advocacy organization meeting in Warsaw, Poland and compared to the KCCure patients. The complete survey can be seen in supplemental material.

Statistical analyses Medians were calculated with a confidence interval (CI) of 95% and an alpha of 0.05 using SPSS statistics 25.0 (IBM Corp., Armonk, New York, USA). We used Kaplan–Meier methods to determine the median duration until response since diagnosis. Significance among the different groups was calculated using Kruskal-Wallis test with a significance level of 0.05.

Results

Out of n=653 potential patients on the webpage n=450 responses were generated for analysis. Responses were collected from the U.S., Canada, South Africa, Great Britain, Australia, France and Germany. Median age was 55.6 years (17-82 years) and 56.4% of the patients were female; 73.6% of the patients had a nephrectomy as primary therapy, while 22.0% had a partial nephrectomy. The majority of the patients had clear cell RCC (76.4%), followed by unclassified RCC (3.9%), papillary type I or type II RCC (3.6%), chromophobe RCC (3.6%), translocation RCC (2.0%), collecting duct carcinoma (0.7%) and renal medullary carcinoma (0.2%), and 9.1% of the patients without knowing their histology.

Median time from initial diagnosis was 78.7 months (CI 69.7 – 87.8) independent of AJCC Stage of the disease. With 29.3% of the patients being Stage I at initial diagnosis, 19.1% Stage II, 22.4% stage III and 25.8% Stage IV., the median time from initial diagnosis was 103,8 mo. (CI 73.9-133.7) for stage I, 108.9 mo. (CI 89.0-128-9) for stage II, 90.0 mo. (CI 75.9-104.1) for stage III and 44.9 mo. (CI 30.7-59.1) for stage IV patients. Time from initial diagnosis was statistically significantly shorter comparing stage I/II and IV ($p<0.0001$); 39.1% of the patients had a recurrence of their RCC, 11.3% within the first year and 6.1% later than 5 years after initial diagnosis. 35.3% were under systemic therapy for metastatic RCC when they took the survey.

The main reason patients would use an adjuvant drug was to achieve prolonged OS in 63.1% of the patients, fol-

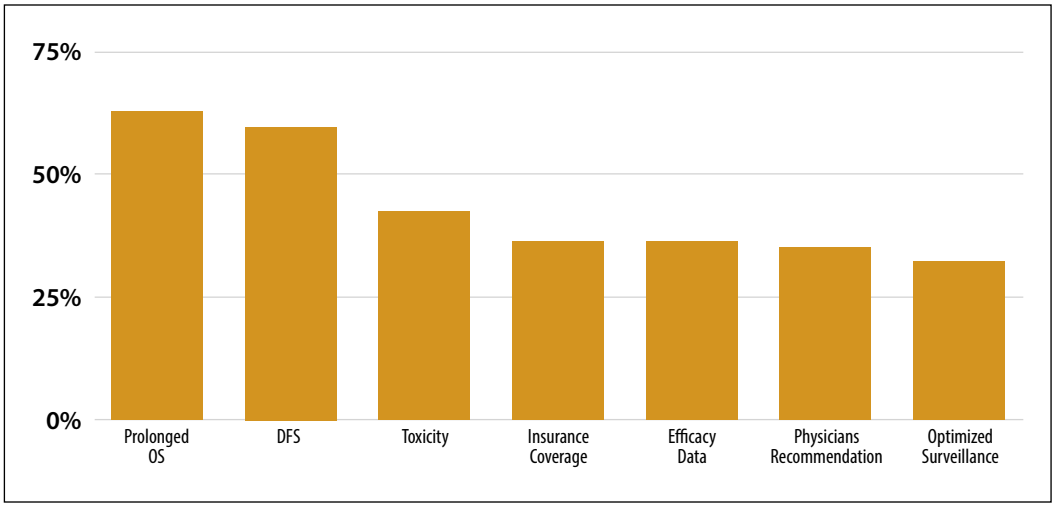

Figure 2. Reasons for patients willing to take an adjuvant drug.

lowed by prolonged disease-free survival in 60.1%, acceptable toxicity in 42.7% and insurance coverage as well as efficacy data, both in 36.7%. Physician's recommendation and a chance for an optimized surveillance were the least significant factors for patients at 35.1% and 32.7% respectively). (**Figure 2**).

Stage, histology, previous surgery, age, and race were distributed equally amongst groups and did not contribute to statistically significant differences in answers. Experience with systemic therapy though was significantly correlated with a wish for a prolonged OS as a reason for taking an adjuvant drug ($p<0.0001$). Previously treated patients also placed a higher emphasis on physician's recommendation versus patients with no history with systemic therapy ($p<0.0001$).

Patients were asked if they would be willing to take a drug for one year following surgery that could help to prevent or delay cancer from recurring. 28.0% of patients wanted more information, 24.2% would only take it with a proven survival benefit, 16.9% would use it if there was moderate toxicity, 13.6% would use it independent of the associated toxicity level, 8.2% would only use it without any toxicity. 3.8% of the patients would not use it at all (see **Figure 3**). There was no difference in the willingness to accept toxicity according to stage ($p=0.11$), but responses of patients being treated or having prior treatment with systemic therapy indicated a significantly higher acceptance of toxicity than patients who had no experience with systemic therapy ($p<0.0001$).

Discussion

This survey reveals that although almost 30% of patients want to have more information, the majority would be willing to take a drug to delay or prevent disease recurrence. Patients who already had or are treated with systemic therapy had a significantly higher acceptance of toxicity than patients who had no experience with systemic treatment. On the other hand, patients who had systemic therapy were more likely to ask for an OS benefit and a physician's recommendation.

Our data reveal that most patients are looking for both DFS and OS from their treatment. This is consistent with other studies showing that cancer patients are willing to undergo significant toxicity in exchange for small incremental benefits.[8] For patients, a scan indicating no evidence of disease might be regarded as equaling OS. Furthermore, in the metastatic setting, patients routinely undergo therapies in the first line setting that don't have proven OS benefits.

Two frontline studies have shown an OS advantage.[9,10] Several other frontline RCC trials have not formally shown an OS advantage, but actuarially, median OS has been improving since these agents became available.[11,12] We now have positive OS data for second-line studies testing cabozantinib, nivolumab and lenvatinib plus everolimus versus everolimus.[9,13,14] There is some evidence that detecting recurrence early may prolong OS and renders some patients curable.[15,16] On the other hand, delaying therapy seems not to be detrimental in patients with limited disease.[17] So far sunitinib is the only agent shown to prolong DFS in the high-risk adjuvant setting and checkpoint antibody therapy may eventually move into the adjuvant setting within the next decade if ongoing studies are positive.[5-7,18]

Disease stage had little impact on how patients responded to the questions. Based on the survey response, patients appeared willing to accept toxicity even if their risk of recurrence was low. This is likely due to the fact that any cancer diagnosis, regardless of stage, invokes significant anxiety among patients and fear of recurrence is high even when the probability may be low. While the UCLA integrated risk classification system was used in the pivotal trials for adjuvant therapy, we still lack a clear and consistent risk stratification system that is used when counseling RCC patients.[3,19,20]

The relatively high rate of grade III and IV toxicities in the adjuvant trials published so far may reflect the high levels of anxiety during the rescanning process itself. [5-7,18] Side effects in the placebo group could be related to fear of eventual cancer recurrence. This lends to a better understanding why patients are willing to accept toxicity for the sake of DFS as shown in our dataset. Anxiety levels measured within our survey were higher in patients under systemic therapy, but in each scenario were above the threshold of 6 according to the NCCN distress score, indicating a need for psycho-oncological support. There were no statistically significant differences in anxiety levels of metastatic patients versus patients without evidence of disease. (data shown elsewhere).

Results from our survey differ significantly from a previous survey amongst patient advocates that Bex et al. recently published by the EAU guidelines panel.[4] According to this study, one third of patients were not willing to take sunitinib as an adjuvant drug, whereas only 3.8 percent of our population were not willing to take adjuvant therapy. The different response rates could be explained by

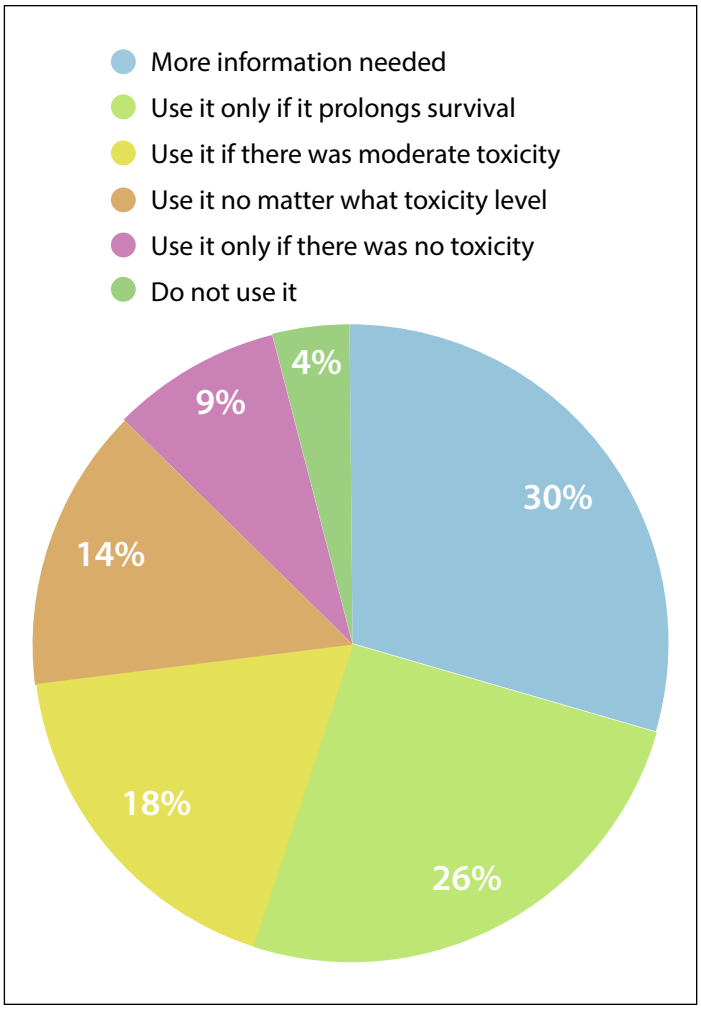

Figure 3. If taking a drug for one year following surgery could help prevent or delay cancer from recurring, would you:

the fact that our question was designed specifically to eliminate bias toward or against therapy decisions. In contrast, the question posed in the previous survey, "After surgery for kidney cancer, if your doctor told that you are at high risk of recurrence (spread), would you consider taking a drug for one year in the hope you could delay the onset of recurrence even if your OS was not improved?" included specific contextualization of the question not included in the current survey. Given the explanatory nature of the question, it can be debated whether the patient's perspective was fully accurately captured with that approach.[21-25] The current questions were designed to estimate what matters to patients, whether the questionnaire recently published by the EAU guidelines panel was investigating the perception of boundaries for acceptance of adjuvant therapy based on estimated results of the S-TRAC trial. Slight differences in questioning patients might lead to different interpretation of the underlying perspective have to be taken into consideration when counseling and analyzing patients needs. S-TRAC was designed with a primary endpoint of PFS, and OS was a secondary endpoint. The FDA approval was given based on the improvement in PFS, with a hazard of 0.76 with an absolute improvement in 5 year DFS of 8%. These data are in line with other approved adjuvant indications, and as no additional analyses are planned, patients should be provided the necessary context to interpret the lack of an OS signal in the S-TRAC study.

Although our dataset was open to the entire patient population and included all histologies and stages it might be biased by the higher rate of females and a lower median age compared to the usual epidemiology of RCC. We suspect that the higher participation rate among these populations was due to an increased willingness to engage in social media and on-line patient support groups; however, highly possible these variances did not significantly impact the overall data. Additionally, our study demonstrates that questionnaires/surveys distributed by a patient advocacy organization on international patient fora can successfully solicit responses from a relatively large cohort of patients and can serve as model for future research on patient preference, understanding and decision making.

Conclusion

Patients opinions seem to differ from physician's expectations. Regardless of stage, patients perceive themselves as being at high risk of recurrence and are willing to undergo adjuvant treatment regardless of toxicity. In addition, patients don't differentiate between DFS and OS.

Given that anxiety across risk groups is high and that the majority of patients are willing to accept toxicity to prevent recurrence, it's critical that if adjuvant treatment is approved, appropriate patient education tools are developed so patients can effectively understand and make informed decisions.

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(Guest Editor's Memo, *continued from inside front cover)*

therapy plus cytoreductive surgery in patients with metastatic RCC (Abstract 4501).
- The randomized phase III study failing to show an improvement in disease-free survival following 52 weeks of pazopanib in patients with mRCC who had no evidence of disease after metastasectomy (Abstract 4502).
- The additional findings that cytoreductive nephrectomy is not superior to sunitinib alone based on either MSKCC or IMDC risk groups (Abstract 4508).
- The IMotion 151 findings showed advantages of atezolizumab + bevacizumab vs sunitinib regardless of PD-L1 status in patients with untreated mRCC (Abstract 4512).
- Patient-reported outcomes in IMotion 150 suggested that atezolizumab alone or with bevacizumab maintained daily function with minimal symptom interference vs sunitinib as first-line in mRCC (Abstract 4515).

As Rana McKay, MD, highlighted in her presentation, we have three combination therapy regimens approved in the first-line setting:
- Nivolumab + ipilimumab (CheckMate 214)
- Pembrolizumab + axitinib (KEYNOTE-426)
- Avelumab + axitinib (JAVELIN Renal 101)

Although ASCO 2019 does not change this paradigm, Dr McKay's slide on the evolution of therapy (See **Figure**) encapsulates how far we have come in 15 years. What will be the next step in this evolutionary sequence as symbolized by our silhouettes? One of the presentations at ASCO highlighted a Phase III study comparing bempegaldesleukin (NKTR-214) plus nivolumab to sunitinib or cabozantinib in treatment naïve mRCC patients. The investigational agent provides rapid activation and proliferation of CD8+ effector T cells and natural killer cells without overactivating the immune system.

How intriguing—and ironic— that this new agent echoes certain aspects of the first drug ever approved for RCC—high-dose IL-2 (aldesleukin, Proleukin) a drug that predates the timeline shown above, going back to the 1990s. The new drug, however, apparently is not associated with the severity of side effects of IL-2. Bempegaldesleukin has an antibody-like dosing regimen similar to the existing checkpoint inhibitor class of approved medicines. Could it be that to some degree we are circling back to some of the precepts that guided our initial selection of therapies when high-dose IL-2 was the only option? We can look forward to how future ASCO Scientific Sessions grapple with this and other provocative issues.

Sumanta (Monty) Pal, MD
Guest Editor
Associate Clinical Professor
Medical Oncology
City of Hope Cancer Center
Duarte, California

Optimizing Prognostication in mRCC: Recent Advances and New Directions, From the Bench to the Bedside

Marie-France Savard, MD, FRCPC
Tom Baker Cancer Centre,
Department of Oncology,
Cumming School of Medicine,
University of Calgary
Calgary, Alberta, Canada

Daniel Y.C. Heng, MD, MPH, FRCPC
Tom Baker Cancer Centre,
Department of Oncology,
Cumming School of Medicine,
University of Calgary
Calgary, Alberta, Canada

Abstract

Histopathologic, clinical and laboratory factors have long been the hallmarks of prognostic classification schemes in metastatic renal cell carcinoma (mRCC). This review offers an outline of state-of-the-art thinking with regard to these traditional variables and provides insights on current and future directions to envision how prognostic models will evolve in the burgeoning field of immune-oncology therapies. Molecular and genomic biomarkers are essentially leading the way, potentially reshaping trial design, and ultimately, risk stratification in clinical practice.

Introduction

Over the last decade, targeted and immune checkpoint blockade-based treatments have ushered in a new era in the management of metastatic renal cell carcinoma (mRCC). The mRCC treatment approach is currently in a state of flux, reflecting the rapid pace with which innovative therapies and strategies, including targeted therapies (TTx) and immune checkpoint inhibitors (ICP) used in combination or sequential approaches, are being studied. These novel treatment options are setting new benchmarks for progression-free survival (PFS) and overall survival (OS).[1,2,3]

Precision medicine is based on the use of individual prognostic and predictive factors to inform treatment decisions. On the one hand, prognostic tools help the clinician to predict the course of the disease and the clinical outcome with the standard therapy. On the other hand, predictive factors are associated with the likelihood of response to a specific therapy and allow the identification of patients who may, or may not, benefit from a particular treatment.[4] With regards to clinical and experimental oncologic practices, the identification of prognostic factors is critical to support patient counseling, guide therapy selection, design rational clinical trials and interpret clinical trial results.

The prognostic models currently used in clinical practice are mainly the *Memorial Sloan Kettering Cancer Center* (MSKCC) and the *International Metastatic RCC Database Consortium* (IMDC) models.[5,6] They took root from the cytokines and TTx periods, respectively. Both rely on a number of histopathologic, clinical and biochemical parameters. New DNA sequencing and proteomic technologies have fueled the identification of an exciting range of molecular and genomic factors that could potentially be used to determine prognosis and to predict response to treatment.

As cutting-edge therapies and strategies are rapidly being integrated in the mRCC treatment algorithm, it is time to take a fresh look at prognostication. New prognostic factors are emerging, and while the traditional system such as the IMDC prognostic model is still considered optimal in clinical practice, it is pending reevaluation with new standards of care. This review chronicles the evolution of state-of-the-art prognostication in mRCC. Our review also highlights some gaps and limitations associated with the use of traditional models and addresses crucial questions underlying the research being done.

Prognostic Models in First-Line Therapy

A number of prognostic models have been proposed, and they all share various histopathologic, clinical and biochemical criteria. These models included the Cleveland Clinic Foundation (CCF) model[7], the French model[8], the International Kidney Cancer Working Group (IKCWG) model[9], the Memorial Sloan-Kettering Cancer Center (MSKCC) model[5], and the International Metastatic RCC Database Consortium (IMDC) prognostic model.[6] (**Table 1**).

In the first-line setting, the two most widely used prognostic models are the MSKCC and IMDC models. Both are practical and used dichotomized variables to stratify risk in three groups: favorable, intermediate and poor. The MSKCC model was derived from patients treated in

Keywords: metastatic renal cell carcinoma, prognostication, prognostic model, prognostic factor, predictive factor, molecular biomarker, genomic biomarker, International Metastatic RCC Database Consortium (IMDC), Memorial Sloan Kettering Cancer Center (MSKCC), precision medicine

Corresponding Author: Daniel Y.C. Heng MD, MPH, FRCPC, Tom Baker Cancer Centre,1331 - 29th St NW, Calgary, Alberta T2N 4N2
Tel: (403) 521-3166 Fax: (403) 283-1651
E-mail: daniel.heng@albertahealthservices.ca

Table 1. Comparison of 5 Prognostic Models used in the mRCC First-Line Setting.

	Cleveland Clinic Foundation (CCF) model 2007 (7)	French model (8)	International Kidney Cancer Working Group (IKCWG) model (9) model (5)	Memorial Sloan-Kettering Cancer Center (MSKCC)	International Metastatic RCC Database Consortium (IMDC) model (6)
Time from diagnosis to treatment	X[$]		X[#]	X[#]	X[#]
Time from diagnosis to metastasis		X			
Previous immunotherapy			X		
Low performance status (ECOG or KPS)	X	X	X	X	X
Number of metastatic sites		X	X[&]		
Liver metastasis		X			
Biological signs of inflammation		X			
Anemia		X	X	X	X
Thrombocytosis	X				X
Neutrophilia	X		X		X
Hypercalcemia	X		X	X[$$]	X[$]
Elevated lactate dehydrogenase			X	X	
Elevated alkaline phosphatase			X		

[$]Time from diagnosis to current treatment <2 years; [#]Time from diagnosis to treatment <1 year; [&] more than one metastatic sites;
[$]calcium value corrected for albumin; [$$] >10 mg/dL
Adapted from (11) with permission from Elsevier and Copyright Clearance Centre

clinical trials of interferon alpha alone or as part of a combination in first-line. This model is composed of five clinical and biochemical variables that are associated with overall survival: Karnofsky performance status (KPS) of less than 80%, lactate dehydrogenase more than 1.5 times the upper limit of normal (ULN), low serum hemoglobin, high corrected serum calcium (>10 mg/dL), and less than one year from initial RCC diagnosis to start of interferon-therapy. It was first validated internally with a bootstrap resampling procedure.[5] Thereafter, an independent set of patients treated with immunotherapy alone (mainly interleukin-2- or interferon alfa–based regimens) or chemotherapy with or without immunotherapy, was used to perform the external validation. This study revealed that 4 out of 5 factors were independent prognostic factors of survival; performance status was deemed not a statistically significant factor. Furthermore, in this external validation study, prior radiotherapy and greater than one site of metastases were associated with a negative prognostic value.[10]

The IMDC prognostic model was developed using a more contemporary cohort of patients treated with anti-VEGF targeted therapies (specifically sunitinib, sorafenib, and bevacizumab plus interferon) as a first-line or after cytokine therapy. This model is composed of six variables that have been identified as independent predictors of poor survival on a multivariate analysis: KPS of less than 80%, less than 1 year from diagnosis to treatment, hemoglobin concentration less than the lower limit of normal (LLN), corrected calcium concentration more than ULN, neutrophil count more than ULN, and platelet count more than the ULN.[6]

Compelling evidence of the IMDC model's external validity came from a large international multi-center cohort of 1,028 patients treated in a real-world or clinical trial setting with their first anti-VEFG treatment including sunitinib, sorafenib, bevacizumab, axitinib, or pazopanib. The median OS of the three prognostic groups was 43 months, 23 months, and 8 months in the favorable, intermediate, and poor risk groups, respectively. One of the strengths of this analysis is that the IMDC database includes unselected patients, making the results more generalizable and applicable to the general population. In addition to being the largest prognostic model external validation, this study also offers a head-to-head comparison of the different mRCC prognostic models. The study demonstrated that the IMDC model has the best global fit and a stronger association with OS outcome than the CCF, French, IKCWG and MSKCC models. The IMDC's discriminative power appears slightly inferior to IKCWG model. However, the latter includes more clinical factors and requires mathematical transformations, which make

Table 2. Comparison of 3 Prognostics Models used in the mRCC Second-Line Setting.

	Three-Factor Memorial Sloan-Kettering Cancer Center (MSKCC) model (14)	International Metastatic RCC Database Consortium (IMDC) model (15)	Gustave Roussy Cancer Campus (GRCC) model (16)
Time from diagnosis to current treatment (< 1 year)		X	
Time from the first- to second-line treatment (< 1 year)			X
Tumor burden			X
Low Karnofsky performance status (<80%)	X	X	X
Anemia (<LLN)	X	X	X
Thrombocytosis (>ULN)		X	X
Neutrophilia (>ULN)		X	X
Hypercalcemia	X*	X$	X$

#Time from diagnosis to treatment <1 year; * >10 mg/dL; $ > ULN calcium value corrected for albumin; & ≥ 100 mm, sum of the long-axis diameter (SLD) of target lesions
LLN: lower limit normal; ULN : upper limit normal

it less practical.[11]

One of the shortcomings identified in the IMDC model is that the majority of patients are classified as intermediate risk, and few patients as favorable or poor risk. The performance of this model could potentially be improved by integrating novel genomic and molecular biomarkers and the use the individual risk factors summation, rather than dividing patients into 3 risk groups.

A good prognostic model predicts the outcomes of patients independently of the therapy used and, thus, it must be validated with the current standard of care. Since ICP combination therapies are becoming a new standard of care, the IMDC criteria may require updating. Interestingly, in two phase III clinical trials presented at 2019 ASCO GU, Javelin Renal 101 and Keynote-426, comparing avelumab plus axitinib versus sunitinib and pembrolizumab plus axitinib versus sunitinib, respectively, the outcomes of the three IMDC prognostic risk groups appear to be very well segregated.[2,3]

Prognostic Model in Subsequent lines of Treatment

From the retrospective analysis of the IMDC real-world dataset, only 51.4% of patients who received first-line treatment will receive second-line treatment, only 24.2% of these will receive third-line therapy and only 7.9% of these will receive fourth-line therapy.[12] The development of good prognostic tools in subsequent lines of therapy is therefore crucial because it may help clinicians to identify the subset of patients that might benefit from further lines of treatment and choose the optimal timing of therapy switch. Furthermore, the biology of the tumor might evolve between subsequent lines of therapy which will influence the prognostic. For instance, from the IMDC data, up to 40% of patients will move from one IMDC risk group to another after the first-line therapy.[13] One might think that new prognostic factors might emerge after treatment and help to better define the survival benefit of second-line treatment.

In the second-line setting, three main prognostic models have been proposed so far: the three-factor MSKCC model, the IMDC model and recently, the Gustave Roussy Cancer Campus (GRCC) model.[14,15,16] The three-factor MSKCC model was developed based on patients treated in MSKCC Institutional Review Board-approved clinical trials conducted between 1975 and 2002.[14] All patients included had received first-line systemic therapy. As second-line therapy, patients received either cytokines (50%) or chemotherapy; none of these trials involved one of the standard TTx. A KPS less than 80, a low serum hemoglobin and high corrected calcium was demonstrated to be independently associated with poor outcomes. The TTx era began shortly after the publication of this model.

The IMDC model is often used as prognostic tool in the second-line setting. The large international multi-center validation study by Ko et al. used a cohort of patients treated with second-line TTx, either an anti-VEGF drug or an mTOR inhibitor, and demonstrated that five of the six IMDC prognostic variables are independently associated with poor OS in this setting and these are: anemia, thrombocytosis, neutrophilia, KPS less than 80, and less than 1 year from diagnosis to first-line TTx.[15] Furthermore, in this study, the prognostic performance of the IMDC model was demonstrated to be superior to the three-factor MSKCC based on the concordance index, likelihood ratio test and reclassification calibration test.

Recently, the NIVOREN GETUG-AFU 26 data suggested that the prognostic capability of the IMDC model holds true in patients treated with second-line nivolumab.[16] The IMDC criteria clearly divide these patients into three risk groups. Additionally, when stratified for number of IMDC criteria, there were marked differences in prognosis between those with 0, 1, 2, 3, 4, 5 and 6 criteria where patients with more criteria have an incrementally worse prognosis.

Earlier this year, Derosa et al. proposed a new prognostic classification scheme in the second line setting, named the GRCC model.[17] In this study, eight prognostic factors were associated with poor outcomes in a cohort of patients who received second-line TTx, ie VEGEF and mTOR inhibitors. Both IMDC and MSKCC are nested in

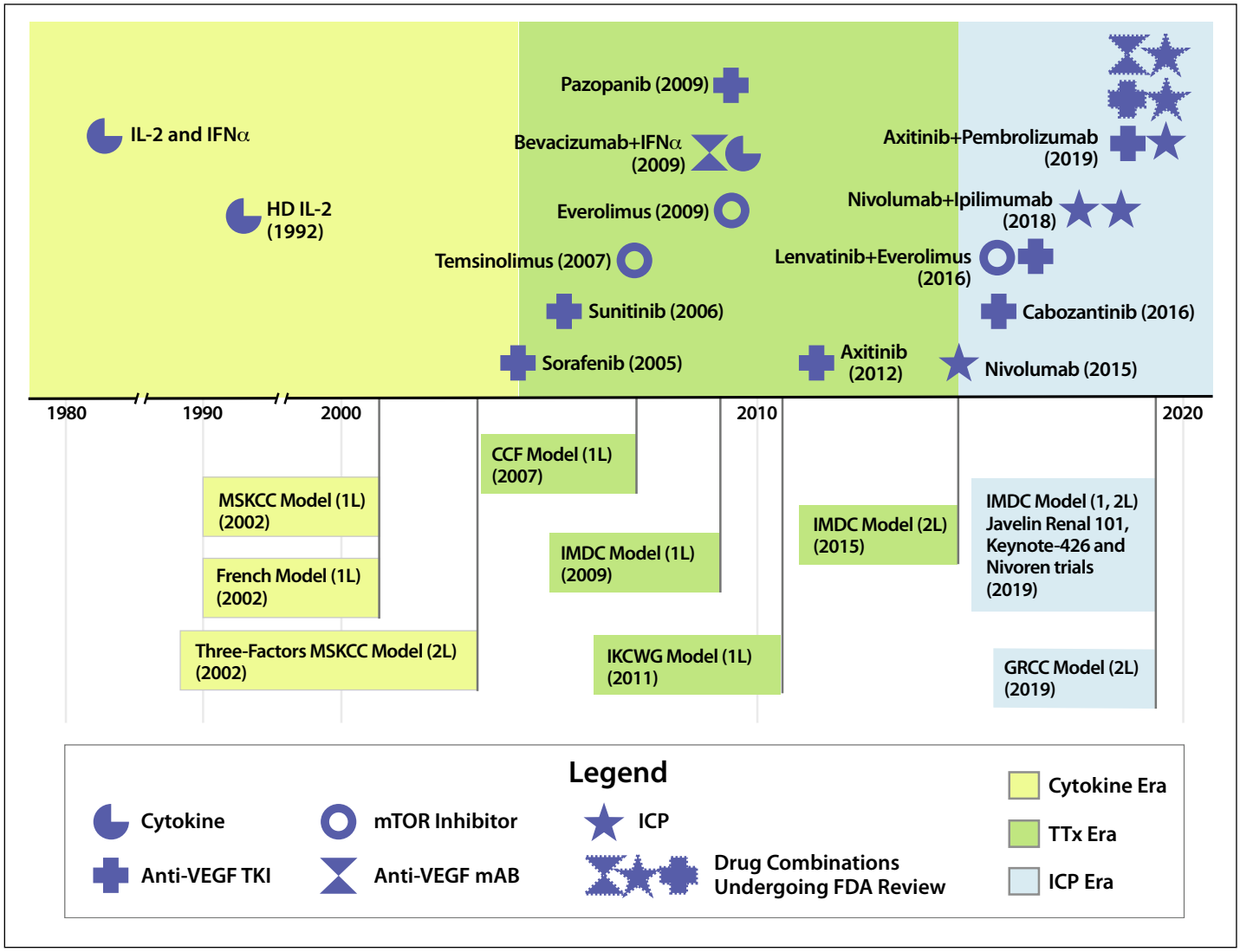

Figure 1. Timeline of Drugs and Prognostic Models Used for mRCC between 1980 and 2019. In parenthesis is the United States Food and Drug Administration (FDA) date of approval. The era in which the models were validated are represented by the yellow, green and blue colors.

IL-2: Interleukine-2; HD-IL2: High-Dose Interleukine-2; IFNα: Interferon-Alpha; MSKCC: Memorial Sloan-Kettering Cancer Center (MSKCC); CCF: Cleveland Clinic Foundation; IMDC: International Metastatic RCC Database Consortium; GRCC: Gustave Roussy Cancer Campus (GRCC); Anti-VEGF TKI: anti-vascular endothelial growth factor tyrosine kinase inhibitor; mTOR: mammalian target of rapamycin; Anti-VEGF mAb: anti-vascular endothelial growth factor monoclonal antibody; ICP: immune checkpoint inhibitor; TTx: targeted therapy.

the GRCC model. The two additional prognostic factors that were found to improve the predictive ability of the model are: tumor burden and time to first to second-line treatment. As opposed to IMDC and MSKCC models, 4 risk groups are defined in the GRCC model: good risk (0 risk factor), intermediate risk (1 to 2 risk factors), low poor risk (3 to 4 risks factors), and high poor risk (more than 5 risk factors). The median OS of these groups are: 49.5 (26.3-NE), 26.6 (23.1 to 33.1), 12.5 (10.0 to 16.6) and 4.3 (3.9 to 7.2) months respectively.

External validation of the GRCC model and its comparison with the IMDC and three-factor MSKCC models was done using a cohort of patients from the INTROSECT and AXIS trials.[17] Overall, the GRCC model has the best performance in the discovery and validation dataset compared to the IMDC and MSKCC models. Using the likelihood ratio, GRCC is found to improve the fit of data in comparison to the MSKCC model and the IMDC model in the discovery cohort. Comparing the association of the prognostic model risk groups and the outcomes with R2 statistics, GRCC strata appears to be more strongly associated with outcomes than the IMDC and MSKCC model risk groups, in the discovery and validation cohorts. However, in the validation cohort, concordance statistics suggests that GRCC might have similar discriminant ability to the IMDC model. Using patients solely from the INTORSECT and AXIS trials, that had received either bevacizumab or sunitinib as first-line therapy, to validate the GRCC model might raise concerns regarding the generalizability of the GRCC model to the real world population.[1,2,3]

A paucity of prognostic models exists in the subsequent lines of treatment. Despite being developed in the first-line setting, evidence also supports the prognostic ability of the IMDC model in third- and fourth-line treatment.[12,18] The use of the IMDC model might have im-

portant clinical implications by helping to select patients that will benefit from a more proactive management.

A vast number of histopathologic, clinical and biochemical parameters have been identified to be prognostic. These include: bone metastasis, liver metastasis, elevated neutrophil-to-lymphocyte ratio, elevated C-reactive protein, nonclear cell RCC histology, papillary RCC histology, high body mass index, brain metastasis and renal dysfunction.[19] However, at this point, none of them have been shown to improve the prognostic performance of the traditional models and the best way to incorporate them in clinical practice remains to be determined.

Predictive Capability of IMDC Prognostic Model: CheckMate 214

As the experience with targeted therapies and IO therapy unfolds, the IMDC model proves to have, not only a prognostic ability, but also a predictive capability. The predictive capability was demonstrated in the CheckMate 214 trial, a phase 3 study evaluating the combination of nivolumab and ipilimumab versus standard VEGF-targeted therapy with sunitinib alone in treatment-naïve mRCC.[1] This pivotal report stratified patients by IMDC prognostic group. The highlights of this trial are that in the IMDC intermediate- and poor-risk groups, combination IO therapy was associated with superior OS as compared with sunitinib (HR, 0.66, $P<0.0001$). PFS was also improved in these patients (HR, 0.82, $P=0.03$), but the result was not statistically significant per the pre-specified threshold ($P=0.009$). On the contrary, in the IMDC favorable risk group, superior outcomes were observed with sunitinib alone in terms of objective response rate (29% vs 52%, $P<0.001$), PFS (HR1.23, P=1.888) and OS (HR 1.22, $P=0.4426$).[20]

These provocative results raise at least two intriguing issues. First, the fact that the intermediate/poor risk groups patients and the favorable group patients derived different benefits from the nivolumab/ipilimumab combination and sunitinib might suggest that their tumor biology is different. A plausible hypothesis is that the favorable risk group tumor has a greater addiction to the VEGF pathway. In other tumor sites such as EGFR-mutated non-small cell lung cancer, ICP was also demonstrated to be less effective than TTx.[21] This leads us to believe that in tumors with a strong angiogenic dependency, using ICP alone is less effective and insufficient to halt tumor growth. Another possible explanation might be related to the immunogenicity of the tumor and its microenvironment. This important question requires to be further elucidated. Recently, the results of Javelin Renal 101 and Keynote-426, two pivotal phase III trials that combine ICP/VEGF-targeted therapy, demonstrated that the combination of ICP and TTx also benefits the favorable-risk group RCC suggesting that the addition of targeted therapy to ICP can prime immune response.[2,3] Furthermore, the other issue raised by CHECKMATE-214, although not specific to RCC, is that PFS and OS are not strongly correlated in trials using ICP alone.[1] The surrogacy of PFS for OS is therefore weak with this class of treatment. The reason for this remains unclear and might imply that the antitumor effect of ICP likely lasts well beyond its administration duration, extending to subsequent therapies, and acting in synergy. In the particular context of immunotherapy, possible new prognostic and predictive factors might emerge over the next year to improve the traditional model.

Integrating Molecular and Genomic Factors in Prognostication

Advances in sequencing technologies have opened up new avenues of investigation, a development that is providing exciting insights into the molecular landscape of mRCC. Equally exciting is the potential of integrating genomic or molecular markers to the IMDC model and other prognostic tools to guide better treatment strategies.

Large scale sequencing analysis has revealed that the most frequent genomic abnormalities found in predominantly early RCC patients are: the inactivation of the VHL tumor suppressor gene, alterations of the 3p chromatin modulators/modifiers (eg, PBRM1, SETD2, BAP1, KDM5C, KMD6A), alterations of the p53 signaling and alterations of the PI3K/AKT/mTOR pathway, recurrent arm level or focal losses on chromosomes 1p, 3p, 4q, 6q, 8p, 9p, and 14q, and gains on chromosomes 1q, 2q, 5q, 7q, 8q, 12p, and 20q.[22,23]

Voss et al. explored the correlation between frequent mutations found in early RCC and OS in patients with mRCC.[24] Using a multivariate Cox regression analysis, BAP1, TP53 and PBRM1 mutations were demonstrated to be independently associated with OS in patients enrolled in the phase III COMPARZ (training set). Mutation status was added to the MSKCC model in an effort to enhance its performance. The analysis showed that the MSKCC model's c-index was improved by the addition of the genomic information in the training set (from 0.595 to 0.628) as well as the validation set (from 0.622 to 0.641), composed of patients from the phase II RECORD3 trial. The clinical relevance of this difference is unclear and more studies are required to establish the predictive utility of adding genomic information.

Similarly, in a smaller dataset, Bosse et al. performed a study using genomic data to refine the IMDC model.[25] The association between OS and alterations in PBRM1, BAP1, SETD2, KDM5C and TP53 was evaluated. Only BAP1 or BAP1 and TP53 combined correlated with worse OS, in multivariate models. Stratifying by IMDC risk groups, only patients in the IMDC poor risk group have a statistically significant worse survival while carrying mutations in BAP1 or BAP1 and TP53 combined.

Overall, this evidence supports the idea that genomic information, originally discovered in early RCC, might have a prognostic significance for mRCC patients and that its integration in traditional prognostic models might be suitable. However, external validation in larger datasets is still warranted. Furthermore, in these two abstracts, another important caveat to consider is that it is unclear if the mutational status was assessed on the primary tumor or metastasis. Taking into account intratumoral heterogeneity and tumor evolution, one might consider the analysis of metastasis tissue more suitable in this setting.

Gene-expression signatures for prognosis may add complementary prognostic information in the metastatic setting. In this line of thinking, De Velasco et al. tested

the prognostic power of two different signatures originally validated in localized RCC, the ClearCode34 (a 34-gene signature model) and an 8-gene signature model, in a cohort of 54 mRCC patients treated with TTx in 5 institutions as part of The Cancer Genome Atlas (TCGA).[26] Only the joint model with ClearCode34 reached statistical significance in improving the IMDC prognostic model accuracy, using C-Index analysis and F-test. The results require further validation in a larger dataset before they can be integrated in guiding clinical decision. Like many of these genomic signature reports, there are few limitations related to the generalizability of data (as the results may be irreproducible with a cohort of different composition or size), heterogeneity of the cancer and sampling artifact. Moreover, from a financial perspective, the incremental increase in c-index from genomic information will need to be evaluated in light of the cost of these tests.

Further clarification of the role of tumor molecular characteristics appeared in the report of Beuselinck et al.[27,28] In this first integrative genomic study of m-ccRCC, Beuselinck et al. identified four molecular subtypes of mccRCC (ccrcc1 to 4) based on unsupervised transcriptome analysis. The ccrc1 and 4 are associated with poorer PFS and OS compared to ccrc2 and 3. Furthermore, the molecular subtypes were correlated to IMDC groups as well as sunitinib response. The good risk IMDC group is enriched by ccrc2 molecular subtype and presents a high expression of genes involved in angiogenesis such as HIF2A, VEGFR1, -2 and -3. Furthermore, the expression of immune-related genes was similar across IMDC subgroups. These findings support the proposed hypothesis that the good-risk IMDC group benefits more from sunitinib compared to intermediate- and poor- risk IMDC group in CheckMate214 because of dependency to the VEGF pathway observed.

The complex interplay between the immune system and cancer development, progression and treatment response is an expanding area of research. With the emergence of ICP, immune-based biomarkers, such as PD-L1 expression, are being studied extensively. In the exploratory analysis of CHECKMATE-214, OS of the intermediate- and poor-risk patients according to PD-L1 expression status was described using the Kaplan-Meier estimate.[1] Although not powered to draw statistically significant conclusions, these results are hypothesis generating. In the intermediate- and poor-risk subgroups treated with sunitinib, the survival rate with PD-L1 expression of 1% or more was lower than for those with PD-L1 expression of less than 1%. Also, intermediate- and poor-risk patients treated with ipilimumab plus nivolumab had an improved survival compared to the patients treated with sunitinib regardless of the PD-L1 expression status. This suggests that PD-L1 expression of 1% or more can on the one hand be a negative-prognostic factor and on the other a positive-predictive factor to ICP. In support of this, the negative-prognostic value of PD-1/PD-L1 expression was also demonstrated in some other reports.[18,29] However, the validation of PD-L1 expression as a biomarker has several limitations related to PD-L1 dynamic expression through the course of the cancer, assay variability, and lack of standardization of sample collection and cell analysis.[30] Currently, PD-L1 testing does not have sufficient negative predictive value to exclude patients from CPI as there are PDL1 negative patients that still benefit from CPI.

Conclusion

Innovative clinical trials of targeted- and immune-based therapies have reshaped the mRCC treatment landscape. Emerging information on these new management approaches has focused greater attention on the importance of updating traditional prognostic models to more accurately determine patient risk stratification and outcomes. To date, the IMDC prognostic model is the most consistently validated system to assess risk groups and, thus, the preferred prognostic model used in clinical practice and trial design. The integration of specific molecular and genomic alterations in the prognostication scheme is an essential part of future directions in this area.

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*(*Interview, *continued from page 34)*

changes to the format or focus of the International Symposium. These symposia allow us to have a 'meeting of the minds' between clinicians, pharma, scientists, and researchers. By collaborating on the highest level, we are able to share valuable findings and create a great sense of hope for the future. Through teamwork with clinical trials, new drugs, and new research, these symposia are essential in distributing information and determining future endeavors.

Q: Do you have any plans to revamp the KCA website, perhaps to create a more interactive focus for physicians? Blogs, etc?

Ms Vaughan: Updating the website to be more user-friendly is a large part of the conversation as we develop our multi-year strategic plan. For physicians and researchers, we want to serve as a resource hub to support them in their efforts to bring an end to death and suffering from renal cancers. For patients, we want to provide easy navigation to the resources available, including the helpline staffed by a dedicated team of nurses, detailed information on understanding and locating clinical trials, and access to the Inspire support platform. Our primary goal is to provide patients, their families, and their caretakers with the information and resources they need in the most efficient and effective way possible. Generally speaking, we expect to refresh the website with new opportunities, content, and information as identified in the strategic planning process. KCJ

Brain Metastases in RCC: New Trials Reveal How Discovery of Underlying Mechanisms, Novel Treatment Approaches Could Improve a Dismal Prognosis

Jun Gong, MD
Medical Oncologist
Assistant Professor
Samuel Oschin Comprehensive
Cancer Institute at
Cedars-Sinai Medical Center
Los Angeles, California

Until recently, the exclusion of patients with brain metastases from clinical trials on treatment of advanced renal cell carcinoma hindered efforts to adequately evaluate management approaches in this high-risk population. The picture is changing, and with the publication of new information from trials including these patients, an improved understanding of how such resistant tumors may be treated is emerging.

Although renal cell carcinoma (RCC) metastasizes less often to the brain than to other sites, the poor prognosis associated with a diagnosis of brain metastases in kidney cancer has focused greater attention on the need to clarify not only the epidemiology of this phenomenon but to more clearly delineate underlying mechanisms and potential therapies that could improve survival. Generally, brain metastases are usually small and asymptomatic when discovered on screening such as routine staging or institution of systemic therapy. However, brain metastases may present symptomatically and can be quite large.[1]

An estimated 64,000 new cases of kidney cancer were diagnosed in the US in 2017, with approximately 14,400 deaths.[2] A clear cell histology predominates in 70% to 80% of RCCs while subtypes other than clear cell include papillary (10-15%) and chromophobe (5%). Although RCC is typically localized at presentation (65% of cases), in 35% of the cases, synchronous regional or distant metastases are identified. Metachronus metastasis will develop in approximately one-third of patients in whom RCC is initially local. Studies within the last five years have further clarified the epidemiology, pointing to lungs, lymph nodes, liver, bone and brain as the most likely sites.[3]

Keywords: brain metastases, renal cell carcinoma, epidemiology, mechanisms, tyrosine kinase inhibitors, cabozantinib, c-MET, PD-L1, NIVOREN trial, checkpoint inhibitors.

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

Epidemiology of Brain Metastases in RCC

A review of the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) found that among 2027 patients with mRCC, the incidence of metastasis to the brain was 8%, compared with 69% to the lungs, 43% to the lymph nodes, 34% to the bones, and 19% to the liver.[3] Other studies have also reviewed the epidemiology with similar results. For example, a population-based analysis from Italy (n=11,157) and a global expanded-access study (n=4543) showed that the incidence of brain metastases ranged from 7% to 8%. They also confirmed that specific sites of metastatic disease were also more associated with brain metastasis: the rate of brain metastases was 2% in patients with abdominal metastases only vs 16% in patients with thoracic and bone metastases.[3]

Further insights on epidemiology appeared in a report by Sun et al[4] who also provided perspectives on clinical, patient, and sociodemographic characteristics of patients presenting with primary RCC and brain metastases (BM) at diagnosis. These authors used a nationally representative cancer cohort originating from the US. While the global incidence of BM at cancer diagnosis was 9.6%, in descending order, its incidence varied according to primary site: lung (20%), melanoma (6.9%), renal (6.5%), breast (5.1%), and colon cancers (1.8%). Possibly with the increased use of improved neuroimaging staging and greater use of magnetic resonance imaging, the incidence of BM is hypothesized to have increased in the last two decades. There is a bit of a conundrum behind the supposed increase in BM in kidney cancer patients. Sun et al suggest that the increase is disconcerting, considering that traditionally, such individuals have been excluded from clinical trials

One of the intriguing aspects of the epidemiology papers such as the report by Sun et al is the extent to which they also explore the implications of emerging data for prognosis in RCC patients with BM. Until recently, the prognostic implications of this subset have not been well delineated. Sun et al[4] categorized patients based on clinical risk factors they evaluated, including white/other race,

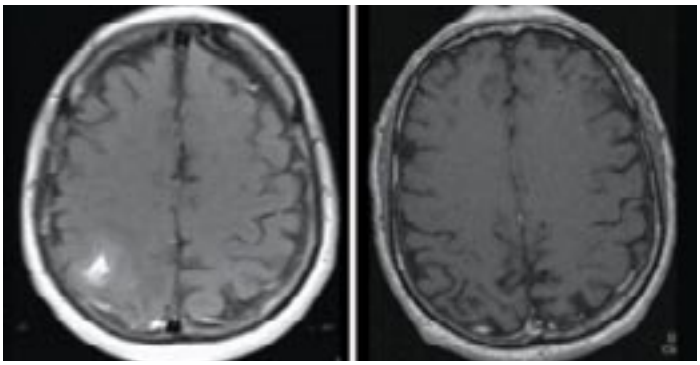

Figure 1. MRI brain. Panel A. An axial, post contrast-enhanced, fat-saturated T1-weighted image of the brain shows a 2.0 x 1.0 cm right parietal mass with ill-defined area of enhancement. Panel B. An axial, contrast enhanced, fat-saturated T1-weighted image of the brain, 3 weeks after therapy with cabozantinib, shows resolution of the prior mass and surrounding enhancement.

clear cell histology, sarcomatoid differentiation, T2-4 disease, tumor dimension >10 cm, and N+ disease. These risk factors were significantly associated with BM at RCC diagnosis. This report found that patients with BM were more likely to succumb to any death than those without BM at diagnosis (median overall survival: 6.4 months vs not reached) based on the Surveillance, Epidemiology, and End Results (SEER) database. Although their model needs further testing, the authors suggest that the real incidence of BM at RCC diagnosis is likely underestimated given that the observed rate likely reflects patients who presented with symptoms.

Our review seeks to address this issue by focusing on clinical trials where RCC patients with BM were not excluded. We also address key areas related to treatment of BM in RCC, including the mechanisms of why some agents presumably would be effective in this setting, the activity of agents studied so far (tyrosine kinase inhibitors and immunotherapies) and issues related to penetrance of the CNS, and novel targets.

Mechanisms Determining Response to therapy

The underestimation of the incidence of BM and the poor prognostic implications of BM in RCC render it imperative to further evaluate what treatments could make a difference and how an awareness of the various mechanisms of these agents can help to inform management strategies. Evidence has focused on a broad spectrum of agents, beginning with the VEGFR tyrosine kinase inhibitors. The TKIs that are FDA-approved for the treatment of mRCC include sunitinib, pazopanib, sorafenib, axitinib, cabozantinib and lenvatinib. Despite their efficacy as standard therapies for patients with metastatic clear cell RCC and extracranial disease, the CNS response rates in RCC with BM have been modest, suggesting that the antiangiogenic mechanism of action of TKIs does not produce the anticipated significant efficacy. Overall, the evidence that TKIs may have activity in the brain is disappointing. There was early evidence of a promising effect. For example, retrospective analysis of a phase 3 trial randomizing patients between sorafenib and placebo found lower crude rates of BM in the group receiving the drug.[5] Similarly, another report found sunitinib and sorafenib to be protective with regard to BM development.[6]

More recent studies, however, tend to conclude otherwise, indicating that the impact of these agents on outcomes in patients with existing BM is limited. A retrospective review by Verma et al[7] suggests that these agents may provide a survival benefit in patients with BM, notably in those who are TKI naïve. Yet the definitive benefit of these agents in this population was unclear as they did not observe any statistically significant improvement either in rate of local control or distant brain metastasis-free survival. Rather, these TKIs are likely to have only a marginal benefit in the management of BM from RCC as any survival benefit is likely due to improved control of systemic disease rather than a direct impact on the brain.

Although the experience with sunitinib and sorafenib in this setting is disappointing, more favorable results with another TKI suggests how its mechanism of action could be associated with significantly improved outcomes. A growing list of studies evaluating the use of cabozantinib delineate why this VEGF TKI may offer a better option to other agents in its class, largely due to a mechanism that differentiates this TKI from sunitinib and sorafenib. One of the problems in evaluating the efficacy of targeted therapies in RCC patients with BM is that this group has historically been excluded from most prospective clinical trials. Consider, for example, the METEOR and CABOSUN trials that allowed treatment of mRCC patients having BM with cabozantinib; however this subset was underrepresented (<1%) in METEOR and not reported in CABOSUN.[8,9] Our case report[10] nevertheless pursued the hypothesis advocating the use of cabozantinib in mRCC patients with BM because the drug targets MET. The rationale is based on previous findings that MET expression was observed in 35% of BM compared to 0% of primary RCC tumors.[11]

We reported the unique case of a heavily pretreated mRCC patient with BM who achieved a complete response to cabozantinib prior to receiving radiation therapy. This case report adds to a growing body of evidence supporting the use of cabozantinib to achieve intracranial antitumor activity. In this report a 48-year-old male had been refractory to treatment with sunitinib and nivolumab. After 8 cycles of nivolumab, and MRI of the brain showed a 2.5 cm enhancing, right parietal mass associated with hemorrhage and edema. Repeat CT CAP showed an enlarging left renal mass and worsening mediastinal lymphadenopathy. Following three weeks of third-line cabozantinib (60 mg daily) a repeat MRI showed complete resolution of the right parietal mass. The patient also reported improvement of his headache and blurry vision; radiation was no longer considered necessary. After eight weeks of cabozantinib, CT showed partial response with reduction in size of mediastinal lymphadenopathy and bilateral renal masses.

The rationale for using cabozantinib in this context was also supported by other reports, including findings in two other cases by Negrier et al.[12] These cases included a 51-year-old man and a 55-year-old man, both of whom had mRCC and were treated with TKIs prior to undergoing subsequent therapy after the reappearance of brain metastasis together with neurologic symptoms. We repor-

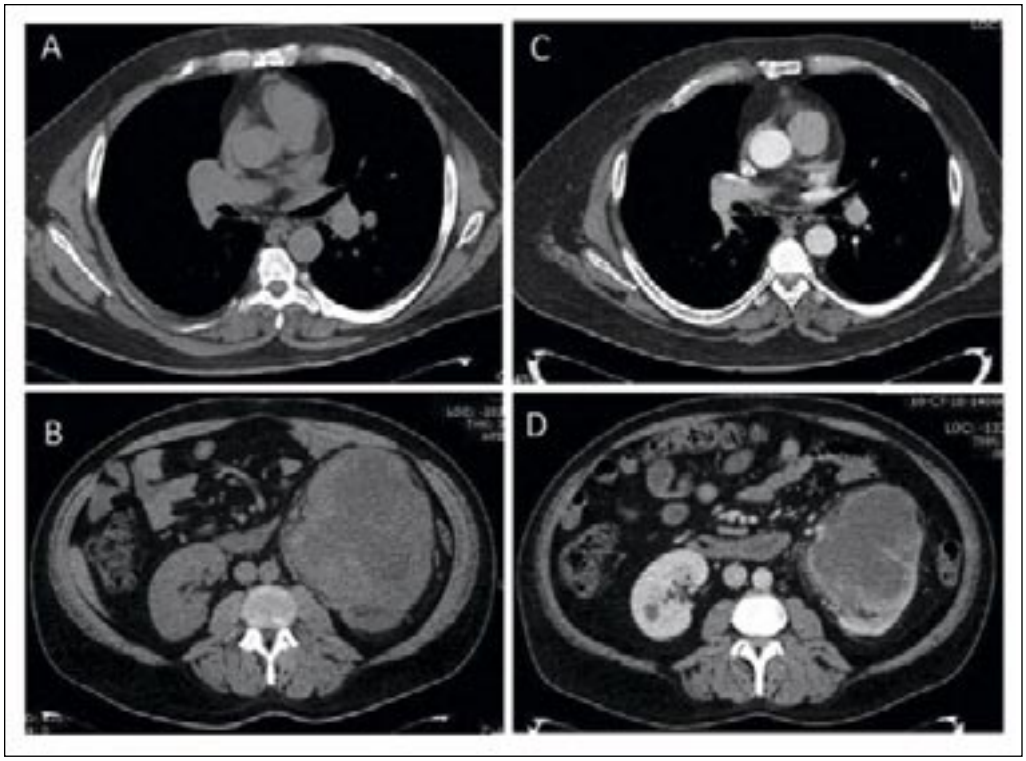

Figure 2. CT CAP. Panel A and B. Axial images of CT CAP showed right sided hilar lymphadenopathy and a large left kidney mass. Panel C and D. Axial images of CT CAP showed improvement in right sided hilar lymphadenopathy and reduction in size of left kidney mass, after 8 weeks of therapy with cabozantinib.

ted the unique case of a heavily pretreated mRCC patient with BM who achieved a complete response to cabozantinib prior to receiving radiation therapy. This case report adds to a growing body of evidence supporting the use of cabozantinib to achieve intracranial antitumor activity. (**Figures 1**,**2**) In the first case, cabozantinib induced a rapid clinical improvement and tumor regression in all sites, including those affecting the brain. There was evidence of a mutation of the MET gene in the first case. Evidence from the second case also supported the use of cabozantinib following the diagnosis of papillary RCC with brain metastases. This patient had had disease control following three years of a TKI, but the brain metastases were resistant to therapy. When the disease finally progressed at all metastatic sites, including the brain, cabozantinib was administered. A CT scan and MRI documented significant tumor regression, although no MET gene mutation was observed.

c-MET: Primary vs Metastatic Sites

With the expanding spectrum of potential treatment of BM in RCC, and the likely importance of c-MET in controlling mRCC, additional studies are seeking an optimal model that could be used to assess predictive biomarkers for c-MET inhibition. A study by Lalani et al[13] followed this line of investigation as it compared the expression of c-MET between paired primary and metastatic sites in clear cell RCC tissues. In contrast to earlier studies in this regard, Lalani et al also evaluated the potential association of c-MET expression with clinicopathological factors and PD-L1 expression in tumor cells in both primary and metastatic sites. As might be expected in this cohort, the authors demonstrated that c-MET expression was signi- ficantly higher in metastatic sites compared to primary tissues. One of the intriguing findings from the report was that PD-L1 positive tumors were found to exhibit higher c-MET expression than the tumors that were PD-L1 negative. Although preliminary, the associations noted here tend to support the emerging data of c-MET and PD-L1 as suitable targets for combination therapeutic trials. If these findings can be replicated, a case could eventually be made for appropriate tissue sampling to facilitate biomarker analysis, thus raising implications for patient selection and clinical trial design. Lalani et al also showed that patients who had high c-MET expression had worse clinical outcomes, which was consistent with earlier evidence that high c-MET expression points toward worse clinical prognosis, according to their review of the literature.[13]

PD-L1 as a Target

The role of PD-L1 as a suitable target is of intense interest with results announced from trials such as the NIVOREN GETUG AFU 26 study. Although the per- meability of monoclonal antibody checkpoint inhibitors across the blood-brain barrier is likely variable, these therapies work by boosting the function of T cells, which likely traffic across the barrier.[14] Furthermore, evidence exists suggesting that brain metastases exist in an inflammatory microenvironment, which may harbor significant quantities of tumor-infiltrating lymphocytes, making checkpoint inhibitors a plausible therapeutic strategy. Several retrospective series have indicated that immune checkpoint inhibitors may achieve a response in treating CNS disease in melanoma and non–small cell lung cancer, and early results of a prospective phase 2 study of patients with previously untreated brain metastasis treated with the programmed death 1 (PD-1) inhibitor pembrolizumab (Keytruda, Merck) showed a 22% response rate in patients with melanoma (n=18) and a 33% response rate in patients with non–small cell lung cancer (n=18).[15]

As mentioned above, a significant proportion of BM in mRCC (tumor cells), as well as immune cells in the microenvironment, are positive for PD-L1. Data from prospective trials of treatment in patients with mRCC are limited, but some early descriptions of patients treated with the PD-1 inhibitor nivolumab (Opdivo, Bristol-Myers Squibb) for mRCC have been reported. One analysis specifically looked at the response rates of patients

with brain metastases in the NIVOREN trial (Nivolumab in Patients With Metastatic Renal Cell Carcinoma Who Have Progresses During or After Prior Systemic Anti-angiogenic Regimen), also called GETUG-AFU 26. NIVOREN was a phase 2 study examining the efficacy of nivolumab in the systemic therapy of mRCC after the failure of at least 1 or 2 previous systemic treatments.[16] Of the 588 patients enrolled, 55 had asymptomatic brain metastases, including 67%, 12%, and 21% with 1, 2, or more than 2 brain metastases, respectively. Of the 55 patients, 37 (67%) had had no previous treatment for brain metastases, 5 (9%) had undergone brain surgery, and 17 (31%) had received radiation therapy. The median duration of therapy in the patients with brain metastases was 2.4 months (range, 0-9 months). Of 44 patients with BM who were assessed for response, 10 (23%) had an objective response and 21 (48%) had progressive disease. (16) Neurologic decline requiring corticosteroid treatment developed in 15 patients (34%).

Although this study was small, it did show a potential response that requires further exploration. Prospective clinical trials, including approaches combining radiotherapy with immune-oncology, are under way (NCT02978-404).

Rothermundt et al[17] presented the case of a 54-year-old woman with clear-cell renal cell cancer, who developed metastases in multiple organs including one brain metastasis (gyrus cinguli). She was treated with pazopanib and the solitary brain metastasis was irradiated with 30 Gy. After 8 months of treatment with pazopanib, there was progression in the brain metastasis as well as development of two new brain metastases. Whole brain radiotherapy was performed leading to a cumulative dose of 52.5 Gy at the site of the gyrus cinguli metastasis.

The patient was subsequently treated with bevacizumab for progressive cerebral edema interpreted as radiation-induced brain necrosis. Upon systemic and central nervous system (CNS) progression 5 months later treatment with axitinib was started—achieving a partial response (PR) However, after 4 months, in March 2015, further systemic and CNS progression was documented

Treatment with pembrolizumab, a novel human programmed death receptor-1 (PD-1)-blocking antibody, was initiated. Pembrolizumab was chosen due to off-label availability at a time when no anti-PD-1 or anti-PD-ligand (L)1 antibody was licensed in Europe. After four infusions, the patient experienced complete resolution of lung metastases, stabilization of other metastases. Importantly, regression of all brain metastases was documented on magnetic resonance imaging. This excellent response was seen despite continued steroid use of 4 mg dexamethasone/day and is still ongoing after 7 months of treatment.[17]

Future Directions, Unresolved Issues and Hypotheses

The next generation of studies will need to address a broad spectrum of issues as they seek to resolve many unresolved questions in this important subset of RCC patients. As Brastianos et al noted in their report[18] on the genomic characterization of BM, it is still unknown whether BM harbor distinct genetic alterations beyond those observed in primary tumors. Currently, decisions for individualized systemic therapies in those with BM are lacking and the conventional treatment approach incorporates systemic agents that are routinely used for mRCC patients with extracranial disease. This is just one conundrum among many that need to be considered as studies explore new targets to improve the dismal prognosis for RCC patients with BM.

Genomically guided clinical trials have been successful at matching patients to novel targeted agents in patients with advanced cancer; however, patients with active BM are routinely excluded from these trials in part due to the poor correlation between systemic response and brain response. Patients will often develop progressive BM in the setting of extracranial disease that is adequately controlled with existing chemotherapies or targeted therapies.[18] Historically, this clinical divergence has been ascribed to inadequate systemic therapeutic penetration of the blood–brain barrier. Aside from need for better CNS penetrance of therapeutic agents in mRCC, further understanding of potentially oncogenic alterations unique in RCC brain metastases may offer novel treatment strategies that are desperately needed in this subset.

Brastianos et al, for example, detected alterations associated with sensitivity to P13K/AKT/mTOR, CDK, and HER2/EGFR inhibitors in brain metastases.[18] Additional studies are needed to clarify the extent to which such genomic analyses can expand our awareness of potential therapeutic targets in mRCC patients. Only limited data are available on whether checkpoint inhibitors could play a larger role in treatment. It appears, from studies like one from Harter et al,[19] that RCC is one of the most immunogenic entities. Their study focused on characterizing tumor-infiltrating lymphocytes and expression of immune checkpoints in respective tumors. One of the future directions will include efforts to further characterize differences in immunotherapeutic responses for BM according to primary tumor site.

Brain Barrier Penetration Remains Unresolved Issue

We recommend that the current management approach for patients with RCC and BM be multidisciplinary with incorporation of treatment strategies such as surgery and/or radiation therapy, when feasible. The ability of cabozantinib to penetrate the CNS is promising and has recently been supported in several tumor types including glioblastoma, RCC metastatic to the brain, and non-small-cell lung cancer metastatic to the brain where cabozantinib demonstrated therapeutic efficacy.[20-22] Based on evidence available to date and our experience, cabozantinib may represent the ideal systemic agent of choice in mRCC patients with BM. Evidence is increasing to suggest that immune checkpoint inhibitors may additionally represent attractive systemic agents in treating this RCC patient subset. Although the majority of clinical trials in mRCC have historically excluded patients with BM, a growing number of trials investigating systemic agents in mRCC subjects are now permitting inclusion of this high-risk subgroup. These studies will provide important knowledge on identifying effective agents and disease characteristics that may inform further treatment selection tailored to the individual with RCC metastatic to the brain. In mouse models exploring the ability of pazopanib to penetrate the CNS, only 1.5% of the con-

centration in plasma was able to reach the brain implying severe restriction of this agent for brain penetration.[23] The variable ability of VEGF-TKIs to penetrate the CNS may be dependent on reliance on active uptake through drug transporters. For example, sorafenib and sunitinib showed low-moderate affinity for the ATP-binding cassette (ABC) transporter, ABCB1, where brain penetration was increased 1.9-fold and 2.9-fold for sorafenib and sunitinib, respectively, in knockout mice with the absence of ABCB1 when compared to controls.[24]

Conclusion

Development of BM in patients with RCC comprises a clinically relevant subgroup with high morbidity and mortality. Although VEGFR TKIs have had success in extracranial disease, the CNS response rates have been modest. Mechanisms of differential response across agent classes may be related to the ability of the agent to penetrate the CNS and presence of molecular alterations unique to RCC BM that are targetable by specific agents. Further evaluation of cabozantinib in this setting is reasonable and results with this TKI appear to be more promising than with other agents in this class. There are preliminary data that the use of checkpoint inhibitors could yield potentially favorable results. There is an unmet need for more studies where BM in mRCC patients are not exclusionary criteria in clinical trials. These studies will inform future investigations seeking to understand the mechanisms of therapeutic resistance of RCC BM and novel strategies to treat this population.

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Incremental But Significant Progress Offers Glimpse of New Directions as IO Combinations Still Dominate the Treatment Narrative

Marc R. Matrana, MD, MS, FACP
Precision Cancer Therapies Program
Ochsner Cancer Institute
New Orleans, Louisiana

As new data continued to emerge, and new combinations of drugs gained regulatory approval for renal cell carcinoma (RCC), the world of cancer, represented by an estimated 40,000 attendees, convened in Chicago for the 55th annual meeting of the American Society of Clinical Oncology (ASCO). Although no major blockbuster revelations in RCC emerged, several updates from important large trials were presented, and interesting data from several smaller studies were discussed.

Immunotherapy Combinations Effective in Variant Histologies

Echoing the trend toward immunotherapy combinations, several studies presented subset analysis and updated results from various studies of immunotherapy and immunotherapy combinations. Among these was a subgroup analysis of patients with untreated metastatic RCC and sarcomatoid histology from the IMmotion151 study. The study analyzed 142 patients (16% of total enrolled subjects) who had any component of sarcomatoid histology. This analysis found a longer overall survival, improved progression- free survival (8.3 vs 5.3 months), and a higher overall response rate (49% vs 14%) in sarcomatoid patients treated with atezolizumab + bevicizumab vs sunitinib, regardless of PD-L1 status.

Similarly, Flippot et al reported the results of a phase II study which tested atezolizumab + bevicizumab in 60 patients with non-clear cell RCC and clear cell RCC with sarcomatoid differentiation. Among 56 patients evaluable for response, overall response rate was 53% in the sarcomatoid patients and 26% in those with non-clear cell RCC. Median progression-free survival was 8.4 months in the overall population, suggesting efficacy of this combination in patients with these variant histologies.

CheckMate 214: Implications for Risk Stratification

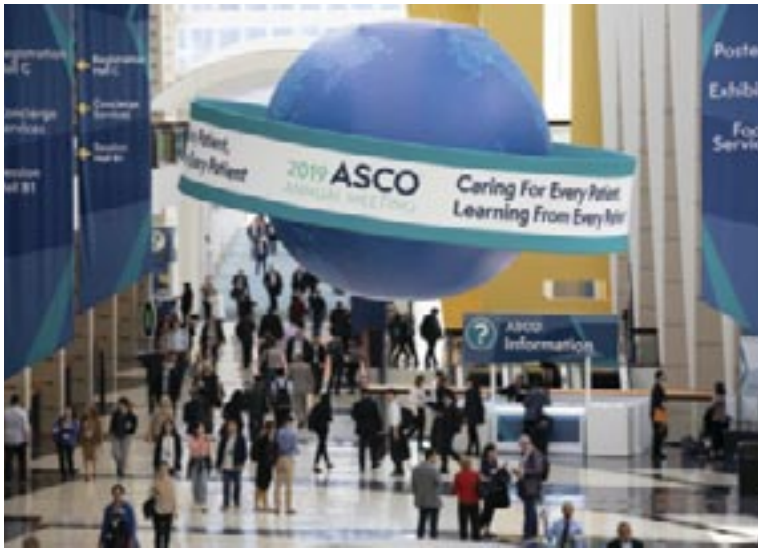
Bernard Escudier and colleagues performed post hoc analysis of CheckMate 214, comparing efficacy of nivolumab combined with ipilimumab vs sunitinib by number of IMDC risk factors present. They found the efficacy of immunotherapy was consistent regardless of the number of risk factors present, while the efficacy of sunitinib worsened in patients with more risk factors, suggesting that traditional risk models for RCC are likely less accurate in the immunotherapy era.

KEYNOTE-427 and KEYNOTE 426

Although most studies focused on immunotherapy combinations, Tykodi and colleagues presented updated results from the clear cell RCC cohort of KEYNOTE-427, an open-label, single-arm, phase 2 study of first-line single-agent pembrolizumab. Of 110 patients enrolled, overall response rate was 36.4% in all patients and 44.2% in patients who were positive for PD-L1 with 3 patients (2.7%) achieving a complete response. Median progression-free survival was 7.1 months (95% CI, 5.6-11.0) and median overall survival was not reached. Toxicities were as expected. The non-clear cell cohort of KEYNOTE-427 was presented as a separate poster. 165 patients with non-clear cell RCC received pembrolizumab and were found to have an overall response rate of 24.8%. 12 month progression free survival was 22.8% and the 12 month overall survival rate was 72.0%, echoing other emerging data which suggests the efficacy of the immunotherapy in patients with non-clear cell RCC and RCC with sarcomatoid differentiation.

Similarly, a subgroup analysis of KEYNOTE-426 presented by Rini et al, also showed benefit of combination immunotherapy and targeted therapy in a combined population of patients with IMDC intermediate or poor risk RCC and patients whose tumors had sarcomatoid features. 68.8% of all randomized patients in the study had IMDC intermediate or poor risk disease (294 in the pembrolizumab plus axitinib arm and 298 in the sunitinib control arm). The combination of pembrolizumab plus axitinib improved overall survival (12-mo rate 87.3% vs 71.3%), median progression free survival (12.6 vs 8.2

months), and overall response rate (55.8% vs 29.5%) in those with intermediate and poor risk disease. 105 patients (18.2%) were identified who had sarcomatoid features; 51 in the pembrolizumab plus axitinib arm and 54 in the sunitinib arm. Pembrolizumab plus axitinib improved overall survival (12-month overall survival rate 83.4% vs 79.5%), progression free survival (median not reached vs 8.4 mo), and ORR (58.8 vs 31.5%) in patients with sarcomatoid features; CR rates were 11.8% vs 0%.



Zibelman et al presented data on a small number of patients from the phase I portion of a combined phase I/II study of combination nivolumab and axitinib in the second- and third-line setting. Twelve patients were enrolled and evaluable, of those, four demonstrated a partial response, four had stable disease, and two progressed. Toxicity was manageable. Enrollment will proceed with the phase II portion of the trial.

Checkpoint Inhibitor Therapy and Comorbid Autoimmune Disease

Most trials of immunotherapy exclude patients with known autoimmune diseases, but Chanza and colleagues presented a retrospective review of 103 patients (57 with RCC and 46 with urothelial carcinoma) with a broad spectrum of comorbid autoimmune diseases such as psoriasis, thyroiditis, rheumatoid arthritis, polymyalgia rheumatica, inflammatory bowel disease, multiple sclerosis, and lupus, who received immune checkpoint inhibitor. 36 of these patients had clinically active autoimmune disease at the time of therapy, some requiring systemic immunosuppression. Exacerbations of these autoimmune diseases occurred in 37% of patients, with the most frequent being arthritis and rash. New onset immune related events occurred in 36% of the patient's analyzed, with the most frequent being colitis, rash, hypothyroidism, and nephritis. Both exacerbations of existing autoimmune diseases and new onset immune related events were generally manageable, and the data suggests that in certain clinical scenarios patients with autoimmune diseases can be safely treated with immune checkpoint inhibitor therapy.

Encouraging Results in Brain Metastases With Nivolumab+Ipilimumab

Most trials of patients with advanced RCC also exclude patients with brain metastases, however trials in melanoma and lung cancer have shown efficacy of combination nivolumab and ipilimumab in patients with brain metastases. Emamekhoo et al, e presented data from 28 patients from the CheckMate 920 trial who had asymptomatic brain metastases and retreated with nivolumab and ipilimumab. Overall response rate was 28.6%, median progression-free survival was 9 months, and overall survival had not been met. Toxicities were as expected. These data suggest encouraging antitumor activity a combination immunotherapy in patients with advanced RCC and brain metastases and suggests that we should more closely evaluate this phenomenon before excluding patients with brain metastases from clinical trials.

Redefiing Systemic Therapy After Cytoreductive Surgery

Several studies sought to better define how to use systemic therapy along with surgery strategies. Jianjun Gao led investigators from MD Anderson who evaluated effects of immunotherapy when combined with cytoreductive surgery. Patients were randomized in a 2:3:2 fashion to receive single agent nivolumab (3mg/kg every 2 weeks for three doses), nivolumab and bevacizumab (10mg/kg every two weeks for three doses) or nivolumab plus ipilimumab (1mg/kg q3wks x2), followed by cytoreductive surgery (nephrectomy, metastasectomy, or biopsy), and then went on to nivolumab maintenance therapy for up to 2 years. Imaging response was assessed and pre- and post-treatment blood and tissue were obtained. 104 subjects were evaluable for response. Best overall response (complete response + partial response) including surgery effect was 55% for single agent nivolumab, 44% for combination nivolumab + bevacizumab, and 43% for nivolumab and ipilimumab. Median progression free survival was 14.5 months for nivolumab, 7.6 months for the combination of nivolumab + bevacizumab, and 7.5 months for nivolumab plus ipilimumab. Overall survival (overall survival) at one year was 86% with nivolumab alone, 73% for combined nivolumab plus bevacizumab, and 83% for nivolumab plus ipilimumab.

Immune and gene profiling analyses demonstrated several interesting observations, including: 1) tumor infiltrating CD8 T cells correlated with imaging response to single agent nivolumab and to combination nivolumab plus bevacizumab, but not to nivolumab combined with ipilimumab; 2) tumor IFN pathway gene expression correlated with responses; and 3) PD-L1 status, tumor mutation or mutation burden, and neoantigens did not correlate with response. Gao et al concluded that immune checkpoint inhibitor therapy is safe and beneficial in mRCC patients when used with cytoreductive surgical techniques.

Results of the ECOG E2810 study were also presented by Leonard Appleman. In this double-blind phase III study, investigators randomized patients to receive adjuvant pazopanib for 1 year versus placebo following complete metastasectomy (all patients had no evidence of

disease following surgery); 129 patients were enrolled, and the trial was unblinded after 83 DFS events had been observed. The median follow-up from randomization was 30 months (with a range of 0.4 – 66.5 months). The study did not meet the primary endpoint: hazard ratio (95% CI) for DFS was 0.85 (0.55, 1.31) p= 0.47 in favor of pazopanib. At the time of unblinding, 22/129 (17%) of subjects had died. The hazard ratio for overall survival was 2.65 (1.02, 6.9) in favor of placebo (p= 0.05). Appleman concluded that adjuvant pazopanib in patients rendered NED following metastasectomy did not improve DFS compared to placebo and there was a trend toward worse overall survival with pazopanib.

New Data Support Active Surveillance in Selected Patients

Active surveillance is commonly practiced in mRCC patients with asymptomatic, low-volume, slow growing disease, although little evidence around this strategy exists to support it. Canadian investigators, Igal Kushnir and colleagues sought to remedy this by analyzing data from the Canadian Kidney Cancer Information System database. They identified 863 patients who underwent active surveillance instead of immediate systemic therapy. Of these, 370 started treatment ≥ 6 months after their initial diagnosis and 493 never received systemic treatment and were alive for ≥1 year. The median time on active surveillance was 14.2 months (range 6 – 71), suggesting that for a select group of patients, systemic therapy may safely be delayed.

Emerging Trials to Watch With Novel Strategies

A few interesting trials in progress were showcased, among them Nizar Tannir's multicenter, randomized, open-label phase 3 study (NCT03729245) with Nektar Therapeutics which will evaluate the efficacy and safety of bempegaldesleukin (NKTR-214) plus nivolumab compared with investigator's choice of first-line TKI (either sunitinib or cabozantinib) in patients with previously untreated advanced or metastatic RCC with clear cell component.

Another trial in progress highlighted was Alliance's A031704, also known as PDIGREE, which is an adaptive phase 3 trial, in which clear cell RCC patients will be treated with upfront nivolumab and ipilumumab. After completing this treatment patients will be randomized based on imaging response. Those who achieve a complete response after nivolumab and ipilimumab will undergo maintenance nivolumab, while patients with progressive disease will switch to daily cabozantinib, and patients with either partial response or stable disease will be randomized to either nivolumab maintenance or nivolumab with daily cabonzantinib.

Updates to ECOG-ACRIN 8143, the PROSPER study were shared. In this global, unblinded, phase 3 study, patients with any histology of RCC and clinical stage ≥T2 or any T stage disease with positive lymph nodes are randomized to receive 1 dose of nivolumab prior to complete resection, followed by an additional 9 doses of adjuvant nivolumab (480mg given every 4 weeks). The control arm undergoes standard nephrectomy followed by observation only. Oligometastatic disease is permitted if those patient's disease can be completely resected with metastasectomy. The study was amended to enhance accrual and patient quality of life (changing nivolumab to the 480mg every 4 weeks dose, for example) and amended a requirement for baseline tumor biopsy, now only in the nivolumab arm.

ASCO 201brought us incremental data that continue to refine care for patients with advanced RCC, especially for those with variant histologies and receiving immunotherapies, ultimately improving survival. KCJ

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Six hundred fifty-seven patients were enrolled and received ≥1 dose of pazopanib. Median PFS and OS were 10.3 months (95% confidence interval [CI], 9.2-12.0) and 29.9 months (95% CI, 24.7 to not reached), respectively, and the ORR was 30.3%. HRQoL showed no or little deterioration over time. Treatment-related serious adverse events (AEs) and AEs of special interest occurred in 64 (9.7%), and 399 (60.7%) patients, respectively. More patients were classified NCTE than CTE (85.2% vs. 14.8%). Efficacy of pazopanib was similar between the two groups.
Conclusion: PRINCIPAL confirms the efficacy and safety of pazopanib in patients with advanced/metastatic RCC in a real-world clinical setting. Implications for practice: PRINCIPAL is the largest (n = 657) prospective, observational study of pazopanib in patients with advanced/metastatic renal cell carcinoma, to the authors' knowledge. Consistent with clinical trial results that often contain specific patient types, the PRINCIPAL study demonstrated that the effectiveness and safety of pazopanib is similarly safe and effective in patients with advanced kidney cancer in a real-world clinical setting. The PRINCIPAL study showed that patients with advanced kidney cancer who are treated with first-line pazopanib generally do not show disease progression for approximately 10 months and generally survive for nearly 30 months.

Metastatic Chromophobe Renal Cell Carcinoma: Presence or Absence of Sarcomatoid Differentiation Determines Clinical Course and Treatment Outcomes. Ged Y, Chen Y-B, Knezevic A, et al. *Clin Genitour Cancer*. 2019;17:e678-e6688.
Summary: Sarcomatoid features (SF) in renal cell carcinoma (RCC) denote poor prognosis. Data for metastatic chromophobe RCC (ChRCC) with SF are limited. We studied clinical outcomes and genomic features in this setting.We performed a retrospective review of newly diagnosed metastatic ChRCC patients; end points included overall survival (OS), time to treatment failure (TTF), and time to metastatic recurrence (TTR) after nephrectomy for localized disease. A subset of patients underwent next-generation sequencing (NGS). Outcomes were compared using nonparametric tests. One hundred nine patients with metastatic ChRCC were identified including 29 with SF. Median TTR after nephrectomy was shorter for patients with versus without SF (2.7 months [95% confidence interval (CI), 0.7-6.9] versus 48.8 months [95% CI, 30.8-80.7], log rank $P < .001$). Median TTF during first-line therapy was shorter for patients with versus without SF (1.8 months [95% CI, 0.9-2.7] vs. 8.0 months [95% CI, 5.1-13.0]; log rank $P < .001$). No responses were observed in 6 patients treated with nivolumab including 4 with SF. Median OS was inferior for patients with versus without SF (38 months vs.7.5 months; hazard ratio, 4.7 [95% CI, 2.7-8.2]; $P < .001$). NGS, performed in 22 patients, showed that 64% and 45% harbored tumor protein P53 and phosphatase and tensin homolog alterations, respectively. Microsatellite instability high status was identified in 3 patients.
Conclusion: Metastatic ChRCC patients with SF had worse outcomes compared with those without SF. Median TTR < 3 months for this subgroup supports close surveillance after nephrectomy for localized tumors. Lack of benefit with various systemic regimens warrants studying underlying biology and investigating novel agents.

Association of Systemic Inflammation Index and Body Mass Index with Survival in Patients with Renal Cell Cancer Treated with Nivolumab. *Clin Cancer Research*. 2019 Apr 9. doi: 10.1158/1078-0432.CCR-18-3661. [Epub ahead of print] De Giorgi U, Procopio G, Giannarelli D, et al. Inflammation indexes and body mass index (BMI) are easily evaluated, predict survival, and are potentially modifiable. We evaluated the potential association of inflammatory indexes and BMI with the clinical outcome of patients with renal cell carcinoma (RCC) undergoing immune checkpoint inhibitor therapy.
Summary: A prospective cohort of patients with metastatic RCC treated with nivolumab enrolled in the Italian Expanded Access Program from July 2015 through April 2016 was examined. Reference measures of inflammation were identified for neutrophil-to-lymphocyte ratio (NLR) </≥ 3, systemic immune inflammation index (SII) </≥ 1,375, and platelet-to-lymphocyte ratio (PLR) </≥ 232. Patients were classified as high BMI (≥25 kg/m^2) versus normal BMI (<25 kg/m^2). Among 313 evaluable patients, 235 (75.1%) were male, and median age was 65 years (range, 40–84 years), with 105 (33.69%) ≥70 years. In univariate analysis, age, performance status, BMI, SII, NLR, and PLR were able to predict outcome. In multivariate analyses, SII ≥1,375, BMI <25 kg/m^2, and age ≥70 years independently predicted overall survival [OS; HR = 2.96, 95% confidence interval (CI), 2.05–4.27; HR = 1.59, 95% CI, 1.10–2.30; and HR = 1.65, 95% CI, 1.07–2.55, respectively). A patient with both SII ≥1,375 and BMI <25 kg/m^2 was estimated to have much worse OS (HR, 3.37; 95% CI, 2.29–4.95; $P < 0.0001$) than a patient with neither or only one risk factor. SII changes at 3 months predicted OS ($P < 0.0001$).
Conclusions: Normal BMI combined with inflammation tripled the risk of death, suggesting that these biomarkers are critical prognostic factors for OS in patients with RCC treated with nivolumab. KCJ

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Table 9. Incidence and Mortality Rates* for Selected Cancers by Race and Ethnicity, US, 2011-2016

Incidence, 2011-2015.	All races	Non-Hispanic white	Non-Hispanic black	Asian/Pacific Islander	American Indian/ Alaska Native†	Hispanic/ Latino
All sites	449.8	465.3	463.9	291.7	398.5	346.6
Male	494.8	505.5	549.1	298.9	418.4	377.6
Female	419.3	438.4	407.0	290.3	386.9	329.9
Breast (female)	124.7	130.1	126.5	92.9	100.9	93.0
Colon & rectum	39.3	39.0	46.6	30.7	44.4	34.4
Male	45.2	44.6	55.2	36.1	49.8	41.7
Female	34.3	34.2	40.7	26.4	40.1	28.8
Kidney & renal pelvis	16.4	16.6	18.4	7.8	23.2	16.2
Male	22.2	22.5	25.4	11.1	29.9	21.1
Female	11.4	11.4	13.1	5.1	17.4	12.2
Liver & intrahepatic bile duct	8.1	6.7	10.7	13.0	14.8	13.3
Male	12.5	10.3	17.6	19.9	20.9	19.7
Female	4.3	3.6	5.2	7.4	9.5	7.8
Lung & bronchus	60.5	64.7	63.8	34.9	61.5	30.7
Male	71.3	74.3	85.4	44.5	69.3	39.2
Female	52.3	57.4	49.2	27.8	55.7	24.6
Prostate	109.2	101.7	179.2	56.0	73.1	91.6
Stomach	6.6	5.4	10.3	10.5	8.4	9.7
Male	9.1	7.8	14.1	13.7	11.2	12.5
Female	4.6	3.5	7.7	8.0	6.1	7.7
Uterine cervix	7.6	7.1	9.2	6.0	9.2	9.6
Mortality, 2012-2016						
All sites	161.0	165.4	190.6	100.4	148.8	113.6
Male	193.1	197.3	239.8	119.1	178.8	138.2
Female	137.7	141.8	160.4	87.0	126.8	96.4
Breast (female)	20.6	20.6	28.9	11.3	14.5	14.3
Colon & rectum	14.2	14.0	19.4	9.9	15.9	11.2
Male	16.9	16.6	24.5	11.7	19.5	14.4
Female	11.9	11.9	16.0	8.4	13.1	8.8
Kidney & renal pelvis	3.8	3.9	3.7	1.8	5.8	3.5
Male	5.5	5.7	5.6	2.7	8.2	5.0
Female	2.3	2.4	2.3	1.1	3.8	2.3
Liver & intrahepatic bile duct	6.5	5.7	8.6	9.4	10.8	9.3
Male	9.6	8.3	13.6	13.9	14.6	13.3
Female	3.9	3.4	4.8	5.8	7.5	6.0
Lung & bronchus	41.9	45.0	45.6	22.8	35.4	18.3
Male	51.6	54.1	63.9	30.3	42.7	25.3
Female	34.4	37.9	33.3	17.4	29.9	13.1
Prostate	19.2	18.1	39.8	8.6	19.1	15.9
Stomach	3.1	2.4	5.7	5.3	5.2	5.1
Male	4.2	3.3	8.4	6.8	7.0	6.5
Female	2.3	1.7	3.9	4.2	3.7	4.0
Uterine cervix	2.3	2.1	3.6	1.7	2.8	2.6

Hispanic origin is not mutually exclusive from Asian/Pacific Islander or American Indian/Alaska Native. *Rates are per 100,000 population and age adjusted to the 2000 US standard population and exclude data from Puerto Rico. †Data based on Indian Health Service Contract Health Service Delivery Areas. Source: Incidence – North American Association of Central Cancer Registries, 2018. Mortality – National Center for Health Statistics, Centers for Disease Control and Prevention, 2018.

(continued on next page)

New Study Compares Bempegaldesleukin (NKTR-214) Plus Nivolumab to Sunitinib or Cabozantinib in Previously Untreated Advanced RCC

CHICAGO – Bempegaldesleukin (NKTR-214) is a CD122-preferential IL-2 pathway agonist that stimulates proliferation and activation of tumor antien-specific $CD8^+$ T cells and natural killer cells within the tumor microenvironment and increases PD-1/PD-L1 expression. These properties make bempegaldesleukin (NKTR-214) a potentially promising agent for combination therapy with checkpoint inhibitors that target and inhibit the PD-1/PD-L1 pathway. In phase 1 studies, NKTR-214 plus nivolumab demonstrated encouraging objective response rates (ORR) in first-line renal cell carcinoma (RCC) and an acceptable safety profile. Immunotherapy with NKTR-214 plus nivolumab may lead to greater clinical benefit than tyrosine kinase inhibitors (TKIs), standard-of-care agents, in this patient population.

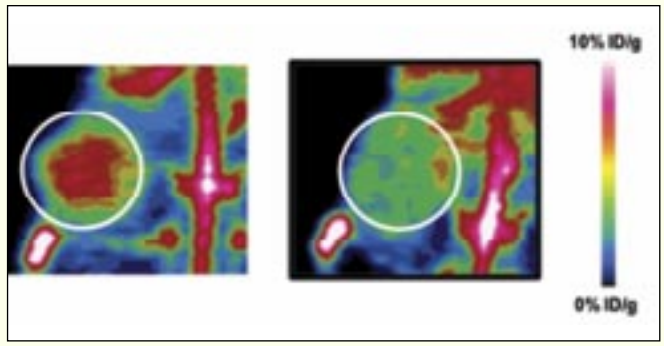
A multicenter, randomized, open-label phase 3 study (NCT03729245) will evaluate the efficacy and safety of bempegaldesleukin (NKTR-214) plus nivolumab compared with investigator's choice of TKI (sunitinib or cabozantinib) in patients with previously untreated advanced or metastatic RCC with clear cell component. Exclusion criteria include active brain metastasis and autoimmune disease. Approximately 600 patients will be randomized in a 1:1 ratio, stratified by PD-L1 status (≥1% vs < 1% or indeterminate), International Metastatic RCC Database Consortium prognostic score (1-2 [intermediate risk] vs 3-6 [poor risk]); and TKI (sunitinib or cabozantinib; cabozantinib percentage to be capped at 50%). Combination therapy will consist of bempegaldesleukin (NKTR-214) 0.006 mg/kg intravenously (IV) every 3 weeks (Q3W) plus nivolumab 360 mg IV Q3W until progression or death or maximum of 2 years. TKI therapy will consist of sunitinib 50 mg orally once daily (QD) for 4 weeks followed by 2 weeks off or cabozantinib 60 mg orally QD. Primary objectives are ORR by blinded independent central radiology (BICR) assessment and overall survival. Secondary objectives are progression-free survival by BICR, safety, predictive value of PD-L1 expression, and quality of life. Enrollment is ongoing.

UT Southwestern Develops Test to Predict Immunotherapy Response

DALLAS – A novel imaging test shows promise for identifying kidney cancer patients most likely to benefit from immunotherapy. Investigators with the UT Southwestern Medical Center Kidney Cancer Program say a new test can illuminate kidney cancers that may respond to checkpoint inhibitors.

The strategy involved transforming an immunotherapy drug, atezolizumab (Tecentriq), into a diagnostic tracer. Atezolizumab binds to and disables PD-L1, a protein that cancer cells display on their surface to shut off approaching killer immune cells. By labeling atezolizumab with zirconium-89 (Zr^{89}), a radioactive metal generated using a cyclotron, the investigators were able to visualize atezolizumab using PET (positron emission tomography). As such, a single, very small dose of Zr^{89}-atezolizumab can be used to evaluate whether tumors deploy PD-L1 to suppress immune cells and whether drugs disabling this pathway may be effective.

Currently, immunotherapy drugs benefit less than 50 percent of kidney cancer patients. With immuno-PET, or iPET, as a screening tool, the investigators hope to identify those patients who will benefit. Marking the first time this type of theranostic (drug turned into a diagnostic test) is



Left, illuminated tumor by iPET expressing immunotherapy target, compared to control tumor (right).

deployed for kidney cancer, the approach opens a molecular window. In proof-of-principle experiments, a team led by Dr James Brugarolas, one of the corresponding authors of the study and the Director of the UT Southwestern Kidney Cancer Program, showed that Zr^{89}-atezolizumab was able to illuminate kidney tumors with high levels of PD-L1. As part of the study, investigators selected tumors from two patients, one with high PD-L1 and another with low PD-L1, and transplanted them into mice. The mice were then injected with Zr^{89}-atezolizumab intravenously and evaluated by PET. As predicted from the mouse studies, the patient with the high PD-L1 tumor had substantial regression of his metastases when treated with nivolumab (Opdivo), which targets the PD-L1 pathway.

"The development of tests predicting which patients respond to immunotherapy is critical," said Dr Hans Hammers, an immunotherapy expert with the Kidney Cancer Program. Zr^{89}-atezolizumab was filed with the FDA by the Cyclotron and Radiochemistry Program led by Dr Xiankai Sun at UT Southwestern, also a corresponding author of the study, and is now proceeding to evaluation in patients in a clinical trial at UT Southwestern's Harold C. Simmons Comprehensive Cancer Center. The clinical trial is made possible through a $600,000 translational award to Dr. Brugarolas' team by the V Foundation for Cancer Research. Support for the preclinical studies was provided through a Specialized Program of Research Excellence (SPORE) grant from the National Cancer Institute. A second trial also is planned at the Simmons Cancer Center using Zr^{89}-atezolizumab to evaluate the impact of stereotactic body radiation therapy (SBRT) on PD-L1 expression in kidney cancer patients. The SBRT trial will be funded by the Kidney Cancer Congressionally Directed Medical Research Program.

First Patient Enrolled in RCC Trial with Pexa-Vec in Combination with Cemiplimab

SAN FRANCISCO— SillaJen, Inc., a clinical-stage, biotherapeutics company focused on the development of oncolytic

immunotherapy products for cancer, has enrolled the first patient in Part 2 of JX594-REN026, a Phase 1b clinical trial of Pexa-Vec (pexastimogene devacirepvec) in combination with Libtayo®(cemiplimab-rwlc), for the treatment of RCC. Enrollment of Part 1 (dose-escalation phase) of the trial was completed in March 2019 without significant safety concerns, and the first seven patients in Part 2 were enrolled in South Korea, with expansion to sites in the United States and Australia anticipated.

SillaJen is collaborating with Regeneron to evaluate Pexa-Vec, SillaJen's lead clinical candidate, in combination with Regeneron's Libtayo®, an anti-PD1 monoclonal antibody Regeneron is developing in collaboration with Sanofi. The aim of the trial is to assess the safety and efficacy of the combination in patients with unresectable or metastatic renal cell carcinoma. The study will also investigate the immune modulating potential of Pexa-Vec given concurrently with checkpoint inhibitor therapy by evaluating multiple blood and tissue biomarkers. KCJ

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