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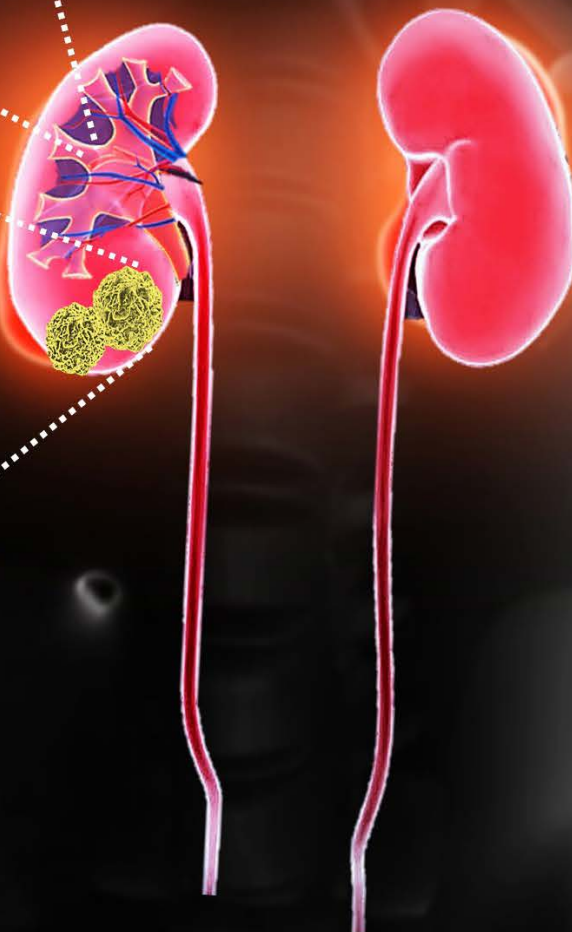
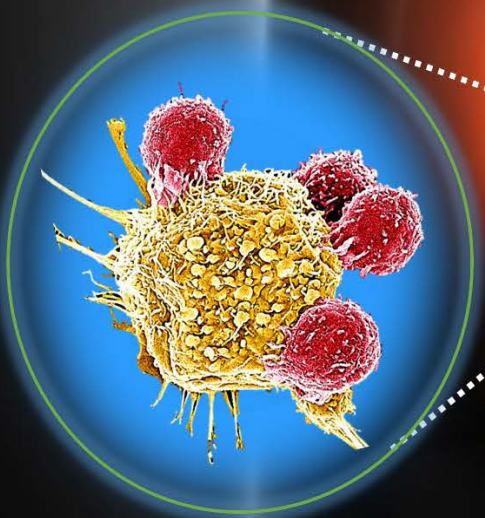
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Impact of Mycobacterial Infections on Outcomes of Patients with Metastatic Renal Cell Carcinoma



Dissecting the role of lymphadenectomy in the management of RCCs

**HIF-inhibitors in RCCs:
A Review of Current Trials**

**Academic Mentorship:
Choosing the Right
Research Mentor(s)**

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

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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.

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ABOUT THE COVER

Illustration of mycobacterial infection during renal cell carcinoma development may improve TKI response with upregulated VEGF and angiogenesis, as a downstream consequence of the immune response, which positively impact on therapy response and improve OS in patients.



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KCJ Editor's Memo

Impact of COVID-19 on Clinical Trial Accrual and Delayed Diagnosis of Cancer



Robert A Figlin, MD

As we are fast approaching the holiday season this year and beginning of 2021, the status of the pandemic still looms large with no signs of slowing down. The COVID-19 pandemic has disrupted virtually every aspect of cancer care and clinical trials – from adding further risks for cancer patients, to impeding the delivery of cancer therapy, and the continuity of cancer clinical trials. For people living with cancer and even for those who have gone into remission but still require continued care/follow-up testing, the COVID-19 pandemic has posed enormous challenges to cope with new normal.

Clinical trials across diseases including cancers are impacted by quarantines, medical resources and drug supply disruptions, shortages of staffs, site closures and travel limitations. Due to the pandemic related logistic barriers, clinical trial accrual fell about 50% immediately after the COVID-19 outbreak with some cancer centers halting enrollment on clinical trials entirely during the height of the pandemic. Major pharma companies have announced delays in enrollment for ongoing studies and initiation of future studies. Since the pandemic, a sharp decline in cancer diagnoses and routine screening were observed around the world. In the patient care setting, COVID-19 pandemic has led to elective and potentially curative surgery delays for patients with cT1b-cT2b renal cell carcinoma. However, preliminary research has indicated that up to and beyond 3 months of surgical delays did not result in an increased risk of pT3a upstaging or compromise overall survival. In the following months, a downstream ripple effect throughout the cancer care continuum could be possible from the drop-off in screenings and diagnoses, decreased patient visits, biopsies, and cancer treatments etc. Most importantly, the global efforts geared towards developing therapeutics or vaccine for COVID-19 are taking up a lot of oxygen in the oncology clinical trial space. Apparently, most of the existing cancer and non-COVID-19 research efforts are largely being set aside in favor of COVID-19 trials. Such government and industrywide push toward COVID-19 remedies shifted focus away from existing lines of clinical research,

(continued on [Page 101](#))

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- 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.

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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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Impact of Mycobacterial Infections on Outcomes of Patients with Metastatic Renal Cell Carcinoma: A Case Series

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ABSTRACT

Objective: Renal cell carcinoma (RCC) is a common cancer, and mycobacterial infections (MBI) are some of the most prevalent infections in the world. Little is known about their overlap and how MBI might affect outcomes of RCC. The objective of this series was to explore the relationship between MBI and RCC in terms of patient survival and treatment response.

Methods: Institutional records were searched for patients with diagnoses of kidney cancer and MBI. Patients with histologically confirmed metastatic RCC diagnosed up to the date of IRB approval were included. Patient demographics, tumor characteristics, clinical data, and treatment modalities and durations were collected and analyzed. Primary outcome was overall survival.

Results: 5 patients were included. Median overall survival (mOS) of patients with RCC and subsequent diagnosis of MBI was ≥ 62 months. mOS of patients carrying both diagnoses without concern for temporal relation was ≥ 24 months.

Conclusion: Development of an MBI during RCC malignancy treatment may positively impact on therapy response and improve OS. Improved TKI response duration may be related to upregulation of VEGF and angiogenesis seen as a downstream consequence of the immune response to mycobacterial infection.

KEYWORDS: Kidney Cancer • MAC • Mycobacterial Infection • Renal Cell Carcinoma • Tuberculosis •

Abbreviations: mRCC – metastatic renal cell carcinoma; MSKCC – Memorial Sloan-Kettering Cancer Center; IMDC – International Metastatic RCC Database Consortium; TKI – tyrosine kinase inhibitor; mOS – median overall survival IFN – interferon; IL – interleukin; TGF – transforming growth factor VEGF – vascular endothelial growth factor; HIF – hypoxia-inducible transcription factors. MBI – mycobacterial infection

INTRODUCTION

Renal cell carcinoma (RCC) is among the top 10 cancers for both men and women, with nearly 74,000 new diagnoses expected in the US this year¹. Even with recent advances, the 5-year relative survival for metastatic RCC

remains low, at approximately 12%¹. Patients with RCC and other malignancies are at higher risk for infection development, but the impact of viral and bacterial infections on outcomes of malignancy remains controversial.

Physicians and researchers have observed the impact of spontaneous

infections on cancers for over 150 years. In 1867, Busch in Germany reported on a cancer that went into remission after a bout of erysipelas. At the turn of the 20th century, this knowledge was harnessed by Dr. William Coley, often referred to as the “father of immunotherapy of cancer.” Coley inoculated patients with *Streptococcus pyogenes* and *Serratia marcescens* bacteria and found patients with sarcomas could often be put into deep and durable remissions². More recent data on the impact of infections are conflicting. Within retrospective studies of post-operative infections in glioblastoma multiforme, De Bonis et al found that post-operative infection led to a significant survival advantage³, whereas Bohman et al found that it did not⁴. Furthermore, while studies have shown that postoperative intra-abdominal infections in patients with stage II colon cancer have a negative impact on disease-free survival and disease-specific survival⁵ and surgical site infections following resection of T4N0-2M0 colon cancers are associated with an increased risk of intraabdominal recurrence and worse survival⁶, post-orthotopic liver transplantation infections tend to improve the outcome of hepatocellular carcinoma patients⁷ and postoperative empyema seems to improve survival in lung cancer⁸.

Mycobacterium tuberculosis is one of the most common infections worldwide, affecting about one quarter of the world's population⁹. Non-tuberculous mycobacterial infections (MBI) are also common¹⁰⁻¹⁴. In our institution, we observed that patients with metastatic

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Author's contributions: Rebecca C. Shay: developed idea for the project, major contributor in drafting the manuscript, literature search, review, editing. Elaine T. Lam: developed idea for the project, substantively revised the manuscript, drafting the manuscript. All authors read and approved the final manuscript.

Patient #	Sex	Race	Ethnicity	Age at diagnosis	Insurance coverage	Year of diagnosis
1	Female	White	Non-Hispanic	71	Public	2008
2	Male	White	Non-Hispanic	75	Public	2010
3	Male	Black	Non-Hispanic	63	Public	2013
4	Male	Asian	Non-Hispanic	62	Uninsured	2014
5	Female	Asian	Non-Hispanic	83	Public	2015

TABLE 1 | Baseline patient characteristics

RCC (mRCC) who at some point in their treatment developed mycobacterial pulmonary infections appeared to have prolonged overall survival (OS) when compared to what is expected in the general mRCC population. This has not been previously reported in the literature. Our objective was to assess the correlation between the presence of prior or concurrent MBI and patient survival and treatment response in mRCC.

Patients and Methods

After local IRB approval, institutional electronic medical records and databases were queried for patients with a diagnosis of both “malignant

neoplasm of kidney, except renal pelvis” (ICD-10 C.64) and either “infection due to other mycobacteria” (ICD-10 A.31) or “respiratory tuberculosis” (ICD-10 A.15). Patient records were then assessed for accuracy of aforementioned diagnostic criteria and for presence of metastatic RCC. Patients with histologically confirmed mRCC with clear cell or non-clear cell histology were included; patients without metastatic disease were excluded. Patients who were diagnosed with RCC up to the date of local IRB approval were included.

The following data were collected: baseline patient demographics, baseline tumor characteristics, clinical data, treatment data, time of diagnosis

of MBI in relation to diagnosis of RCC, treatment for MBI, outcomes including duration of response to anticancer therapy before and after MBI infection, and OS, defined as the time from diagnosis of mRCC to the time of death from RCC.

Results

Twenty-seven patients were initially identified throughout the University of Colorado Health system applying the above diagnostic criteria. Sixteen were excluded due to only nonmetastatic localized disease, five did not truly carry a diagnosis of renal cell carcinoma, and one was excluded for squamous cell differentiation and a lack of clarity surrounding the primary tumor of origin. Five patients were therefore assessed in this series, with baseline patient characteristics as described in Table 1. Two female and three male patients, ages 62–83, were included in the series.

Characteristics of the patients' mRCC are outlined in Table 2. One patient harbored sarcomatoid features. Patients initially presented at both localized and metastatic disease stages. Three patients had International Metastatic RCC Database Consortium

Patient #	RCC Histology	Sarcomatoid features	Fuhrman Grade	Laterality	Stage at Initial Diagnosis	Locations of metastatic disease	IMDC Risk category	MSKCC Risk category
1	Clear cell	No	2	Left	I	Bone, Nephrectomy Bed, LNs, Lung, Brain	Intermediate	Intermediate
2	Clear cell	No	Unknown	Right	IV	Mediastinum, Bone, Brain	Intermediate	Intermediate
3	Clear cell	Unknown	2	Left	III	RP Soft Tissue, Lung	Favorable	Favorable
4	Clear cell	No	Unknown	Left	IV	Lung, Liver, Bone	Intermediate	Intermediate
5	Clear cell	Yes	4	Right	IV	Lung, Nephrectomy Bed	Poor	Poor

TABLE 2 | Renal cell carcinoma characteristics. Key: IMDC – International Metastatic RCC Database Consortium (1 point each for <1 year from diagnosis to start of therapy, Karnofsky Performance Status <80%, Hemoglobin < lower limit of normal (LLN), calcium > upper limit of normal (ULN), neutrophils > ULN, platelets > ULN; 0 points favorable risk, 1–2 points intermediate risk, 3+ points poor risk). MSKCC – Memorial Sloan-Kettering Cancer Center (1 point each for <1 year from diagnosis to start of therapy, Karnofsky Performance Status <80%, Hemoglobin < LLN, calcium > 10 mg/dL, LDH > 1.5x ULN; 0 points favorable risk, 1–2 points intermediate risk, 3+ points poor risk).

(IMDC) and Memorial Sloan-Kettering Cancer Center (MSKCC) Intermediate Risk category disease, one had poor risk disease, and one had favorable risk disease. Sites of metastases included lymph nodes, bone, lung, liver, soft tissue, brain, and in the nephrectomy bed.

The treatment modalities used are included below (Table 3). Four patients had prior nephrectomy. Two patients received local radiation therapy to metastatic sites. Four patients received systemic therapy, including tyrosine kinase

mRCC diagnosis. Only one patient underwent treatment of MBI diagnosed after RCC diagnosis: standard triple therapy of ethambutol, isoniazid, and rifampin. Overall survival ranged from 2 to 117 months.

Discussion

Mycobacterial infections are common infections clinically ranging from asymptomatic to morbid. Generally speaking, infections have negative impact on patients in the short term, but

approximately 20 – 30 months¹⁵⁻¹⁹. Analysis of our cohort found that, in the three patients who were diagnosed with MBI after already diagnosed with RCC, their OS ranged from 12 to 117 months. The mean and median OS in among these patients were 63.7 months and 62 months, respectively. If we also include the two patients who either had a history of MBI or were diagnosed with the infection at the same time as diagnosis of the RCC, the mean OS and median OS

decreases to 43.4 months and 24 months, respectively. In summary, if a patient with mRCC was diagnosed concurrently or prior to MBI, OS was not necessarily improved. However, patients in our cohort who developed MBI after diagnosis of RCC appeared to have substantially improved OS when compared

Patient #	Nephrectomy	Radiation	Systemic Therapy for mRCC	Time from mRCC diagnosis to MB infection diagnosis	Duration of systemic RCC treatment prior to MB infection diagnosis	Treatment for MB infection	Duration of systemic RCC treatment after MB infection diagnosis	Overall survival	Survival status
1	Yes	Yes	Yes, initiated 4 mo from mRCC diagnosis	36 mo	32 mo (27 mo Pazopanib, 5 mo Sorafenib)	Yes: Ethambutol, INH, rifampin	30 mo (7 mo Sorafenib, 10 mo Axitinib, 3 mo Nivolumab, 10 mo Cabozantinib)	62 mo	Dead
2	Yes	Yes	Yes, initiated at time of mRCC diagnosis	39 mo	29 mo (14 mo Sunitinib, 14 mo Pazopanib, 1 mo Axitinib), followed by 10 mo drug holiday	No	72 mo (18 mo Pazopanib, 50 mo clinical trial HIF-2a inhibitor, 4 mo Nivolumab), 6 mo drug holiday interspersed	117 mo	Dead
3	Yes	No	Yes, initiated at time of mRCC diagnosis	0 mo (but 60 mo from initial RCC diagnosis)	0 mo	No	12 mo (9 mo Pazopanib, 3 mo Nivolumab)	At least 12 mo	Unknown
4	No	No	No	0, diagnosed at same time	NA	No	NA	2 mo	Dead
5	Yes	No	Yes, initiated at time of mRCC diagnosis	NA – patient diagnosed with infection prior to RCC diagnosis	0 mo	Yes: Unknown therapy	24 mo (Nivolumab)	24 mo	Dead

TABLE 3 | Treatment of mRCC and MBI data. Key: INH – isoniazid, TB – tuberculosis, LTBI – latent tuberculosis infection, mo – months, MB – mycobacterial, NA – not applicable.

and experimental drugs. Two patients enjoyed durations of 32 and 39 months of systemic therapy with TKIs prior to their MBI diagnosis. Four patients received systemic therapies subsequent to their infection diagnosis, with durations ranging from 24 months to 72 months of therapy. One patient previously had pulmonary tuberculosis, two patients were diagnosed with an MBI at the same time as their mRCC diagnosis, and two patients were diagnosed after their

it is unknown whether there is a positive impact for patients with mRCC. While the cohort of patients in this retrospective analysis was small, patients who developed MBI after mRCC diagnosis seemed to have prolonged PFS and OS.

Within the past decade, there have been vast improvements in mRCC treatment options that prolong life and improve quality of life. The median overall survival (mOS) for advanced and metastatic RCC is reported to be

compared with that of the general population of patients with mRCC and demonstrated longer duration of treatment and disease stability following MBI.

The beneficial results seen in patients who were diagnosed with MBI after diagnosis of RCC may be confounded by other factors. Two patients had long treatment responses to TKIs prior to MBI, which reflects favorable biology of RCC; however, it is noteworthy that

both these patients also had brain metastases, which normally would confer poor prognosis. Patient 5 harbored sarcomatoid features and had poor risk disease, yet she an OS of 24 months, much longer than what would be expected for sarcomatoid RCC.

We had predicted that patients with MBI would respond better to immune checkpoint inhibitors based on their increased immune system activation, but interestingly patients in this cohort received PD-1 checkpoint inhibitor therapy for only a short time prior to progressing. Patients 1 and 2 had the most impressive OS, at 62 and 117 months, and had prolonged responses to VEGFR TKI therapies both prior to and after MBI. Additionally, these patients maintained excellent control of their mRCC in the chest, but had recurrences in the brain, requiring local treatments. It is interesting to consider if the infection perhaps conferred some benefit systemically that is unable to cross the blood brain barrier into the central nervous system (CNS) to then affect the same benefit.

There are no existing models to demonstrate the mechanism of this possible benefit. The pathogenesis of pulmonary disease due to *M. tuberculosis* is well understood, and the pathogenesis of other MBI are presumed to have similarities to that of tuberculosis²⁰. The cellular response first involves alveolar macrophages, where the mycobacterium is taken up and proliferates within their vacuoles as an intracellular pathogen via immune-evasion mechanisms. These macrophages activate T lymphocytes and NK cells via cytokine release, and the mycobacterial antigens are also presented on macrophages to T lymphocytes leading to subsequent expansion of T lymphocyte clones. IL-2, IL-12, TNF-alpha, and IFN-gamma are major players in the immune response to MAC, and IL-6, IL-10, and TGF-beta are important in modulating the immune response²¹.

TGF-beta, a regulator of the immune response, is also involved in upregulation of VEGF and angiogenesis^{22, 23}. During MBI, not only is TGF-beta released locally for regulation and suppression of the immune system in MBI, but there are higher levels of TGF-beta found systemically in the blood of patients with MBI^{24, 25}. Theoretically, if TGF-beta is elevated systemically to mitigate the proinflammatory cytokines released in response to the infection, then VEGF and resultant angiogenesis should also be upregulated throughout the body and throughout sites of metastatic disease. This upregulation could possibly then make the tumor cells of the RCC more susceptible to our standard anti-angiogenic therapies with TKIs which inhibit VEGF and TGF-beta pathways²⁶. In support of this hypothesis, Patients 1 and 2 had prolonged responses (27 and 18 months, respectively) to TKI therapy following their diagnoses of MBI, even when the TKI was used as third- and fourth-line therapies and beyond, when we might expect time to progression on these drugs to be quite low. Another hypothetical mechanism that could explain a local protective response would be related to the local damage and relative hypoxia induced by a mycobacterial pulmonary infection. Hypoxia should locally upregulate hypoxia-inducible transcription factors (HIFs), which are integral in the subsequent upregulation of VEGF-A and angiogenesis²⁷⁻²⁹. Again, this may then allow the RCC to be more susceptible to TKIs, as seen in Patients 1 and 2, and could also explain Patient 2's remarkable duration of response of 50 months to the HIF-2a inhibitor he received as part of a phase I clinical trial. The role of TGF-beta, HIF, VEGF, and angiogenesis, and the response to therapies directed against angiogenesis could also help to explain why the patients with history of MBI prior to their RCC diagnosis did not derive the same benefit from TKI therapy as the patients

who already had RCC at time of infection diagnosis.

This series shows a trend toward improved outcomes in patients who experienced an MBI during the time of treatment for mRCC, although we cannot draw generalizable conclusions due to the small cohort of patients. By expanding our search to multiple institutions, one would expect a broader distribution of patients with both favorable and unfavorable tumor characteristics and clinical characteristics, and a wider range of patients who experienced their MBI before, simultaneously, and after mRCC diagnosis. It would be interesting to assess whether a benefit of MBI is seen across all risk stratifications, different histologies, treatment modalities, etc. Additional lines of query could then include whether other types of infections have impact on outcomes in mRCC, or whether a protective benefit against development of metastases could be seen in the brain if the MBI was serious enough to involve the CNS (as in the case of tuberculous meningitis or tuberculoma).

Conclusions

Renal cell carcinoma is a common cancer, and tuberculous and non-tuberculous MBI are among the most common infections throughout the world; the intersection of these two diagnoses brought into question the impact of the latter on the former. This series of five patients within a single institution revealed that simply carrying a diagnosis of both mRCC and MBI did not improve OS, but suggested that the development of MBI during ongoing malignancy had an impact on response to TKI therapy and improved OS. Additional consideration of these findings within a larger cohort of patients is necessary, as it may offer further insight into the issue, even assisting in prognostication of disease outcomes for individuals or prediction

of their responsiveness to specific therapies.

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EDITOR'S MEMO (continued from Page 94)

which creates uncertainty as to how to proceed with future cancer clinical trials. Even with those trials that are not terminated, the outbreak changed the way cancer clinical trials are conducted and reported, with potentially lasting implications due to pandemic-related logistical barriers.

While COVID-19 has complicated the treatment of cancer patients and continuing clinical research, it has also spurred creative solutions especially remote or decentralized clinical trials. The newly developed recommendations in light of COVID-19 impact could improve the overall trial process and also serve as a silver lining to the trials in the long term. Several measures including the leveraging of telehealth, use of e-signatures, remote monitoring of trials, and outside lab testing are effectively being exploited to make the best out of the situation. Other changes include delaying recruitment, implementing COVID-19 screening procedures, expediting changes in trial protocol and exploring alternative drug administration methods are already in place. The NCI also has released guidance specific to cancer clinical trials, including recommendations on the overnight shipping of medications to trial participants. Amid the outbreak, the widespread use of telemedicine has emerged as one of the positive changes to clinical trials. Some studies involving patients with cancers indicate that telehealth was not only associated with a higher quality of life and less depression and distress compared with usual care but also can be just as effective as in-person meetings.

In the past decade alone, breakthroughs in immunotherapy including anti-PD-1 and anti-PD-L1 based agents have revolutionized the cancer management. However, now there may be a lag before this development can take off post COVID-19 pandemic as the pandemic threatens to set back the pipeline of such oncology agents by several years. Currently, it still remains unclear whether immune checkpoint inhibitors and other immunotherapies worsen or benefit the outcomes in patients who have cancer and COVID-19 infection. Recent study

conducted at the MSKCC highlighted that there was an association of immune check inhibitors with increased ICU admission rate, but did not increase the risk of mortality¹. Given the limited and conflicting data on the benefit/risk of ICI therapies to patients with cancer in the pandemic setting, oncologists are left alone to carefully assess the risks and benefits managing ICI therapy on a case-by-case basis. Physicians should weigh the advantages of relapse-free survival benefit against the COVID-19 associated risks. Given the lack of robust clinical data, caution must be taken while continuing ICIs in patients with cancer who may be affected by COVID-19. It seems reasonable to suggest in patients with metastatic disease without COVID-19, ICI therapy may not be withheld. Multicenter retrospective studies will be required to provide more definitive guidance on the role of immune checkpoints in COVID-19 infection for clinicians.

Ever since the outbreak, the most inspiring aspect is that oncologists and their team members showed incredible resilience and resolve to deal with the unforeseen crisis, by exploiting timely strategies including adopting telehealth, workflow reorganization, and safety processes enhancements at their clinics. It is imperative for clinicians and researchers to learn and continuously adapt to the new standards of cancer care and risk management through implementing reforms, with the hope that we can find a silver lining in improving research efficiency and outcomes in the face of the pandemic crisis.

Reference: 1. [Determinants of COVID-19 disease severity in patients with cancer. Robilotti EV et al. Nat Med. 2020 Aug; 26\(8\):1218-1223.](#)

Robert A Figlin, MD
Editor-in-Chief



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Now enrolling!

A clinical trial is exploring adjuvant immuno-oncology agents for RCC patients

Bristol Myers Squibb is currently conducting a clinical trial exploring immuno-oncology (IO) agents for early-stage, high-risk renal cell carcinoma (RCC): CheckMate 914.

CheckMate 914 is a randomized, phase 3 clinical trial evaluating adjuvant nivolumab alone or in combination with ipilimumab in patients who underwent radical or partial nephrectomy and who are at high risk of relapse.



Timing is critical

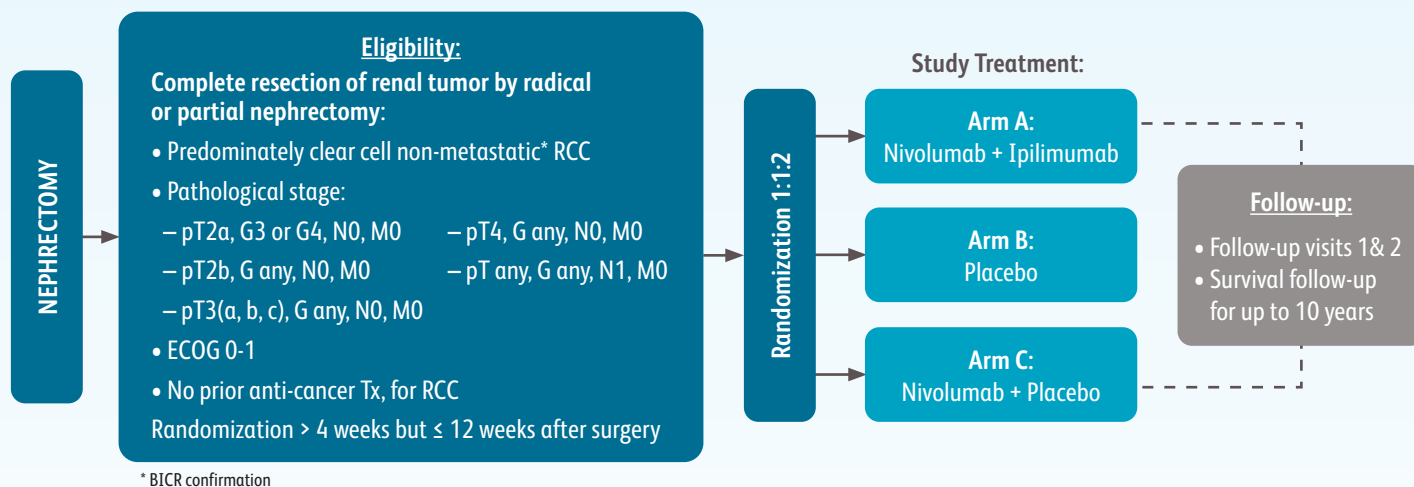
Research post-surgery plans **before** surgery happens. For this clinical trial, randomization must occur between 4 and 12 weeks from the date of nephrectomy



Exploring beyond observation

This study seeks to investigate the role of an IO agent compared to the current standard of care (observation)

CHECKMATE 914 Study Design



To find out if your patients are eligible for this trial, learn more at [BMSSStudyConnect.com](https://www.bmsstudyconnect.com).

Reference: Data on file. Clinical protocol CA209-914. Princeton, NJ: Bristol-Myers Squibb Company, 2020.

STUDY CONNECT
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 **CheckMate 914**
CHECKpoint pathway and
nivolumab clinical Trial Evaluation

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Dissecting the role of lymphadenectomy in the management of renal cell carcinoma: past, present, and future

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ABSTRACT

Lymph node involvement in renal cell carcinoma (RCC) portends a poor prognosis. However, the role of lymph node dissection (LND) at the time of tumor resection is not fully understood. Conflicting data have been published regarding the survival implications of LND during RCC surgery, and the optimal patient population for which LND might be beneficial has yet to be identified. Based on recent data characterizing the outcomes of node-positive RCC, some have advocated for revising the current staging guidelines to better reflect these findings. Given the paucity of high-quality evidence supporting or refuting the routine use of LND in RCC, further research is needed to shed light on this important topic. There are a number of ongoing clinical trials evaluating the role of perioperative (neoadjuvant and adjuvant) systemic therapy, which include patients with node-positive RCC, and will serve to guide changes in treatment practices for this patient population moving forward.

KEYWORDS: • Renal Cell Carcinoma • lymphadenectomy • lymph node dissection • kidney cancer • survival •

INTRODUCTION

Renal cell carcinoma (RCC) is one of the most common solid organ malignancies, with over 74,000 new cases and 15,000 deaths anticipated in the United States in 2020 alone¹. Staging of RCC allows clinicians to characterize disease based on similar survival outcomes, which further aids in prognostication, selection of optimal treatment modalities, and clinical trial eligibility. The criteria for RCC staging as outlined by the American Joint Committee on Cancer (AJCC) are highlighted in Table 1².

For many urologic malignancies, concurrent lymph node dissection (LND) at the time of primary tumor resection offers essential treatment and diagnostic value. Removing malignant lymph nodes may significantly reduce a patient's overall tumor burden. Furthermore, detection of positive lymph nodes critically informs the probability of disease risk stratification

and the requirement for additional treatments. For example, immediate administration of androgen deprivation therapy for node-positive prostate cancer, which was detected by pelvic LND, has demonstrated clinically significant survival benefits³. Patients with pathologically node-positive bladder cancer after pelvic LND achieve a greater survival benefit from adjuvant chemotherapy compared to node-negative patients⁴⁻⁶. Similarly, adjuvant chemotherapy has been shown to lower recurrence rates among nonseminomatous germ cell testis cancer patients who have positive nodal disease after retroperitoneal LND⁷.

However, existing literature remains unclear regarding the clinical utility of LND for RCC. The American Urologic Association (AUA) and the National Comprehensive Cancer Network (NCCN) have published contemporary guidelines, but these

recommendations are not supported by strong evidence. The AUA states that LND should be performed only when there is suspicion of lymphadenopathy, as LND could potentially aid in staging⁸, and NCCN guidelines recommend that LND should only be performed when there are palpable or enlarged lymph nodes on preoperative imaging tests⁹. Still, the supporting literature has not identified which patients derive the greatest benefit, if any, from LND. This uncertainty is exacerbated by unpredictable lymphatic drainage patterns of the kidney, as well as the fact that there is no universal template for LND during kidney cancer surgery^{10,11}.

While retrospective studies have shown a survival benefit of LND for RCC^{12,13}, the only randomized clinical trial to have studied LND for RCC, EORTC 30881, showed no oncologic benefit of LND with regards to overall survival, time to progression, or progression-free survival¹⁴. In this review, we consider lymph node positivity in RCC as it relates to staging, outcomes, patient selection for lymph node dissection, and the role of systemic therapy.

Patient Selection for Lymph Node Dissection

Given the uncertainty behind the benefit of LND in treating RCC, fewer urologists have been performing LND over the past decade^{15,16}. In an analysis of 37,279 patients who underwent radical nephrectomy for RCC between 1988 and 2015 selected from the Surveillance, Epidemiology, and End Results (SEER) registry, Kates et al. identified a 63% reduction in LND rates among localized tumors¹⁶. In 2005, LND rates in the US had fallen below 5% for all RCC surgeries¹⁷. This decrease in LND rate can, at

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Stage	8E AJCC ²	Proposed staging		
		Shao <i>et al.</i> ³⁰	Yu <i>et al.</i> ²⁹	Patel <i>et al.</i> ³⁵
I	T ₁ NoMo	1a: T ₁ NoMo	T ₁ NoMo	T ₁ NoMo
		1b: T ₂ NoMo		
II	T ₂ NoMo	T ₃ NoMo	T ₂ NoMo	T ₂ NoMo
III	T ₁₋₂ N ₁ Mo, T ₃ N _{any} Mo	T ₁₋₃ N ₁ Mo, T ₄ NoMo	T ₃ NoMo	T ₃ NoMo
IV	T ₄ N _{any} Mo, T _{any} N _{any} M ₁	T ₄ N ₁ Mo, T _{any} N _{any} M ₁	T ₁₋₃ N ₁ Mo, T ₄ N _{any} Mo, T _{any} N _{any} M ₁	IVa: T ₃ N ₁ Mo, T ₃ NoM ₁ , T ₄ NoMo
				IVb: T ₄ N ₁ Mo, T ₄ NoM ₁ , T ₄ N ₁ M ₁

TABLE 1 | Comparison of AJCC staging groups to other proposed classification schemes. Modified, with permission, from Patel *et al.*³⁵.

least partially, be attributed to the clinical stage migration toward early-stage RCC (i.e. patients who are unlikely to receive LND), which has followed advancements in imaging capabilities since the 1980s¹⁸.

In a retrospective analysis of 110,963 patients with non-metastatic RCC from the National Cancer Database (NCDB), Radadia *et al.* reported that only 11,867 (11%) had LND at time of

surgery¹⁹. Those patients undergoing LND were more likely to have clinically node-positive disease (OR: 18.68, 95% CI: 16.62 – 21.00, $p < 0.01$) and less likely to undergo minimally invasive / robotic surgery (OR: 0.73, 95% CI: 0.64 – 0.77, $p < 0.01$)¹⁹. In this same cohort, however, only 14.8% of patients receiving LND had clinically node-positive disease, suggesting a large majority of patients who received LND had no preoperative evidence of nodal disease¹⁹. In a subsequent analysis of this patient population, Farber *et al.* showed that a disproportionate amount of LNDs were performed for low-stage RCC. Surgeons performed LND in 5% and 23% of patients with pT1 and pT2 RCC, respectively, despite lymph node involvement in only 1.1% and 2.3% of cases, respectively²⁰. This apparent overutilization of LND for lower risk renal tumors likely reflects the ambiguity surrounding guidelines and the lack of strong contemporary evidence for LND

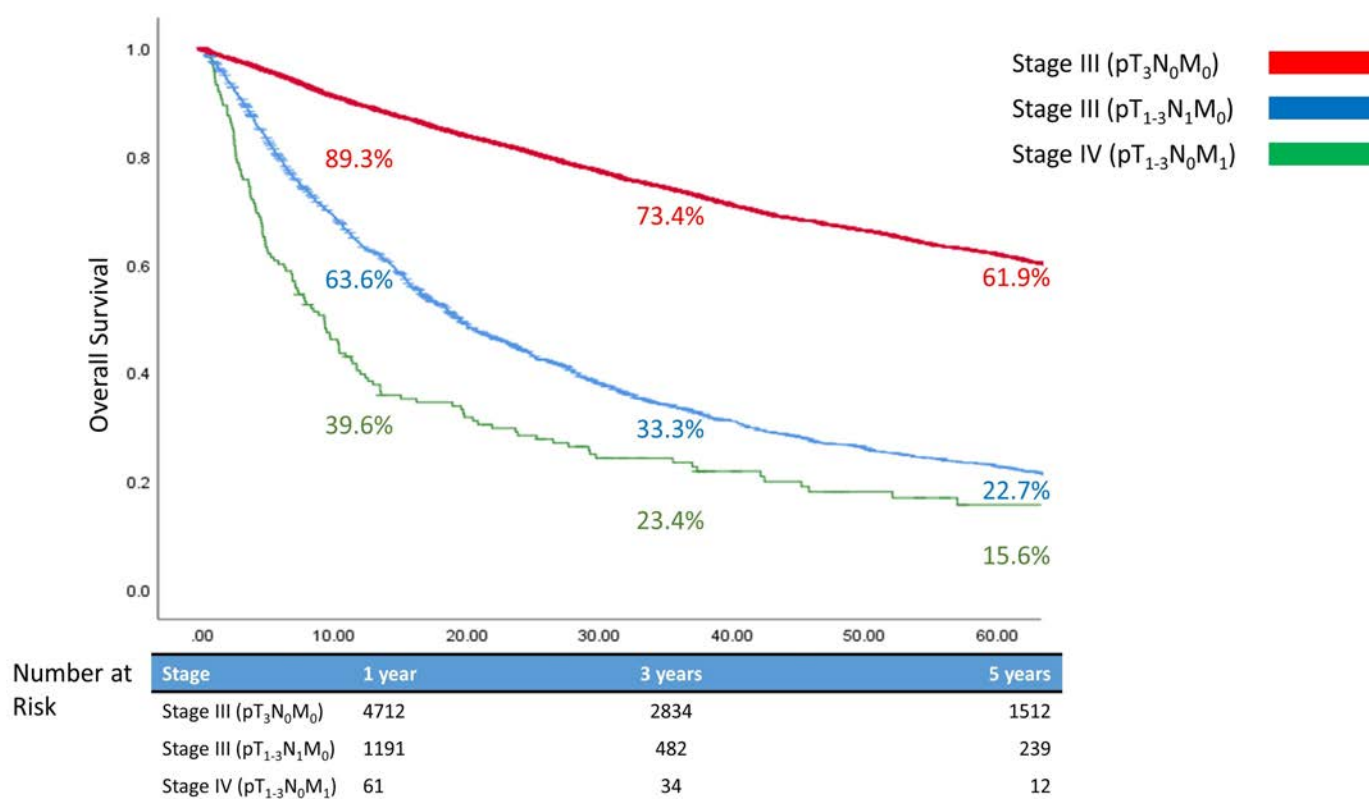


FIGURE 1 | Overall survival of NCDB patients with renal cell carcinoma stratified by American Joint Committee on Cancer stage of disease and lymph node status. Red indicates lymph node-negative stage III disease (pT₃N₀M₀); blue, lymph node-positive stage III disease (pT₁₋₃N₁M₀); green, stage IV metastatic disease (pT₁₋₃N₀M₁). Reproduced, with permission, from Srivastava *et al.*³¹.

implementation.

Part of this ambiguity may reflect limitations in preoperative staging. Determining candidacy for LND currently relies heavily on clinical lymph node (cLN) status and lymph node size, as determined by preoperative imaging^{19,21}. Preoperative computed tomography (CT) and magnetic resonance imaging (MRI) are the primary methods used to detect nodal metastases, but have sensitivities of only 77% and 73%, respectively, and have limited ability to identify nodal micro-metastases²¹. Unpredictable lymphatic drainage of the kidney makes it difficult to identify a consistent template for LND, which may contribute to overlooked nodal disease on preoperative imaging²². Additionally, the correlation between cLN status and pathological lymph node (pLN) status can be difficult to determine. In a retrospective analysis of 2,954 patients with RCC who underwent either partial or radical nephrectomy with LND, only 29% of patients with lymphadenopathy on preoperative CT were confirmed to be pLN positive after LND²³.

Furthermore, in EORTC 30881, only 20% of patients with palpable lymphadenopathy had nodal disease after LND¹⁴. Aside from lymph node size, some have proposed using other imaging findings to determine candidacy for LND, such as evidence of perinephric or renal sinus fat invasion on CT²⁴. Others have proposed utilizing alternative imaging techniques to better identify LND candidates. A pilot study investigating lymphotropic nanoparticle enhanced MRI (LNMRI) showed promising results in diagnosing pLN status, with 100% sensitivity and 96% specificity²⁵. Clearly, current modalities for staging RCC are insufficient for determining cLN and pLN status, and more accurate and reproducible preoperative methods are needed to identify optimal LND candidates.

Outcomes in Node-Positive Disease and Implications for Staging

Prior studies have established that lymph node-positive disease portends worse survival in RCC²⁶. Cancer-specific survival (CSS) in patients with lymph node positivity ranges from 21-38% at 5 years and 11-29% at 10 years, and those patients with positive nodes have near-

Trial	Status	Treatment Compared	Stage for inclusion	Histology	Primary Outcome	Reference
ASSURE	Reported	Sunitinib Vs. sorafenib Vs. placebo	pT1b (G3-4), pT2-4, or pTanyN1	Clear cell or non-clear cell	DFS; no difference	48
S-TRAC	Reported	Sunitinib Vs. placebo	pT3-4	Clear cell only	DFS; improved	49
PROTECT	Reported	Pazopanib Vs. placebo	pT2 (G3-4), pT3-4, or pTanyN1	Clear cell or predominantly clear cell	DFS; no difference	51
ATLAS	Reported	Axitinib Vs. placebo	pT2 or pTanyN1	Clear cell or predominantly clear cell	DFS; no difference, stopped early due to futility	50

TABLE 2 | Reported clinical trials evaluating perioperative or adjuvant tyrosine kinase inhibitors for RCC

ly 8-fold higher risk of mortality compared to those with negative nodes^{27, 28}. Notably, current AJCC staging criteria consider both pT3N0M0 (node negative) and pT1-3N1M0 (node positive) patients to have stage III RCC. However, this common grouping has been studied more closely in recent years. Several studies have proposed modification of current AJCC staging groups, lending support to the role of LND among patients with advanced RCC²⁹⁻³¹. More specifically, these studies note that patients with node-positive Stage III RCC have survival more closely resembling Stage IV patients, including those with metastasis, rather than their node-negative Stage III counterparts. In an institutional retrospective analysis of 4,652 patients with advanced RCC, Yu et al. reported comparable oncologic outcomes between pT1-3N1M0 (Median CSS = 2.8 years, 95%CI: 1.8-4.8 years) and pT1-3N0/xM1 (Median CSS = 2.4 years, 95%CI: 2.1-3.0 years); however, both had distinctly inferior outcomes compared to pT1-3N0M0 patients (Median CSS = not reached, 95% 10.2 – no estimate years)²⁹. Shao et al. conducted an analogous study of 2,120 patients from a single institution which was then validated with over 74,000 patients from the SEER database. The authors noted longer overall survival (OS) for T3N0M0 compared to T1-3N1M0 (72.7% vs 38.1%), similar survival for T1-3N1M0 and T4N0M0 (38.1% vs 36.2%), and greater survival for T1-3N1M0 compared to TanyNanyM1 disease (38.1% vs 12.6%)³⁰. Using the NCDB, Srivastava et al. conducted a retrospective analysis of 8,988 patients with stage III/IV

RCC, which compared patients with pT-3N0M0, pT1-3N1M0, and pT1-3N0M1 disease. The results, depicted in Figure 1, showed greater 5-year OS among patients with pT3N0M0 (61.9%) compared to pT1-3N1M0 (22.7%), and similar OS between pT1-3N1M0 and pT1-3N0M1 (15.6%) disease. Of note, the results of this study also showed node positivity to be predictive of OS among Stage III-IV patients³¹. Similar survival outcomes of pN1 and metastatic RCC suggest that many patients with lymph node involvement may have occult metastases at time of surgery. In a series described by Gershman et al., metastasis-free survival at 1-year was only 37%, and CSS rates were expectedly poor³².

Based on the results of these studies, some have advocated for reclassifying T1-3N1M0 RCC as stage IV instead of stage III³³⁻³⁵. These proposed staging revisions are shown in Table 1. In an era where the precise genomic and epigenetic factors are not entirely understood, cancer staging offers clinical insight into tumor biology based on objective factors. As such, in addition to its prognostic implications, revamping the classification of localized node-positive RCC could potentially better inform treatment modalities and refine eligibility for clinical trials.

Given the mortality associated with nodal disease, one might expect that LND at the time of nephrectomy would offer a survival benefit, however, mixed results have been published on this matter over the past several decades. Early work from Herrlinger et al. showed an OS advantage among patients undergoing complete LND

Trial	Status	Treatment Arms	Stage for Inclusion	Histology	Primary Outcome	Reference
SOURCE	Ongoing	Sorafenib (3 years) vs. sorafenib (1 year) vs. placebo	Leibovich score 3 to 11	Clear cell or non-clear cell	DFS	NCT00492258
EVEREST	Ongoing	Everolimus vs. placebo	pT1b (G3-4) pT2-4 pTanyN1	Clear cell or non-clear cell	RFS	NCT01120249
Checkmate 914	Ongoing	Nivolumab vs nivolumab + ipilimumab vs. placebo	pT2a(G3-4) N0M0 pT2a(Gany) N0M0 pT3(Gany) N0M0 pT4Gany N0M0 pTany(Gany)N1M0	Predominant clear cell histology	DFS	NCT03138512
RAMPART	Ongoing	Durvalumab + tremelimumab vs. durvalumab	Leibovich score 3 to 11	All RCC (except pure oncocytoma, collecting duct, medullary and transitional cell cancer)	DFS and OS	NCT03288532
PROSPER RCC	Ongoing	Nivolumab vs. observation	≥ T2Nx TanyN+ M1 NED	All RCC histology	EFS	NCT03055013
KEYNOTE	Ongoing	Pembrolizumab vs. placebo	pT2(G4 or sarcomatoid)N0M0 pT3-4(Gany)N0M0 pTanyN+M0 M1 NED	Clear cell component +/- sarcomatoid features	DFS	NCT03142334
IMmotion010	Ongoing	Atezolizumab vs. placebo	TanyNanyM0	Clear cell or sarcomatoid	DFS	NCT03024996

TABLE 3 | Ongoing clinical trials evaluating perioperative or adjuvant tyrosine kinase, mTOR inhibitors, and/or checkpoint inhibitors for RCC. RCC: renal cell carcinoma; DFS: disease-free survival; RFS: recurrence free survival; OS: overall survival; NED: no evidence of disease; EFS: event free survival.

compared to those undergoing partial or absent node dissection^{12, 36}. Similarly, other studies found increased OS and CSS among patients with node-positive disease who underwent LND compared to those who did not^{13, 37, 38}. To date, only one prospective, randomized phase 3 trial has assessed the utility of LND in RCC. The EORTC 30881 trial, published in 2009, showed no survival benefit among patients who underwent nephrectomy with LND compared to patients who underwent nephrectomy alone¹⁴. However, multiple limitations to this study make it difficult to interpret and implement the findings of this study for clinical practice. Most notably nearly 70% of the study population had pT1 or pT2 disease, and only 4% of patients in the trial population had nodal metastasis³⁹. Therefore, the majority of patients in the trial were unlikely to benefit from node dissection⁴⁰. EORTC 30881 was also limited in that there was no universal LND template required, and therefore results could have varied significantly based on surgeon, template, and center. Despite these shortcomings, subsequent retrospective studies attempting to clarify the impact

of LND have shown similar results to EORTC 30881^{20, 41-44}. In a study of the NCDB, Farber et al. did not find any survival benefit associated with LND when comparing 11,867 patients with non-metastatic RCC undergoing partial or radical nephrectomy with LND to a propensity-score matched cohort of patients who did not receive LND (OS 34.7 vs. 34.9 months, respectively)²⁰. The NCDB has also been used to emulate the methods of EORTC 30881 using propensity score matching, with results showing no survival advantage of LND, even when adjusted to include a greater proportion of high-risk patients⁴¹.

The Role of Adjuvant and Perioperative Therapy in Node-Positive RCC

While nephrectomy is considered the gold standard treatment for non-metastatic RCC, up to 40% of patients may recur after an extirpative intervention⁴⁵. Recurrence rates can be as high as 80% in those with node-positive disease, with 5-year survival as low as 11-35%^{46, 47}. Thus, exploration of multimodal therapy is vital to addressing the shortcomings of nephrectomy and improving out-

comes in node-positive RCC. Due to the significant risk of progression to metastatic disease, patients with node-positive RCC are prime candidates for early intervention³³.

Thus far, four adjuvant trials that included patients with node-positive RCC have reported their results (Table 2). The ASSURE trial randomized 1,943 patients with completely resected pT1b, pT2-4, or TanyN+ RCC to one of three arms: sunitinib, sorafenib, or placebo, for 54 weeks⁴⁸. The analysis showed no difference in disease free survival (DFS) for either sunitinib or sorafenib compared to placebo (HR 1.02, 97.5% CI 0.85 – 1.23; p=0.8038 and HR 0.97, 97.5% CI 0.80 – 1.17; p=0.7184, respectively)⁴⁸. The S-TRAC trial randomized 615 pT3-4 or TanyN+ to sunitinib or placebo. The results of S-TRAC were more encouraging than those of ASSURE, concluding that patients in the sunitinib arm had significantly longer DFS compared to placebo (HR 0.76, 95% CI 0.59 – 0.98; p=0.03)⁴⁹. The ATLAS trial randomized 724 patients with previously-resected RCC (≥pT2 and/or N+) to axitinib or placebo. On the primary analysis of

DFS, there was no significant difference in the intention-to-treat population (HR 0.87, 95% CI 0.660 – 1.147; $p=0.3211$)⁵⁰. The PROTECT trial randomized 1,538 patients with pT2, pT3, and pT4 disease to pazopanib or placebo. Initially, the dose was set at 800 mg daily, but was later reduced to 600 mg due to significant adverse effects. Interestingly, while the 600 mg group showed no significant reduction in DFS (HR 0.86, 95% CI 0.70 – 1.06; $p = 0.165$), the 800 mg group did (HR 0.69, 95% CI 0.51 – 0.94; $p=0.02$)⁵¹.

Akin to the prior efforts to orchestrate immune-mediated antineoplastic activity through cytokines, checkpoint inhibitors have come to the forefront as a promising therapeutic option for metastatic RCC. In the Checkmate 025 trial, the checkpoint inhibitor nivolumab showed significant improvement in OS with fewer adverse effects when compared to everolimus (HR of death 0.73, 98.5% CI 0.59 – 0.93; $p=0.002$)⁵². Checkmate 214, the landmark phase III trial that compared nivolumab plus ipilimumab versus sunitinib in metastatic RCC, demonstrated improved complete response rate (9% vs 1%) and improved OS for the checkpoint inhibitor arm (HR 0.63, 99.8% CI 0.44-0.89, $p<0.001$)⁵³. Given the success of these agents in the management of metastatic RCC, integrating these therapies as adjuvant therapies may be a logical next step for patients at high-risk for metastatic progression, such as node-positive RCC. However, to date there have been no reported results from trials examining the role of checkpoint inhibitors as adjuvant therapy.

Noteworthy ongoing phase III trials for perioperative/adjuvant therapy are highlighted in Table 3. SORCE (NCT00492258) is an ongoing trial comparing sorafenib 3 years vs. sorafenib 1 year vs. placebo. However, preliminary results presented at European Society for Medical Oncology 2019 showed no significant increase in DFS for patients in the sorafenib arms⁵⁴. Similarly, EVEREST (NCT01120249) is an ongoing clinical trial investigating the potential of the mTOR inhibitor everolimus. The recent success of Checkpoint 025 and Checkpoint 214 in demonstrating clinical utility

of nivolumab and ipilimumab for RCC has led to five ongoing phase III clinical trials to implement checkpoint inhibitors in the adjuvant/perioperative space: Checkmate 914 (NCT03138512) – nivolumab plus ipilimumab vs. versus nivolumab vs. placebo, RAMPART (NCT03288532) – durvalumab plus tremelimumab vs. durvalumab vs. observation, PROSPER RCC (NCT03055013) – perioperative nivolumab vs. observation, KEYNOTE (NCT03142334) – pembrolizumab vs. observation, and IMmotion010 (NCT03024996) – atezolizumab vs. observation. Notably, PROSPER RCC incorporates a neoadjuvant aspect, potentially allowing for translational studies of tissue and sera by comparing pre- and post-nivolumab treated tissue⁵⁵.

There is a significant need to address the limitations of nephrectomy and LND in node-positive RCC. However, there is a dearth of evidence to direct the therapy for those with nodal disease. While 5%-47% of the patient population in the aforementioned trials – ASSURE, S-TRAC, ATLAS, PROTECT, Checkmate 025 and Checkmate 214 – were node-positive, no study completed a subgroup analysis in this population of interest⁴⁸⁻⁵³. It is imperative that investigation into this unique population is included in future trials exploring the role of systemic therapies in the treatment of locally advanced and metastatic RCC.

Conclusions

The presence of pathologic lymph nodes in patients with non-metastatic kidney cancer has crucial prognostic value. Outcomes from several recent studies suggest that revising staging categories may lead to improved prognostication for patients with advanced RCC and have implications for therapy selection and clinical trial participation.

It remains unclear whether LND can be a beneficial surgical option for a select subset of patients with RCC. Much of this uncertainty stems from a lack of level one evidence regarding nodal disease in RCC. However, with several ongoing and upcoming clinical trials that include patients with node-positive RCC, anticipated results may lead to a paradigm shift in the management

of this disease. It is imperative that physicians work to enroll patients in clinical trials in order to gain a better understanding of the complexities of this disease, and ultimately improve the care of our patients.

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HIF-inhibitors in Renal Cell Carcinomas: A Review of Current Trials

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ABSTRACT

Hypoxia is common in solid tumors, due to poorly functional tumor vasculature and rapidly proliferating malignant cells outgrowing their blood supply.¹ Hypoxia-inducible factor 1 (HIF-1) and hypoxia-inducible factor 2 (HIF-2) inhibitors are a new experimental therapy in treating clear cell renal cell carcinomas (RCC)s. There are many clinical trials that have evaluated the inhibition of HIF-1/2 α in human tumors.²⁻¹¹ Non-selective drugs targeting both HIF-1/2 α have shown modest-to-disappointing results to date, but drugs selectively targeting HIF-2 α have shown more promise in both preclinical and early human trials. This paper discusses the mechanisms of HIF-1/2 α inhibitors as well as the current clinical trials studying both direct and indirect targeting/inhibition.

KEYWORDS: Kidney cancer • Renal Cell Carcinoma • Hypoxia inducible factor • HIF-inhibitors • targeted therapy •

INTRODUCTION

Hypoxia is common in all types of solid tumors, due to poorly functional tumor vasculature and rapidly proliferating malignant cells that outgrow their tenuous blood supply. But, the roles that hypoxia-inducible factor 1 (HIF-1) and hypoxia-inducible factor 2 (HIF-2) play in driving the development of clear cell renal cell carcinomas (RCC) are distinct, and have led to the creation of a new class of experimental targeted therapeutics aimed at inhibiting HIF. These new drugs are currently under investigation in several trials. If they gain regulatory authority approval as expected, they are likely to represent a new wave of targeted therapies for RCC.

HIF-inhibitors are HIF-1/2 are heterodimeric proteins that transactivate genes involved in many cancer processes including

cell de-differentiation, genetic instability, pH regulation, invasion/metastasis, glucose metabolism, and resistance to chemotherapy^{2,3}. They are composed of oxygen sensitive α and β subunits, which are activated by hypoxia. They are often over-expressed in cancers due to intratumoral hypoxia as well as genetic mutations in oncogenes and loss-of-function in tumor-suppressor genes. Increased HIF-1 α and HIF-2 α levels are generally associated with treatment failure and increased mortality in cancer patients. Drugs that inhibit HIF create anti-tumor effects by stopping metastasis and resistance to antineoplastic therapies. Clinical trials are now underway to establish how these drugs can affect those with many various cancers, especially renal cell carcinoma.

Molecular Basis

HIF-1 α and HIF-2 α each have two transactivation domains (TAD) on the NH₂-terminal (N-TAD) and COOH-terminal (C-TAD). C-TAD interacts with the p300/CREB-binding protein (CBP) co-activators under hypoxic conditions, and N-TAD stabilizes HIF- α . HIF-1/2 α is degraded through the von Hippel-Lindau protein (pVHL) pathway. Under normal conditions, HIF α is rapidly hydroxylated by prolyl hydroxylase (PHD), which mediates the binding by pVHL, and promotes degradation. Under hypoxia, PHD loses its activity, thus preventing VHL binding and HIF-1/2 α can accumulate.

HIF- α Inhibitors for Cancer Therapy

Since the discovery of the HIF and its mechanisms, researchers have been utilizing downstream VEGF and mTOR pathways to directly and indirectly, target cancer. Targeted therapies that influence multiple mechanisms such as modulating expression, protein synthesis, protein accumulation and degradation, dimerization, and/or DNA binding and transcription by targeting the PI3K/AKT/mTOR pathways or the VEGF pathway

Renal Cell Carcinoma and HIF1/2- α

Renal cell carcinoma (RCC) is the most common kidney cancer in

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TRIAL NAME	CLINICAL TRIAL ID	PHASE	INTERVENTION	PATIENT POPULATION	# OF SUBJECTS EXPECTED	RANDOMIZED	ASSIGNMENT	STATUS	EST COMPLETION	COUNTRIES	SPONSOR
A Phase 1b Adaptive Dose-Finding Study of ARO-HIF2 in Pts with Adv Clear Cell Renal Cell Carcinoma	NCT04169711	1	ARO-HIF2	Adv ccRCC	18	No	Sequential	Recruiting	Mar 30, 2022	USA	Arrowhead Pharma
A Phase 1, Multiple-Dose, Dose-Escalation Trial of PT2385 Tablets, a HIF-2a Inhibitor, in Pts with Adv Clear Cell Renal Cell Carcinoma	NCT0293980	1	PART 1: PT2385 PART 2: PT2385 in combination with nivolumab PART 3: PT2385 in combination with cabozantinib	Adv ccRCC	110	No	Single Group	Active, not recruiting	Nov 30, 2021	USA	Peloton Therapeutics
A Trial of PT2977 in Combination with Cabozantinib in Pts with Clear Cell Renal Cell Carcinoma	NCT03634540	2	Cohort 1: PT2977 in combination with cabozantinib in pts who have not received prior systemic therapy for ccRCC Cohort 2: PT2977 in combination with cabozantinib in pts who have not received prior immunotherapy & no more than 2 prior treatments	Adv ccRCC	118	No	Parallel	Recruiting	Aug 14, 2023	USA	Peloton Therapeutics
An Open Label Phase 2 Study to Evaluate PT2385 for the Treatment of Von Hippel-Lindau Disease-Associated Clear Cell Renal Cell Carcinoma	NCT03108066	2	PT2385	VHL associated ccRCC	25	No	Single Group	Active, not recruiting	Jun 15, 2021	USA	Peloton Therapeutics
A Phase 1, Multiple-Dose, Dose-Escalation and Expansion Trial of PT2977, a HIF-2α Inhibitor, in Pts With Adv Solid Tumors	NCT02974738	1	Part 1A: PT2977 for adv solid tumors Part 1B: PT2977 for adv ccRCC Part 2A: PT2977 for other specified solid tumors Part 2B: PT2977 for recurrent GBM who have been previously treated with radiation therapy and temozolomide	Adv ccRCC, Adv solid tumors, glioblastoma	125	No	Single Group	Active, not recruiting	Apr 14, 2023	No Locations Provided	Peloton Therapeutics
Proof of Concept for Lenvatinib and Everolimus Prior to Nephrectomy in Eligible Pts with Local and Metastatic Renal Cell Carcinoma (RCC)	NCT03324373	1	Lenvatinib & Everolimus prior to cytoreductive nephrectomy	Local and metastatic RCC	15	No	Single Group	Recruiting	Apr 30, 2021	USA	University of Iowa Hospitals and Clinic, Eisai Inc
Phase 2 Study of MK-6482 in Participants with Adv Renal Cell Carcinoma	NCT04489771	2	Dose A: Standard dose of MK-6482 Dose B: Higher dose of MK-6482	Adv RCC with clear cell component	150	Yes	Parallel	Recruiting	Oct 4, 2025	USA, Israel	Merck
An Open-label, Randomized Phase 3 Study of MK-6482 Versus Everolimus in Participants with Adv Renal Cell Carcinoma That has Progressed After Prior PD-1/L1 and VEGF-Targeted Therapies	NCT04195750	3	Experimental: 120 mg of MK-6482 orally once daily Active Comparator: 10 mg Everolimus orally once daily	Adv RCC	736	Yes	Parallel	Recruiting	Sep 17, 2025	USA and others*	Merck

Table 1 | Selected Current Trials of HIF-inhibitors in RCC Patients

adults and accounts for 3% of all malignancy, with more men than women being affected. Surgical resection, when feasible, is recommended as a potentially curable option, but many patients with advanced and metastatic RCC have unresectable disease. Also, approximately one third of patient who undergo potentially curative resection of RCC develop a recurrence. In these cases, systemic therapy with immunotherapy, targeted therapies, or combinations of these has become standard of care to delay disease progression and improve survival time.

Clear cell RCC can develop sporadically when the VHL protein is inactivated. Most sporadic ccRCCs having somatic inactivation of both VHL alleles leading to loss of function of the VHL tumor suppressor protein (pVHL). About 60–80% of ccRCC have either loss-of-function mutations in the VHL gene, chromosomal abnormalities on chromosome 3p25 at the VHL locus, or hypermethylation of the VHL promoter.

As briefly discussed earlier, VHL also works to decrease HIF-1/2 α during normoxia. When VHL is lost, there is increased activation of HIF-1/2 α even under normoxic conditions. This can be the result of hereditary mutations as seen in Von Hippel Lindau Syndrome, due to exposure to toxins, or as is often the case through sporadic mutations. A few studies have investigated the polymorphisms in the HIF-1/2 α gene and found that an increase in many haplotypes activated by HIF- α in those with RCC.^{5,6} There are also multiple studies that confirm a direct increase in HIF-1/2- α expression in those with RC.^{5,6} Clear cell RCC was found to have the highest expression levels of HIF-1/2 α .⁵

A clinical trial entitled “Imaging Correlates of Renal Cell Carcinoma Biological Features” is currently analyzing RCC tumors in patients with >3cm mass. These patients will undergo contrast-enhanced magnetic resonance-Fluorodeoxyglucose-positron emission tomography (MR-FDG-PET) scans. The tumors will also be tested and undergo biomarker assessment for HIF-1/2 α . The primary outcome is to evaluate HIF activation by examining both imaging and tumor tissue.

HIF1/2- α Inhibitors and Renal Cell Carcinoma Clinical Trials

There are many clinical trials that have evaluated the inhibition of HIF-1/2 α in human tumors.⁷⁻¹⁶ Given the driving mechanism of HIF-1/2 α and the development of ccRCC, there has been much work in recent towards the development on HIF inhibitor therapy in the clinical setting. Non-selective drugs targeting both HIF-1/2 α have demonstrated modest-to-disappointing results to date, but drugs selectively targeting HIF-2 α have shown more promise in both preclinical and early human trials.

One of the first major positive human studies of these agents was presented at the 2020 Genitourinary Cancers Symposium. The phase I/II study of HIF-2 α inhibitor MK-6482 enrolled 55 patients in the dose expansion cohort. All patients had previously received at least one line of systemic therapy for advanced RCC. The study found an overall response rate of 24% with 13 confirmed partial responses. Thirty-one patients (56%) had SD, for a disease control rate (CR+PR+SD) of 80%. The drug was found to have an acceptable toxicity profile.¹⁷

Selected Ongoing HIF-inhibitor Clinical Trials in RCC

Several ongoing clinical trials are examining HIF-inhibitors in ccRCC. The study, “*ARO-HIF2 in Patients With Advanced Clear Cell Renal Cell Carcinoma*” is evaluating the safety and efficacy of ARO-HIF2, which is a HIF-2 α inhibitor, as well as determining the recommended Phase 2 dose in the treatment of patients with advanced ccRCC. The study is recruiting participants with histologically confirmed locally advanced or metastatic ccRCC that have progressed during or after two prior therapeutic regimens which must include VEGF-targeted therapy and an immune checkpoint inhibitor therapy. The participants must have an ECOG performance status 0 or 1, estimated life expectancy of longer than 3 months, and adequate organ function at screening.¹⁸

Another institution is also evaluating another HIF-2 α inhibitor, PT2385, to define the maximum tolerated dose (MTD) and the recommended phase 2 dose in patients with advanced ccRCC, as well as the MTD in combination with nivolumab or cabozantinib. This study is entitled, “*A Phase 1, Dose-Escalation Trial of PT2385 Tablets In Patients With Advanced Clear Cell Renal Cell Carcinoma*.” Inclusion criteria in their trial include participants who have locally advanced or metastatic ccRCC and progressed during treatment with at least one and no more than three prior systemic treatment regimens, and must have received at least one but not more than two prior anti-angiogenic therapy regimens, and must have received at least one VEGFR targeting tyrosine kinase inhibitor. The study is active and enrolling patients at the time of this writing.¹⁹

An additional phase II clinical trial called “*A Trial of Belzutifan (PT2977, MK-6482) in Combination With Cabozantinib in Patients With Clear Cell Renal Cell Carcinoma (ccRCC)*” is evaluating another HIF-2 α inhibitor, PT2977/MK-6482 also known as belzutifan in combination with cabozantinib, with a primary outcome of ORR in patients with advanced ccRCC. Secondary outcomes include PFS, duration of response (DOR), time to response (TTR), and OS. Participants must have locally advanced or metastatic RCC with predominantly clear cell subtype, at least one measurable lesion as defined by RECIST version 1.1, ECOG 0-1, adequate organ function, and cohort 1 must have not received prior systemic therapy for advanced or metastatic ccRCC while cohort 2 must have received prior immunotherapy and no more than two prior treatments. The study is currently recruiting participants.²⁰

This company is also evaluating ORR in VHL disease-associated ccRCC in VHL patients treated with the oral HIF-2 α inhibitor PT2385 through the trial, “*PT2385 for the Treatment of Von Hippel-Lindau Disease-Associated Clear Cell Renal Cell Carcinoma*.” Participants must have at least 1 measurable ccRCC lesion and no solid ccRCC tumors greater than 3.0 cm, based on radiologic diagnosis. Patients may have VHL disease-associated lesions in other organ systems and had a diagnosis of VHL based on germline VHL alteration. The study is active and but currently recruiting.²¹

Furthermore, they are conducting an additional trial, “*A Trial of Belzutifan (PT2977, MK-6482) Tablets In Patients With Advanced Solid Tumors*.” PT2977 assess’ the MTD and the recommended phase 2 dose in patients with advanced

solid tumors and once determined, expanded to patients with advanced ccRCC, other specified solid tumors, up to 3 different tumor types, including glioblastoma multiforme (GBM). Participants must have a diagnosis of locally advanced or metastatic solid tumor, with a life expectancy of 6 months or more, with adequate organ function. The study is active.²²

Another institution is evaluating different doses of belzutifan (PT2977/MK-6482) in a randomized phase II study of RCC patients: “*A Study of Belzutifan (MK- 6482) in Participants With Advanced Renal Cell Carcinoma (MK-6482-013)*.” Patient are randomized to receive a higher doses or the standard dose with a primary outcome of ORR. Secondary outcomes include PFS, DOR, and clinical benefit rate (CBR). Inclusion criteria includes participants who have a histologically confirmed diagnosis of locally advanced/metastatic RCC with clear cell component, measurable disease per RECIST 1.1 as assessed by BICR, have progressed on or after having received first-line systemic treatment for locally advanced or metastatic RCC with prior anti-PDL 1 therapy plus anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA4) combination OR anti-PD-1/ L1 plus a VEGF tyrosine kinase inhibitor combination, and have received no more than 3 prior systemic regimens for a locally advanced or metastatic RCC. This study is still recruiting participants.²³

They also studied a large (736 patients), randomized phase III study they are conducting is being done to compare belzutifan to everolimus. This is called, “*A Study of Belzutifan (MK-6482) Versus Everolimus in Participants With Advanced Renal Cell Carcinoma (MK-6482-005)*.” The primary

outcomes are PFS and OS in patients with advanced RCC. Secondary outcomes are ORR, DOR, number who experienced adverse events, number who discontinued study due to adverse events, time to deterioration in health-related quality-of-life, time to deterioration in physical functioning, and time to deterioration in disease symptoms. Participants must have unresectable, locally advanced or metastatic ccRCC, had disease progression on or after having received systemic treatment for locally advanced or metastatic RCC with PD-1/L1 checkpoint inhibitor and VEGF-TKI in sequence or in combination, have received no more than 3 prior systemic regimens for locally advanced or metastatic RCC, and have adequate organ function. This study is still recruiting. This trial could provide greater clarity on the utility of direct inhibition of HIF- α 2 rather than indirect inhibition of HIF-1 α through the mTOR pathway.²⁴

Lastly, there is a large (708 subjects), randomized trial of belzutifan in combination with lenvatinib or cabozantinib is expected to begin recruiting patients in November 2020. This is entitled, “*A Study of Belzutifan (MK-6482) in Combination With Lenvatinib Versus Cabozantinib for Treatment of Renal Cell Carcinoma (MK-6482-011)*.”²⁵

Discussion

Inactivation of the VHL gene is a hallmark of ccRCC that results in HIF overactivation and upregulations of angiogenic pathways. The last decade and a half has brought unprecedented treatment options for advanced RCC, mainly focused around anti-angiogenic targeted therapies and immunotherapies, and more recently, combinations of

these. Despite great progress, most patients with advanced RCC still develop resistance to these drugs, necessitating the development of novel therapies for these patients.

HIF-inhibitors represent an emerging class of targeted therapies that will likely be approved for the treatment of advanced RCC. By targeting the underlying molecular driver of clear cell RCC, these drugs provide a unique mechanism of action. The number of treatment options in advanced RCC continues to grow with new combinations of immunotherapies and targeted therapies dominating the treatment landscape. In which clinical scenarios and in what potential combinations HIF-inhibitors will be most useful is yet to be determined. Data from many ongoing studies are expected to emerge during the next couple of years and more studies are anticipated.

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Academic Mentorship: Choosing the Right Research Mentor(s)

Nirmish Singla, MD, MSCS¹

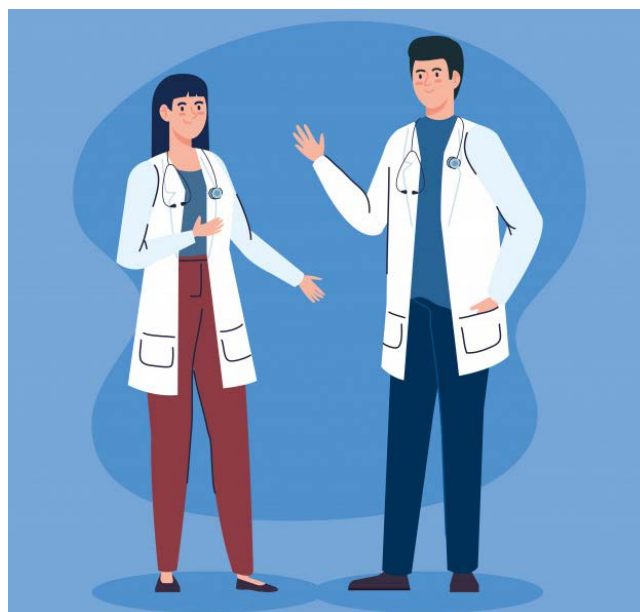
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Selecting an academic mentor is not a trivial process and warrants close attention given the potential influence on one's research interests and career trajectory. While finding a mentor who is accomplished—academically productive and prominent in the field of kidney cancer—is preferred, this should not serve as the sole factor in selecting a mentor¹. Other important factors to consider in choosing the ideal mentor include finding someone who is:

- Respected: has good relations with others in the field
- Trusted: has a track record of successful mentoring in kidney cancer
- Accessible: has time for mentees and meets with them regularly
- Invested: shares interest and enthusiasm in mentees' work and in developing their careers
- Funded: can provide logistical support and resources

A mentor should also serve as an advocate for mentee visibility and promotion in the form of conference presentations, coauthorship on manuscripts, and award nominations. Mentors should provide men-

tees with guidance, intellectual input, and thoughtful critique of their work. By constantly challenging their mentees, mentors should strive to facilitate mentees in their transition to their next career phase.



Successful mentorship is bidirectional, however, and mentees play a critical role that cannot be overlooked in the reciprocal mentor-mentee relationship². Mentees must show self-awareness and be cognizant of their goals, skills, and weaknesses. Mentees should prepare adequately for every meeting with their mentors, ideally by crafting a structured agenda, and demonstrate investment in

the research opportunity by reading, addressing weaknesses, and meeting or surpassing mentor expectations. Furthermore, mentees should take an active role in learning how to mentor others in preparation for transitioning to the next phase of their careers³.

Finally, as kidney cancer research is largely multidisciplinary, mentees should not feel limited to only one mentor. Co-mentorship models are becoming increasingly common and offer multiple advantages. Aside from integrating varied backgrounds and experiences, co-mentorship models may enable mentees to learn about another field and may increase the impact of both manuscripts and grant applications in kidney cancer.

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Disclosures: None

Kaelin Delivers A Keynote Lecture On The Future Of The Treatment Paradigm In VHL Disease-Associated RCC at IKCS 2020 Virtual Conference.

William G. Kaelin Jr, MD, a co-recipient of the 2019 Nobel Prize in Physiology or Medicine, Sidney Farber Professor of Medicine, Dana-Farber Cancer Institute and Harvard Medical School, and an investigator at Howard Hughes Medical Institute, delivered a keynote address for the International Kidney Cancer Symposium (IKCS 2020). Dr. Kaelin spoke of recent investigation on effective treatment to target von Hippel-Lindau (VHL) disease-associated renal cell carcinoma (RCC)¹. “Inactivation of VHL is not sufficient for renal carcinogenesis, even if it is an initiating event. In sporadic clear cell RCC, however, VHL inactivation is the initiation event and should be targeted. HIF2 inhibition is both necessary and sufficient for VHL tumor suppression. We think HIF-2 is the driver, or oncoprotein, in VHL-associated renal cell carcinoma cells and, if anything, HIF-1 seems to act as a tumor suppressor and is frequently lost in such tumors,” Kaelin said.

“You can start to dream what an eventual kidney cancer curative combination will look like. I suspect that it will contain a VEGF inhibitor, an immune checkpoint inhibitor, maybe a HIF-2 α inhibitor, maybe a CDK4/6 inhibitor, and maybe even a MET inhibitor,” said Kaelin. Once, p53 was believed as an important target in these patients, however research has revealed that an intact p53 pathway is not essential for clear cell RCC HIF2-dependence, and TP53 knock-out doesn’t alter PT2399 sensitivity of OSRC2 cells. “We no longer think p53 status is a biomarker for HIF2 dependence,” said Kaelin.

Though single agent TKIs such as bevacizumab (Avastin), sunitinib (Sutent), sorafenib (Nexavar), axitinib (Inlyta), pazopanib (Votrient), cabozantinib (Cabometyx), and lenvatinib (Lenvima) are indicated for RCC treatment, their use as single agents do not lead to responses in all patients, and in those who do, they eventually relapse.

Studies demonstrated that HIF-2 inhibitors alone did not generate responses in all patients. VHL -/- RCC is hypersensitive to the MET ligand hepatocyte growth factor/scatter factor in RCC, emphasizing that MET depletion preferentially kills VHL-/- cells, emphasized Kaelin. For example, the dual MET/VEGF inhibitor cabozantinib demonstrated an improvement in overall survival (OS) compared with everolimus (Afinitor), with a median OS of 21.4 months (95% CI, 18.7–not estimable) with cabozantinib and 16.5 months with everolimus (95% CI, 14.7–18.8), leading to a 34% reduction in the risk of death (HR, 0.66; 95% CI, 0.53–0.83; P = .0003).²

CRISPR-based lethal screens and utilizing CDK4/6 could be other synthetic lethality methods which appears to be HIF-independent. In an orthotopic VHL-/- kidney cancer mouse model, the CDK4/6 inhibitor palbociclib (Ibrance) was found to prolong survival, Kaelin added. Beyond its potential use in combination with HIF-2 α inhibitors, CDK4/6 inhibitors could also be used as a way to enhance immunotherapy in solid tumors. “I think we might learn something from our friends in the world of breast cancer, because they already learned that combining tamoxifen with a CDK4/6 inhibitor is a good thing to do, and maybe that’s because when you add an ER agonist you lower cyclin D1 transcription, and cyclin D1 is then the partner for CDK4/6, which you’re now going to inhibit with a small molecule. Maybe we can do something analogous in kidney cancer by combining PT2399 with a CDK4/6 inhibitor at least for those tumors that are still HIF2 dependent,” Kaelin elaborated.

The most recent data, presented at the 2020 ASCO Virtual Scientific Program, showed that the HIF-2 α inhibitor MK-6482 led to favorable efficacy and tolerability in patients with VHL disease-associated RCC.

In a phase 2 study (NCT03401788) in patients with VHL disease who have at least 1 measurable RCC tumor, did not receive prior systemic anticancer therapy, did not have metastatic disease, and had an ECOG performance status of either 0 or 1, investigators evaluated the efficacy of MK-6482, HIF-2 α inhibitor. Results showed that treatment with MK-6482 led to a confirmed objective response rate (ORR) of 27.9% (95% CI, 17.1–40.8), which comprised 17 partial responses (PRs).³ 43 patients (70.5%) achieved stable disease with the HIF-2 α inhibitor. At 52 weeks, the progression-free survival (PFS) rate was 98.3%.⁴ The HIF-2 α inhibitor also showed promising single-agent activity in patients with heavily pretreated clear cell RCC⁵. Based on these data, the FDA granted a break-

through therapy designation to MK-6482 for the treatment of patients with VHL disease-associated RCC who have nonmetastatic tumors of less than 3 centimeters, unless immediate surgery is necessitated.

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The FDA Granted A Priority Review To Nivolumab Plus Cabozantinib In Advanced Renal Cell Carcinoma.

The FDA has granted a Priority Review designation to supplemental application for the nivolumab (Opdivo) plus cabozantinib (Cabometyx) combination for the treatment of patients with advanced renal cell carcinoma (RCC)¹. The designation was granted based on data from the phase 3 pivotal CheckMate-9ER clinical trial (NCT03141177). This trial demonstrated that the combination reduced the risk of disease progression or death by 49% versus sunitinib (Sutent) in treatment-naïve patients with advanced RCC, with a median progression-free survival of 16.6 months versus 8.3 months, respectively (HR, 0.51; P < .0001).² Additional findings showed that, at a median follow-up of 18.1 months, the median overall survival was not reached in either arm, and there was a 40% reduction in the risk of death with the combination (HR, 0.60; P = .0010).

The ORR was 55.7% with the combination compared with 27.1% with sunitinib (P < .0001). In the nivolumab/cabozantinib arm, the complete response (CR) rate was 8.0%, and the partial response (PR) rate was 47.7%, while 32.2% of patients had stable disease (SD). In the sunitinib arm, CRs occurred in 4.6% of patients, PRs in 22.6%, and SD in 42.1, while 13.7% had PD and 17.1% were not evaluable/assessed.

More than 50% of patients in the combination arm required a dose reduction of cabozantinib due to adverse events (AEs). The most common any-grade and high-grade treatment-related AEs (TRAEs) appeared similar between the 2 arms. TRAEs led to treatment discontinuations in 15.3% of patients in the combination arm versus 8.8% in the control arm, and 3.1% discontinued the combination due to AEs, 5.6% discontinued nivolumab, and 6.6% discontinued only the cabozantinib. The overall rate of serious AEs was similar between the 2 arms, but liver toxicity was more common with the combination regimen compared with sunitinib. In addition, 19% of patients in the combination arm had required corticosteroids due to immune-related AEs, 4% of which required corticosteroids for at least 30 days.

The data from CheckMate-9ER study were presented during the 2020 European Society for Medical Oncology (ESMO) Virtual Congress. “With their complementary mechanisms of action and evidence that cabozantinib may promote a more immune-permissive environment, we believe there is opportunity for additive or synergistic effects with this potential combination regimen,” stated Gisela Schwab, MD, president, product development and medical affairs and chief medical officer, Exelixis.¹

Cabozantinib was approved by the FDA in December 2017 for use in previously untreated patients with advanced RCC. The FDA approved nivolumab in November 2015 for use in patients with metastatic RCC who progressed on an angiogenesis inhibitor. Nivolumab also has an FDA-approved RCC indication in the frontline setting for use in combination with ipilimumab (Yervoy) as a treatment for intermediate- and poor-risk patients with advanced disease.

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Pembrolizumab Plus Lenvatinib Demonstrated Statistically Significant Improvement in Progression-Free Survival, OS and ORR Versus Sunitinib as First-Line Treatment for Patients with Advanced Renal Cell Carcinoma

In the pivotal Phase 3 KEYNOTE-581/CLEAR trial (Study 307) trial, combinations of KEYTRUDA®, Merck's anti-PD-1 therapy, plus LENVIMA, the orally available multiple receptor tyrosine kinase inhibitor discovered by Eisai, and LENVIMA plus everolimus were evaluated versus sunitinib for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

KEYTRUDA plus LENVIMA met the trial's primary endpoint of progression-free survival (PFS) and its key secondary endpoints of overall survival (OS) and objective response rate (ORR), demonstrating a statistically significant and clinically meaningful improvement in PFS, OS, and ORR versus sunitinib in the intention-to-treat (ITT) study population. LENVIMA plus everolimus also met the trial's primary endpoint of PFS and a key secondary endpoint of ORR, demonstrating a statistically significant and clinically meaningful improvement in PFS and ORR versus sunitinib in the ITT study population. The ITT population included patients across all Memorial Sloan Kettering Cancer Center (MSKCC) risk groups (favorable, intermediate, and poor). The safety profiles of both KEYTRUDA plus LENVIMA and LENVIMA plus everolimus were consistent with previously reported studies. Merck and Eisai will discuss these data with regulatory authorities worldwide, with the intent to submit marketing authorization applications based on these results, which will be presented at an upcoming medical meeting.

"The results for KEYTRUDA plus LENVIMA versus sunitinib, which showed a statistically significant improvement in progression-free survival, overall survival, and objective response rate, build on the growing scientific evidence that supports the investigation of KEYTRUDA-based combinations for the first-line treatment of advanced renal cell carcinoma," said Dr. Gregory Lubiniecki, Associate Vice President, Oncology Clinical Research, Merck Research Laboratories.

"The results from KEYNOTE-581/CLEAR (Study 307) support the potential use of KEYTRUDA plus LENVIMA for the first-line treatment of advanced RCC. These data also support the potential first-line use of LENVIMA plus everolimus, which is already approved in advanced RCC following prior antiangiogenic therapy," said Dr. Takashi Owa, Vice President, Chief Medicine Creation and Chief Discovery Officer, Oncology Business Group at Eisai.

Source: "KEYTRUDA® (Pembrolizumab) Plus LENVIMA® (Lenvatinib) Demonstrated Statistically Significant Improvement In Progression-Free Survival (PFS), Overall Survival (OS) And Objective Response Rate (ORR) Versus Sunitinib As First-Line Treatment For Patients... - Merck.Com". 2020.

Novel HIF-2α Inhibitor Achieved Durable Responses in VHL-Associated RCC

Treatment with MK-6482, an investigational HIF2α inhibitor, demonstrated durable efficacy as treatment of patients with Von Hippel-Lindau-associated renal cell carcinoma and non-renal lesions, according to phase 2 data presented during the 21st Annual Meeting of the Society of Urologic Oncology.

In the open-label phase 2 study, MK-6482 (NCT03401788), an investigational small molecule HIF-2α inhibitor, has shown demonstrated durable efficacy as treatment of patients with Von Hippel-Lindau (VHL)-associated renal cell carcinoma (RCC) and non-renal lesions, according to presented during the 21st Annual Meeting of the Society of Urologic Oncology (SUO).

Patients received 120 mg of oral MK-6482 once daily. At a median follow-up of 68.7 weeks (range, 18.3-104.7), the objective response rate (ORR) in RCC lesions among 60 evaluable patients was 36.1%, comprising 22 confirmed partial responses (PRs). There were also 7 unconfirmed PRs. Overall, 91.8% (n = 56) of patients had at least some decrease in the size of target lesions. The median duration of response had not yet been reached and the progression-free survival rate at 52 weeks was 98.3%. Thirty-eight (62.3%) patients reached stable disease, 1 patient was not evaluable for response, and 0 patients had progressive disease. Fifty patients had an ECOG performance status of 0, 10 patients had a performance status of 1, and 1 patient had a performance status of 2. Key eligibility criteria for the open-label phase 2 study (NCT03401788) included a confirmed diagnosis of VHL disease (based on germline mutation), at least 1 measurable RCC tumor, and an ECOG performance status of 0 or 1. Prior systemic anticancer therapy was not allowed and patients with metastatic disease were excluded from enrollment. At a minimum follow-up of 60 weeks, 56 (91.8%) patients remained on treatment.

"Promising clinical activity was observed with MK-6482 in treatment-naïve patients with VHL-associated RCC," said lead study author Ramaprasad Srinivasan, MD, PhD, National Cancer Institute, Bethesda, Maryland. Clinical activity with MK-6482 was observed in non-RCC lesions. The confirmed ORR in pancreatic lesions was 63.9%, including 4 complete responses. The confirmed ORR in brain hemangioblastomas was 30.2%, with a CR rate of 11.6%. Also, 11 (68.8%) of 15 patients with retinal lesions demonstrated improvement in these lesions, with the 4 other patients reaching stable disease. Safety data showed that 60 of the 61 patients had at least 1 treatment-related adverse event (TRAE). The most common all-cause AE was grade 1/2 anemia, occurring in 51 (83.6%) patients. Eight (13.1%) patients had a grade 3 TRAE. Four (6.6%) patients had grade 3 anemia. There were no grade 4/5 TRAEs. There was 1 discontinuation due to a TRAE (grade 1 dizziness).

Reference: Srinivasan R, Donskov F, Iliopoulos O, et al. Oral HIF-2α inhibitor MK-6482 for Von Hippel-Lindau (VHL) disease-associated ccRCC evaluation of RCC and non-RCC disease. 21st Annual Meeting of the Society of Urologic Oncology; December 2-5, 2020; Abstract 10

Neoadjuvant Nivolumab Safe for Nonmetastatic High-Risk RCC

In a phase 1 trial (NCT02575222), Nivolumab (Opdivo) given as a Neoadjuvant has demonstrated tolerability in patients with nonmetastatic high-risk clear cell renal cell carcinoma as reported in a poster presentation during the 21st Annual Meeting of the Society of Urologic Oncology (SUO).¹

Currently, Nivolumab plus ipilimumab (Yervoy) has demonstrated significant efficacy in treating patients with treatment-naïve metastatic RCC compared with the prior standard-of-care sunitinib (Sutent).² The investigators sought to discover if the benefit of PD-1/PD-L1 inhibitors could be extended to the neoadjuvant setting, as an earlier study of neoadjuvant treatment with the multikinase inhibitor axitinib (Inlyta) had demonstrated significant shrinking of RCC tumors prior to surgery.³

The study was a prospective, open-label, single arm phase 1 trial that explored the safety and tolerability of nivolumab prior to surgery in patients with resectable nonmetastatic high-risk RCC. Patients with T2a-T4 with or without positive lymph nodes were eligible for the study if they were scheduled to undergo a partial or radical nephrectomy, had an ECOG performance status of 0 or 1, and adequate organ and bone marrow function. Nivolumab was administered at 3 mg/kg on day 1 of each of a total of 3 consecutive 14-day cycles. A total of 17 patients were included in the early-phase trial consisting of 16 with ccRCC and 1 with papillary disease. Fifteen had stage cT3a disease, 2 had cT3b, and all were negative for lymph node involvement.

At 24.7 months of median follow-up, the 2-year metastasis-free survival rate was 85.1%, and the overall survival rate was 100%. The 15 patients with ccRCC were restaged prior to surgery, but an overall minimal difference was observed in both the long and short axes from baseline to after treatment with nivolumab. However, 1 patient had an immune-related pathologic response and the rest had stable disease by radiographic criteria. The 1 patient who achieved a pathologic response demonstrated a regression bed with features of wound healing as well as immune infiltration.

Grade 3 adverse events (AEs) were reported in 11.8% of patients, and no grade 4 or 5 events were reported. No delays were reported in surgery, and no postoperative complications of Clavien grade 3 or higher were observed. "Early phase trial demonstrates the safety of neoadjuvant PD-1 blockade with preserved [quality of life] when administered to patients with nonmetastatic high risk ccRCC," the study authors, led by Hiten D. Patel, MD, MPH, of the Department of Urology at Loyola University Medical Center, wrote in their poster.

Neoadjuvant nivolumab is also currently being studied in the phase 3 PROSPER RCC study in comparison with observation for patients with RCC undergoing nephrectomy (NCT03055013).

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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.

Molecular Subsets in Renal Cancer Determine Outcome to Checkpoint and Angiogenesis Blockade. Motzer RJ, Rini B, et al. *Cancer Cell*. 2020;S1535-6108(20)30542-0. PMID: 33157048 DOI: 10.1016/j.ccell.2020.10.011

ABSTRACT: Integrated multi-omics evaluation of 823 tumors from advanced renal cell carcinoma (RCC) patients identifies molecular subsets associated with differential clinical outcomes to angiogenesis blockade alone or with a checkpoint inhibitor. Unsupervised transcriptomic analysis reveals seven molecular subsets with distinct angiogenesis, immune, cell-cycle, metabolism, and stromal programs. While sunitinib and atezolizumab + bevacizumab are effective in subsets with high angiogenesis, atezolizumab + bevacizumab improves clinical benefit in tumors with high T-effector and/or cell-cycle transcription. Somatic mutations in PBRM1 and KDM5C associate with high angiogenesis and AMPK/fatty acid oxidation gene expression, while CDKN2A/B and TP53 alterations associate with increased cell-cycle and anabolic metabolism. Sarcomatoid tumors exhibit lower prevalence of PBRM1 mutations and angiogenesis markers, frequent CDKN2A/B alterations, and increased PD-L1 expression. These findings can be applied to molecularly stratify patients, explain improved outcomes of sarcomatoid tumors to checkpoint blockade versus antiangiogenics alone, and develop personalized therapies in RCC and other indications.

Prognostic significance and immune correlates of CD73 expression in renal cell carcinoma. Tripathi A et al. *J Immunother Cancer*. 2020 Nov;8(2):e001467. doi: 10.1136/jitc-2020-001467.

BACKGROUND: CD73-adenosine signaling in the tumor microenvironment is immunosuppressive and may be associated with aggressive RCC. We investigated the prognostic significance of CD73 protein expression in RCC leveraging nephrectomy samples. We also performed a complementary analysis using The Cancer Genome Atlas (TCGA) dataset to evaluate the correlation of CD73, CD39 and A2AR transcript levels with markers of angiogenesis and antitumor immune response.

METHODS: Patients with RCC with available archived nephrectomy samples were eligible for inclusion. Tumor CD73 protein expression was assessed by immunohistochemistry and quantified using a CS. Samples were categorized as CD73negative (CS=0), CD73low or CD73high. Multivariable Cox regression analysis compared disease-free survival DFS and OS between CD73 expression groups. In the TCGA dataset, samples were categorized as low, intermediate and high NT5E, ENTPD1 and ADORA2A gene expression groups. Gene expression signatures for infiltrating immune cells, angiogenesis, myeloid inflammation, and effector T-cell response were compared between NT5E, ENTPD1 and ADORA2A expression groups.

RESULTS: Among the 138 patients eligible for inclusion, 'any' CD73 expression was observed in 30% of primary tumor samples. High CD73 expression was more frequent in patients with M1 RCC (29% vs 12% Mo), grade 4 tumors (27% vs 13% grade 3 vs

15% grades 1 and 2), advanced T-stage ($\geq T_3$: 22% vs T_2 : 19% vs T_1 : 12%) and tumors with sarcomatoid histology (50% vs 12%). In the Mo cohort (n=107), patients with CD73high tumor expression had significantly worse 5-year DFS (42%) and 10-year OS (22%) compared with those in the CD73negative group (DFS: 75%, adjusted HR: 2.7, 95% CI 1.3 to 5.9, $p=0.01$; OS: 64%, adjusted HR: 2.6, 95% CI 1.2 to 5.8, $p=0.02$) independent of tumor stage and grade. In the TCGA analysis, high NT5E expression was associated with significantly worse 5-year OS ($p=0.008$). NT5E and ENTPD1 expression correlated with higher regulatory T cell (Treg) signature, while ADORA2A expression was associated with increased Treg and angiogenesis signatures.

CONCLUSIONS: High CD73 expression portends significantly worse survival outcomes independent of stage and grade. Our findings provide compelling support for targeting the immunosuppressive and proangiogenic CD73-adenosine pathway in RCC.

Randomized trial assessing impact of probiotic supplementation on gut microbiome and clinical outcome from targeted therapy in metastatic renal cell carcinoma. Nazli Dizman *Cancer Med*. 2020. <https://doi.org/10.1002/cam4.3569>

ABSTRACT: Studies suggest a link between the gut microbiome and metastatic renal cell carcinoma (mRCC) outcomes, including evidence that mRCC patients possess a lower abundance of Bifidobacterium spp. compared to healthy adults. We sought to assess if a Bifidobacterium-containing yogurt product could modulate the gut microbiome and clinical outcome from vascular endothelial growth factor-tyrosine kinase inhibitors (VEGF-TKIs). mRCC patients initiating VEGF-TKIs, regardless of the line of therapy, were randomized to probiotic-supplemented (two 4 oz. servings of the probiotic yogurt product daily) or probiotic-restricted arms. Stool samples were collected prior to therapy and at weeks 2, 3, 4, and 12. Microbiome composition was assessed using whole-metagenome sequencing. A total of 20 patients were randomized. Bifidobacterium animalis, the active ingredient of the probiotic supplement, reached detectable levels in all patients in the probiotic-supplemented arm versus two patients in the probiotic-restricted arm. Clinical benefit rate was similar in probiotic-supplemented versus probiotic-restricted arms (70% vs. 80%, $p = 0.606$). Linear discriminant analysis (LDA) effect size analysis of MetaPhlAn2 abundance data predicted 25 enriched species demonstrating an LDA score >3 in either clinical benefit or no clinical benefit. In patients with clinical benefit (vs. no clinical benefit), Bacteroides fragilis, Akkermansia muciniphila were significantly more abundant ($p = 7.4 \times 10^{-6}$ and $p = 5.6 \times 10^{-3}$, respectively). This is the first prospective randomized study demonstrating modulation of the gut microbiome with a probiotic in mRCC. Probiotic supplementation successfully increased the Bifidobacterium spp. levels. Analysis of longitudinal stool specimens identified an association between B. fragilis, A. muciniphila, and clinical benefit with therapy. Trial Registration: NCT02944617.

Grading Chromophobe Renal Cell Carcinoma: Evidence for a Four-tiered Classification Incorporating Coagulative Tumor Necrosis. Avulova S et al. *Eur Urol.* 2020 Nov 7;S0302-2838(20)30784-3. doi: 10.1016/j.eururo.2020.10.007.

BACKGROUND: Although grading systems have been proposed for chromophobe renal cell carcinoma (ChRCC), including a three-tiered system by Paner et al (Paner GP, Amin MB, Alvarado-Cabrero I, et al. A novel tumor grading scheme for chromophobe renal cell carcinoma: prognostic utility and comparison with Fuhrman nuclear grade. *Am J Surg Pathol* 2010;34:1233-40), none have gained clinical acceptance, and the World Health Organization (WHO) currently recommends against grading ChRCC.

OBJECTIVE: To validate a previously published grading scheme and propose a scheme that includes tumor necrosis.

DESIGN: A total of 266 patients who underwent nephrectomy for nonmetastatic ChRCC between 1970 and 2012 were reviewed for ChRCC grade according to the Paner system and coagulative tumor necrosis. Outcome measurements and statistical analysis: Associations with cancer-specific survival (CSS) were evaluated using Cox proportional hazard regression models and summarized with hazard ratios (HRs).

RESULTS AND LIMITATIONS: Twenty-nine patients died from RCC; the median follow-up was 11.0 (interquartile range 7.9-15.9) yr. ChRCC grade according to the Paner system was significantly associated with CSS, including the difference in outcome between grade 1 and 2 tumors. Among patients with grade 2 tumors, the presence of tumor necrosis helped delineate patients with worse CSS. As such, the Paner system was expanded to four tiers separating grade 2 into those with and without tumor necrosis. HRs for associations of the proposed grade 2, 3, and 4 tumors with CSS were 4.63 ($p = 0.007$), 17.8 ($p < 0.001$), and 20.9 ($p < 0.001$), respectively. The study is limited by the lack of multivariable analysis including additional pathologic features.

CONCLUSIONS: The expansion of a previously reported ChRCC grading system from three to four tiers by the inclusion of tumor necrosis helps further delineate patient outcome and can, therefore, enhance patient counseling following surgery. It also aligns the number of ChRCC grades with the WHO/International Society of Urologic Pathology four-tiered grading systems for clear cell and papillary RCC.

Stereotactic Radiotherapy for the Treatment of Patients With Oligo-progressive Metastatic Renal Cell Carcinoma Receiving Vascular Endothelial Growth Factor Receptor Tyrosine Kinase Inhibitor: Data From the Real World. Vittorio Gebbia, Andrea Girlando, Alfio DI Grazia et al., *Anticancer Res.* 2020 Dec;40(12):7037-7043. DOI: 10.21873/anticancer.14730

AIM: This retrospective observational study evaluated the role of hypo-fractionated stereotactic radiotherapy (SRT) in patients with oligo-progressive metastatic renal cell carcinoma (mRCC) treated with first-line oral tyrosine kinase inhibitors (TKI). Data on local control, delay of further progression, and safety are reported.

PATIENTS AND METHODS: Between January 2010 and December 2016, 28 patients with mRCC who showed oligo-progressive

disease while receiving first-line pazopanib were treated with hypofractionated SRT to progressive metastatic sites to delay the change of systemic therapy. First and second progression-free survival (PFS-1 and PFS-2) were recorded, as well as objective response and toxicity.

RESULTS: After pazopanib therapy, nine partial remissions (32%), 12 stable disease (43%) and seven progressions (25%) were recorded. The median time to progression from first-line pazopanib until oligo-progression was 9.45 months (PFS-1 range=2-30 months). Seventeen patients (61%) showed progression at pre-existing tumor sites, and 11 patients (39%) showed the appearance of new metastases. Progression-free survival after radiation therapy was 4.55 months (PFS-2 range=1-11 months). PFS-1 plus PFS-2 was 14.0 months (range=3-41 months). Severe grade 3-4 toxicities were seen only occasionally.

CONCLUSION: Patients with oligo-progressive mRCC treated with first-line pazopanib may benefit from hypo-fractionated high-dose SRT at progressing sites achieving a further increase in median progression-free survival. Further studies and prospective validation are required to establish if this minimally invasive approach may have a positive impact on overall survival and reported outcomes.

An Italian, multicenter, real-world, retrospective study of first-line pazopanib in unselected metastatic renal-cell carcinoma patients: the 'Pamerit' study. Mosca A et al. *Front Pharmacol., Jpn J Clin Oncol.* 2020;hyaa193. doi: 10.1093/jco/hyaa193.

OBJECTIVE: The aim of this study is to add information about efficacy and safety of pazopanib as first-line treatment in metastatic renal cell cancer patients not enrolled into clinical trials.

METHODS: Retrospective analysis (the PAMERIT study) of first-line pazopanib in real-world metastatic renal cell cancer patients among 39 Centers in Italy. Outcomes were PFS, OS, OSR and treatment-related AEs. Kaplan-Meier curves, log-rank test and multivariable Cox's models were used and adjusted for age, histology, previous renal surgery, International Metastatic RCC Database Consortium score and pazopanib initial dose.

RESULTS: Among 474 patients, 87.3% had clear cell metastatic renal cell cancer histology. Most of them (84.6%) had upfront renal surgery. Median progression-free survival and overall survival were 15.8 and 34.4 months, respectively, significantly correlating with International Metastatic RCC Database Consortium's good prognosis ($P < 0.001$), ECOG PS 0 ($P < 0.001$), age (< 75 years, $P = 0.005$), surgery ($P < 0.001$) and response to pazopanib ($P < 0.001$). After 3 months of pazopanib, overall disease control rate have been observed in 76.6% patients. 57/121 (47%) showed complete/partial response. No unexpected AEs emerged.

CONCLUSIONS: In this real-world study, mRCC patients treated with first-line pazopanib reached greater progression-free survival and overall survival than in pivotal studies and had high response rates, without new toxicities. Pazopanib has been confirmed a valid first-line option for IMRCC Database Consortium's good prognosis mRCC patients who cannot be submitted to immunotherapy.



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