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KCJ REVIEW ARTICLE

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Treatment of Recurrent Metastatic Renal Cell Carcinoma After Adjuvant Immunotherapy

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ABSTRACT

The treatment of renal cell carcinoma (RCC) has evolved dramatically in the past two decades. For metastatic RCC (mRCC), first-line treatment currently consists of vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKI), Immune Checkpoint inhibitors (ICI), or combinations of the two. In localized RCC, a recent major advancement has been the approval of the ICI pembrolizumab for adjuvant treatment of patients with a high risk of recurrence after nephrectomy. Little is known, however, regarding the optimal treatment strategy for patients with progression of disease on adjuvant therapy or recurrence after completing adjuvant therapy. Trials to inform this topic are ongoing. In the absence of this prospective data, we provide recommendations for clinicians based on existing evidence in the form of three patient scenarios. For a patient who progresses on adjuvant ICI, we generally recommend treatment with single-agent VEGFR TKI. For a patient with metastatic recurrence after completing adjuvant pembrolizumab, treatment recommendations differ based on the time from the last ICI dose until recurrence given the persistent receptor occupancy of ICI even months after discontinuation. If recurrence occurs within 6 months of the last dose of ICI, we recommend single-agent VEGFR TKI. If recurrence occurs >12 months from the last dose of ICI, we recommend resumption of ICI in combination with VEGFR TKI or dual ICI therapy. The choice between these strategies should be based on validated risk stratification instruments, time from completion of therapy, and patient-specific factors. Patients who have a recurrence within 6-12 months provide the most challenging scenario, and we would generally recommend ICI in combination with VEGFR TKI in this setting. For patients who did not tolerate adjuvant ICI, a decision on treatment with combination ICI and VEGFR TKI versus single agent VEGFR TKI should depend on the severity of the immune-related adverse event(s) resulting in intolerance as well as the time from the last dose of therapy. Individual patient considerations must also always inform treatment decisions.

INTRODUCTION

Kidney cancer is diagnosed in more than 400,000 patients worldwide each year[1]. Among kidney cancers, greater than 90% are renal cell carcinomas (RCC), of which approximately 70% demonstrate clear cell histology[2]. Clear cell RCC accounts for the substantial majority of kidney cancer morbidity and mortality and thus has been the subject of most kidney cancer research. Clear cell RCC will be the focus of this review and designated as RCC. At the time of diagnosis, roughly 30% of patients with RCC will have advanced locoregional or metastatic disease, and up to 40% of patients initially presenting with locoregional disease will eventually develop metastases[3]. Fortunately, great progress has been made in the treatment of metastatic RCC (mRCC) over the past two decades. Median survival has increased from approximately 15 months in the early 2000s to greater than 4 years in recent trials[4,5].

The landscape of medical therapies for mRCC has evolved dramatically. Interferon (IFN) and interleukin-2 (IL-2) were introduced in the 1980s and 1990s[6,7] and

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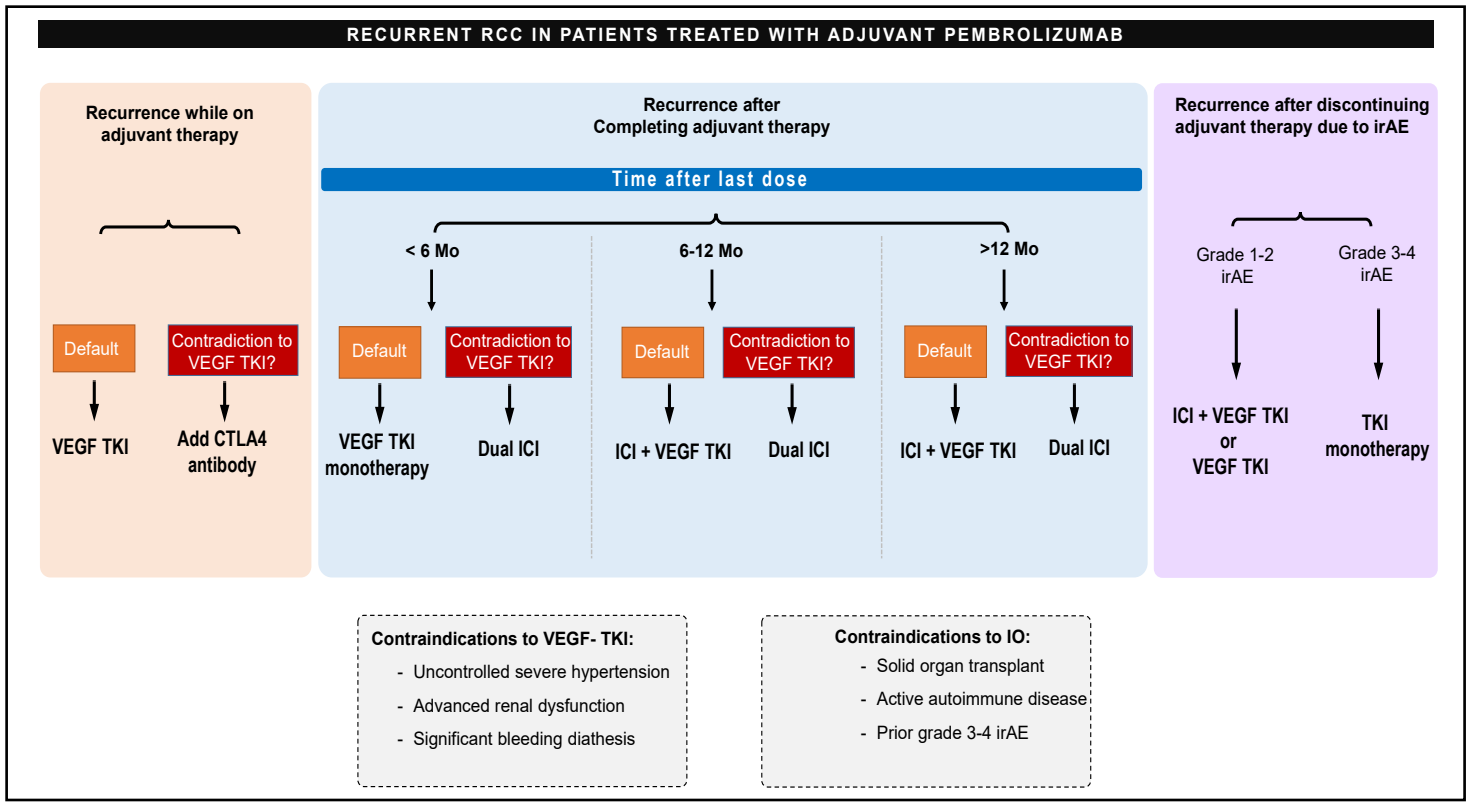

FIGURE 1. Proposed Treatment Algorithm of Metastatic Renal Cell Carcinoma Recurrence After Adjuvant Immunotherapy

remained the only proven systemic therapies for over 20 years. The VEGFR-TKI sunitinib was approved for advanced RCC in 2006[8] and revolutionized treatment. In the following years, six additional VEGFR TKIs were approved for mRCC. Agents from an additional drug class, mammalian target of rapamycin (mTOR) inhibitors, were also approved including temsirolimus[9] and everolimus[10]. Even more recently, ICIs have provided the next leap forward in mRCC. Nivolumab was the first ICI with demonstrated benefit in mRCC[11], and several subsequent single-agent ICI trials have also demonstrated efficacy. Multiple options now exist for first-line therapy in mRCC, most of which are combinations of ICI and VEGFR TKIs[12]. Important developments have also been made in surgical and ablative techniques for RCC and mRCC[13,14].

The most recent major advancement in the treatment of RCC has been the introduction of adjuvant ICI. The results of the KEYNOTE-564 trial, published in 2021, showed improved disease-free survival (DFS) in localized RCC patients treated with adjuvant pembrolizumab after nephrectomy[15]. While overall survival (OS) data are not mature, this practice is quickly becoming a standard of care. It remains unknown, however, how best to treat patients who progress on adjuvant therapy or recur after its completion. Trials that will inform management in this clinical scenario are underway (Table 1)[16-20]. We review the current evidence and propose a treatment algorithm (Figure 1) to guide clinicians in managing patients with mRCC with recurrence on or after adjuvant immunotherapy.

Adjuvant therapy for RCC

Surgical approaches including nephrectomy, partial nephrectomy, and ablation strategies are first line therapy for most patients with localized RCC[21]. Carefully selected patients with metastatic disease may even undergo resection of the primary tumor and concomitant metastasectomy to remove one or a limited number of metastases[22]. Unfortunately, greater than 35% of patients who undergo initial resection will have progression or recurrence[23]. Adjuvant treatment has been investigated extensively over the past 30 years with largely negative results. Multiple trials of adjuvant cytokines showed no benefit[24,25]. VEGFR TKIs have also been studied repeatedly, with 5 trials to date[26-30]. These have shown adjuvant VEGFR TKI therapy to be largely ineffective. While the S-TRAC trial comparing sunitinib to placebo did demonstrate a modest benefit in disease free survival (DFS), OS was unchanged and the treatment arm experienced greater toxicity. Furthermore, the ASSURE trial[26] and several other negative studies of adjuvant VEGFR TKIs were discordant with the S-TRAC results. Active surveillance, therefore, remained a standard of care after surgery, regardless of risk category.

KEYNOTE-564 was the first reported trial of ICI in the adjuvant setting for RCC. Accrual began in 2017 and results were published in 2021 with 24 months of follow up[15]. Inclusion criteria were similar to

	CONTACT-03	TiNivo-2	PDIGREE	RAMPART	Lite-Spark-011
Design	Phase III, open-label, randomized multicenter study	Phase III, open-label, randomized multicenter study	Phase III, adaptive, randomized, multicenter study	Phase III, open-label, randomized, multicenter study	Phase III, open-label, randomized multicenter study
Key Inclusion Criteria	Advanced or metastatic RCC with progression on or after ICI treatment	RCC with progression on or after ICI treatment	Intermediate or poor risk mRCC with no prior treatments	Locally advanced RCC after resection with no evidence of disease	Advanced RCC with progression on or after ICI treatment
Comparator Groups	Cabozantinib + atezolizumab vs cabozantinib alone	Tivozanib + nivolumab vs tivozanib alone	Starting treatment with ipilimumab + nivolumab, patients with CR receive nivolumab maintenance, patients with PD switch to cabozantinib, and patients without CR or PD are randomized to nivolumab vs nivolumab + cabozantinib	Active surveillance vs durvalumab vs durvalumab + tremelimumab	Pembrolizumab + lenvatinib + belzutifan vs pembrolizumab + quavonlimab + lenvatinib vs pembrolizumab+ lenvatinib
Primary Endpoints	PFS, OS	PFS	OS	OS. DFS	PFS, OS
Key Secondary Points	ORR, Duration of Response	OS, ORR, Duration of Response	PFS, CR, OR	n/a	ORR, Duration of Response
Expected Completion	12/11/2024	08/01/2025	09/15/2023	12/01/2024	10/29/2026

TABLE 1. Summary of Key Clinical Trials in the Management of Metastatic Renal Cell Carcinoma After Prior Therapy

other adjuvant trials, with eligible patients having undergone surgery (partial nephrectomy, nephrectomy, and/or metastasectomy) with negative margins but meeting investigator criteria for high risk of recurrence. This included patients who were diagnosed with tumor stage 2 with nuclear grade 4 or sarcomatoid differentiation, tumor stage 3 or higher, regional lymph-node metastasis, or stage M1 (distant metastases). All patients were disease-free at the time of trial entry as assessed by site investigators. Patients were randomized to adjuvant pembrolizumab for 17 cycles (approximately 1 year) or placebo. The trial was positive, meeting the primary endpoint of improved DFS with a hazard ratio (HR) of 0.68, 95% confidence interval (CI) 0.53 – 0.87. At 24 months, 77.3% of patients in the pembrolizumab arm and 68.1% of the patients in the placebo arm were alive and recurrence free. The secondary endpoint of OS was also improved (HR 0.54, 95% CI 0.30 – 0.96), with 96.6% of patients in the pembrolizumab arm and 93.5% of patients in the placebo arm alive at 24 months. Grade 3 or higher adverse events occurred in 32.4% of patients in the pembrolizumab arm compared to 17.7% of patients in the placebo arm. There were no deaths attributable to pembrolizumab or placebo.

An additional 6 months of follow-up data for KEYNOTE-564 were presented in February 2022[31]. With a median follow-up of 30.1 months, DFS remained superior in the pembrolizumab group compared to placebo (HR 0.63, 95% CI 0.50 – 0.80). A trend toward OS benefit was maintained (HR 0.52, 95% CI 0.31 – 0.86) though statistical significance was not achieved. No new safety signals were observed. Adjuvant pembrolizumab therefore has become adopted as a standard of care in patients with RCC and increased risk of recurrence.

Notably, results of 3 different trials of adjuvant and perioperative ICI for RCC were published or presented in September 2022. The IMmotion010 trial[32] was a multicenter randomized study in which patients with increased risk of recurrence after nephrectomy were treated with atezolizumab or placebo for 1 year. The primary endpoint of increased DFS was not met (HR 0.93, 95% CI 0.75-1.15, p=0.50). The CheckMate 914 trial[33] compared adjuvant nivolumab plus ipilimumab to placebo and demonstrated no difference in the primary endpoint of DFS (HR 0.92, 95% CI 0.71-1.19, p=0.53). Lastly, the PROSPER trial compared a strategy of "perioperative" nivolumab, in which 1 dose was given prior to surgery and 9 doses were given after, to surgery alone. This open label study was stopped early due to futility, with no differences in recurrence free survival (HR 0.97, 95% CI 0.74-1.28) or OS (HR 1.48, 95% CI 0.89-2.48). Therefore, pembrolizumab remains the only proven ICI agent for adjuvant therapy.

Management of Patients with Recurrence: Existing Guidance

No consensus exists, however, regarding the optimal management of patients with recurrence during or after adjuvant ICI. This novel category of patients may be increasingly encountered by clinicians given the United States Food and Drug Administration (FDA) approval of adjuvant pembrolizumab in November of 2021[34] and ongoing trials that may expand the use of ICI in this setting[19] (19).

In the most recent guidelines from the National Comprehensive Cancer Network (NCCN), published in 2022[21], guidance is given for patients considered to have relapsed disease. However, this category is directed at patients who have progressed through first line therapy for mRCC. Given the novelty of adjuvant ICI, however, there is no data specific to patients with disease recurrence either on or after adjuvant therapy. Considerations include that adjuvant pembrolizumab is dosed for a fixed period of 1 year, not based on tolerability and clinical response as in metastatic disease, and that pembrolizumab may have a long period of receptor occupancy after discontinuation. Pharmacokinetic studies of nivolumab show that in a patient who receives at least 3 doses, the drug continues to occupy 40% of T cell PD-1 receptors for nearly 9 months[35]. Similar receptor occupancy data for pembrolizumab are not readily available, but we speculate that similar prolonged binding may occur given the similarity in their mechanisms, terminal half-life, and clearance[36]. Therefore, patients treated with pembrolizumab in the adjuvant setting may be managed differently based on the timing of their recurrence.

SCENARIO 1: Patients with Recurrence On Adjuvant Immunotherapy

For patients who have disease recurrence while receiving adjuvant ICI, we favor treatment with single agent VEGFR TKI. In the KEYNOTE-564 trial, approximately 15% of patients randomized to adjuvant therapy had recurrence during the 12 month period during which they were receiving pembrolizumab. While this scenario would appear to be relatively uncommon based on these data, clinicians may increasingly encounter such patients as use of adjuvant ICI expands and more variable populations are treated in real world settings.

Given the two mainstays of mRCC treatment are either targeting the immunogenic tumor microenvironment or angiogenesis, it is reasonable to target an alternative mechanism if patients were to progress while receiving ICI, as the ICI clearly was not controlling the disease. Prospective data supports the approach of using single agent VEGFR TKI after progressing with prior ICI. In a phase II single-arm study of axitinib for patients who had previously been treated with ICI, an overall response rate (ORR) of 38.7% was observed[37]. These were all partial responses. Among the 40 patients included in the trial, 63% had been most recently treated with nivolumab monotherapy. These patients differ from our proposed population, however, in that 71% had received two or more prior therapies before enrollment.

Additional prospective data demonstrating efficacy of VEGFR TKI after prior treatment with ICI can be found in subgroup analyses[38] of the METEOR trial[39], which randomized patients with advanced RCC after prior antiangiogenic therapy to cabozantinib vs everolimus. Among 18 patients who had also received anti-PD-1 or PD-L1 therapy and were subsequently treated with cabozantinib, an objective response was observed in 4 patients (22%). No responses were seen among the 14 patients with prior VEGFR TKI and ICI therapy who were randomized to everolimus.

Retrospective data also support that cabozantinib is effective in patients who have progressed after receiving ICI. In a retrospective analysis of 86 patients who were treated with cabozantinib monotherapy after progression on ICI[40], an ORR of 36% was observed. These were all partial responses. Of the patients included in the trial, 64% had been previously treated with ICI alone, while 36% had received combination therapy with ICI and either VEGFR TKI or another therapy. The median number of prior therapies in these patients was 2, with a range of 1-10.

Similar efficacy appears to be preserved across different agents in the VEGFR TKI class. A retrospective study of 70 patients who progressed after first-line ICI therapy included patients who were subsequently treated with axitinib, cabozantinib, pazopanib, or sunitinib[41]. An ORR of 41.2% was observed, with 1 complete response. These patients are similar to those currently being treated with adjuvant ICI in that their first systemic therapy is an ICI. Thirty-six percent of these patients, however received combination therapy with ICI + VEGFR-TKI.

There are also data to suggest that patients who receive a VEGFR TKI after progression on ICI may have better outcomes if not previously treated with a VEGFR TKI, which may be attributable to acquired TKI resistance. A retrospective analysis was conducted of 68 patients from clinical trials who received VEGFR TKI therapy after ICI with or without VEGFR TKI[42]. Patients who previously received a VEGFR TKI had an ORR of only 10% with VEGFR TKI rechallenge, while patients treated only with ICI had an ORR of 36%, a difference that was statistically

significant (P = 0.039). The insight from this study may allow for more optimistic interpretation of other data regarding patients treated with VEGFR TKI after ICI. Many of these patients had previously received a VEGFR TKI, and might have had a better response if previously treated with ICI alone, similar to the patients receiving adjuvant ICI.

It is unclear whether patients who have progressed on ICI would benefit from continued ICI in addition to VEGFR TKI. Based on pre-clinical studies, it is understood that VEGFR TKI therapy may reverse immunosuppression in the RCC tumor microenvironment, promoting an immune-permissive state and improving the efficacy of ICI[43]. Data from the phase 2 KEYNOTE-146 trial[44] show that 55.8% of patients previously treated with ICI responded to lenvatinib plus pembrolizumab, which is an impressive post-ICI ORR. However, 57% of patients had grade 3 or higher immune related adverse event (irAE). This knowledge raises the question of whether patients receiving VEGFR TKI therapy after progression on adjuvant pembrolizumab would still benefit from continuing ICI.

For patients with contraindications to VEGFR TKIs, the addition of an anti-CTLA-4 antibody to ICI can also be considered. In the TITAN-RCC trial[45], patients with intermediate and poor risk advanced RCC were initially treated with nivolumab, and those with early significant PD or non-responders at 16 weeks received "boost" cycles of nivolumab plus ipilimumab. Of 28 patients who received ipilimumab boosts for PD on first-line nivolumab, 3 (11%) had a PR and 8 (29%) achieved stable disease.

Additional insight will be gained from ongoing trials evaluating the safety and efficacy of ICI + VEGFR TKI in advanced RCC patients with progression on or after therapy containing ICI. CONTACT-03 is a randomized phase III study assessing cabozantinib plus atezolizumab versus cabozantinib monotherapy following progression on or after ICI in advanced RCC[16]. TiNivo-2 is a randomized phase III study comparing tivozanib plus nivolumab to tivozanib monotherapy in a similar patient population[17]. Estimated study completion dates are December, 2024 and August, 2025, respectively. Lastly, PDIGREE is an adaptive trial in which patients with intermediate or poor risk RCC will receive induction therapy with ipilimumab and nivolumab and if noted to have progressive disease after 3 months, will be switched to cabozantinib monotherapy. We eagerly await the results of these important trials, but until then, we recommend VEGFR TKI monotherapy for those who progress on ICI to avoid the known toxicity that comes with combination therapy in the setting of unknown benefit.

SCENARIO 2: Patients with Recurrence After Completion of Adjuvant ICI Therapy

In KEYNOTE-564, adjuvant pembrolizumab was given for a maximum of 1 year (17 cycles of doses every 3 weeks). In follow-up data published in September 2022, approximately 12% of patients who did not have recurrence while on adjuvant therapy went on to have recurrence in the next 18 months[46]. For patients that recur after the completion on adjuvant ICI therapy, we favor treatment selection based on the International Metastatic RCC Database Consortium (IMDC) risk score as outlined in the NCCN guidelines for first line treatment of mRCC as well as the time until recurrence.

In favorable risk disease, the NCCN guidelines currently list several combinations of ICI plus VEGFR TKI with category 1 recommendations (defined as being based on high level evidence with uniform consensus amongst committee members). Active surveillance can also be considered in select patients[47,48] as well as single agent TKI[8] for those with contraindications to ICI, such as uncontrolled autoimmune disease or solid organ transplant. In intermediate-to-high risk disease, dual ICI and combination ICI with VEGFR TKI are category 1 recommendations. Multi-disciplinary discussion of local treatment with repeat metastasectomy or radiation therapy can also be considered in select patients with oligometastatic disease.

Beyond IMDC risk stratification, clinicians may select the initial regimen based on the speed with which a response is needed, comorbid conditions, and toxicity profile, among other factors. For patients in whom a more rapid response is desired, such as those with impending visceral crisis or very high tumor burden, combination ICI with VEGFR TKI would be preferred over dual ICI given the generally accepted faster response observed with TKIs (49). For patients with recent hemorrhagic events, uncontrolled hypertension, or severe kidney disease, dual ICI may be favored over combination ICI with VEGFR TKI. Lastly, clinicians often prioritize the chance of a complete response and the potential of discontinuing therapy at some point in the future (with resulting improved quality of life), which may favor dual ICI therapy[50].

Another factor that will influence therapeutic decision making is the time from completion of therapy to metastatic recurrence. While the half-life of pembrolizumab has been reported at 12-26 days[35,51], indicating that most drug should be cleared within approximately 4 months, receptor occupancy data for the similar drug nivolumab suggests that PD-1/PD-L1 inhibitors may remain bound to their targets for considerably longer. In patients who received multiple doses, nivolumab appeared to occupy 70% of T-cell PD-1 receptors at 2 months, and

remained bound to 40% of receptors for nearly 9 months. No receptor occupancy was observed by 1 year after the last dose[35]. Similar receptor occupancy data for pembrolizumab is not readily available. It is also unknown to what degree receptor occupancy translates into clinical efficacy.

Furthermore, the duration of ongoing immune activation after exposure to pembrolizumab remains unknown. There have been rare reports of delayed immune related adverse events (DIRE) occurring after discontinuation of ICI, with a systematic review of such cases suggesting a median interval to diagnosis of 6 months after the last dose[52]. It is unclear whether the ICI was physiologically active at those times, or whether an autoimmune process had been initiated earlier in the treatment course. The overall absence of evidence regarding duration of ICI activity limits our recommendations to expert opinion. Based on existing data and clinical experience, we consider 12 months after the last dose to be a time point at which the ongoing effect of pembrolizumab is clinically insignificant. Therefore, in patients with recurrence 12 months or longer after completing adjuvant therapy, we recommend either ICI with VEGFR TKI or dual ICI therapy based on IMDC risk stratification and patient specific factors. For patients who have metastatic recurrence within the first 6 months of completing adjuvant therapy, we consider the patient to have recurred while checkpoint inhibition is ongoing and recommend VEGFR TKI monotherapy. For patients with recurrence 6-12 months after completing adjuvant therapy, it is unclear if the ICI remains active and thus, we generally recommend VEGFR TKI in combination with ICI, although TKI monotherapy or dual ICI could be considered based on patient specific factors. The results of CONTACT-03, TiNivo-2, and PDIGREE will further inform whether additional ICI with VEGFR TKI might benefit patients with early relapse after completing adjuvant therapy.

Although patients who have received adjuvant pembrolizumab have had exposure to the immune targeted approach, retrospective data indicates that treatment with dual ICI may still be effective in patients who have received prior ICI. Similar efficacy (ORR 20%) was observed in a retrospective study of 49 patients who received dual ICI after progression on prior ICI[53]. The time from last ICI treatment appeared to be longer in patients who responded to this "salvage" approach, which suggests a sensitization of tumor to ICI over time or may simply reflect less aggressive underlying disease. The applicability of efficacy data from these studies to the post-adjuvant setting, however, is limited by the heterogeneity of first line ICI therapies that patients received. A variety of anti-PD-1/PD-L1 antibodies were employed, and often in combination with anti-CLTA-4 antibodies or other targeted therapies.

Of note, an argument can be made for using single agent ICI at recurrence. A retrospective study evaluated the outcomes of 69 patients with mRCC who received at least 2 separate lines of ICI[54]. The ORR to a second line of ICI was 23%. Importantly, response rates did not appear to differ whether patients received second line therapy consisting of single agent ICI, dual ICI, or ICI + targeted therapy. Among the 15 patients who responded to second line therapy 7 (46%) received single agent ICI alone, compared to 5 (33%) who received dual ICI and 3 (30%) who received ICI + targeted therapy. While adverse effects were reported in total and not stratified according to the composition of second line therapy, this data suggests that rechallenge with single agent ICI may be reasonable from the perspectives of both efficacy and resource stewardship. However, this is a small study, and given the robust data for combination therapy in the first line treatment of mRCC, we still recommend combination therapy if possible based on patient factors.

SCENARIO 3: Patients Who Do Not Complete Adjuvant Immunotherapy Due to Toxicity

In KEYNOTE-564, 8.9% of patients randomized to adjuvant pembrolizumab did not complete the trial regimen, with adverse events cited as the most common reason for discontinuation (21.3%). For those who discontinue treatment and have subsequent metastatic recurrence, the decision on a treatment regimen should depend on the severity of the irAE in addition to time until recurrence, IMDC risk stratification, and patient specific factors. We agree with the NCCN guidelines regarding the management of immunotherapy-related toxicities[55]. In general, patients who have non-endocrine grade 3 or 4 irAEs should not be re-challenged with ICI and those who have return of toxicity upon ICI re-challenge should permanently discontinue ICI. In patients with grade 3 or 4 irAEs from adjuvant pembrolizumab, we favor treatment with single agent VEGFR TKI as in patients who progressed on adjuvant pembrolizumab.

For patients with contraindications to VEGFR TKIs, a retrospective study suggests that ICI rechallenge may be safe and reasonably efficacious. In 499 patients with advanced RCC who received ICI, 71% patients experienced an irAE. Of patients who were given ICI in their second line of therapy, only 45% experienced an irAE. Similarly, grade 3 or higher irAEs were observed in 26% and 16% of the patients during their first and second lines of ICI, respectively. Even patients who experience clinically significant irAEs may have a safe and efficacious ICI re-challenge therapies. Among 80 patients whose ICI treatment was interrupted due to an irAE, 36 (45%) were again

treated with ICI, and only 7 (19%) experiences a grade 3 or higher irAE (56). These data are biased in that fewer patients with irAEs leading to hospitalization or steroid treatment were later rechallenged with ICI. Among those who were retreated, however, ICI appeared to be moderately effective with an ORR of 34%.

Given the pharmacokinetics of pembrolizumab and these safety data, we would re-challenge patients with ICI if they recur 12 months or more after discontinuation. ICI plus VEGFR TKI as enumerated in the NCCN guidelines for first line treatment or mRCC would be favored, and VEGFR TKI monotherapy could also be considered. For patients with progression in less than 6 months after ICI discontinuation after an irAE, we would recommend treatment with VEGFR TKI monotherapy. For patients with recurrence between 6-12 months, the severity of the irAE, the IMDC risk, and patient specific factors would guide a more individualized approach.

CONCLUSION

With the FDA approval of pembrolizumab for adjuvant treatment of localized RCC with high recurrence risk, decision making surrounding treatment of metastatic recurrence is challenging.

In the absence of significant prospective data or treatment guidelines, we provide recommendations for clinicians based on existing evidence. In general, for patients who progress while on adjuvant ICI, we recommend treatment with single agent VEGFR TKI. For patients with recurrence after completing adjuvant pembrolizumab, we recommend resumption of ICI with either combination ICI and VEGFR TKI, or dual ICI based on IMDC risk, time from completion of therapy (<6, 6-12, or >12 months), and patient specific factors. For patients who did not tolerate adjuvant ICI, decision on treatment with combination ICI with VEGFR TKI versus single agent VEGFR TKI is dependent on the severity of the irAE and time from discontinuation of therapy. Results from ongoing clinical trials and future prospective clinical trials are necessary to determine the best treatment strategies for these patients.

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ONLINE CONTENT

Full online contents with additional information can be accessed at https://kidney-cancer-journal.com/KCJ20n4-r1.php

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Dear Colleagues,

This year's IKCS2022 Annual meeting offered a dynamic agenda unveiling the latest scientific advances and pivotal data from a broad spectrum of topics in kidney cancers, including a significant amount of emerging data on renal cell carcinoma. From early-phase clinical trials to updates on novel therapeutics, the sessions offered a unique opportunity to gauge progress on a broad spectrum of topics and envision how new information could have translational importance. The oral and poster presentations were worth reviewing to get a sense of where investigative work will point toward directions to be explored at future scientific sessions. Altogether, oncologists and researchers gathered at the IKCS meeting offered an intriguing picture of how the field is evolving in many directions, from prognostic factors, genetic analysis, stratification, genetic ancestry, IO/immunotherapeutic strategies, depth of response, and biomarkers. During this important discussion at the meeting, investigators debated some hot topics including treatment with adjuvant or without adjuvant therapy, doublet vs triplet therapeutic strategies, and surveillance vs interventions in renal cancers.

At this year's IKCS2022 meeting, two newly established awards were given by the Kidney Cancer Association. Importantly, the inaugural "*Kidney Cancer Association Nicholas J. Vogelzang Humanitarian Award*" was dedicated and awarded to the KCA's late co-founder, kidney cancer trailblazer, and colleague, Dr. Nicholas J. Vogelzang, MD, FACP, FASCO. The KCA will award this award annually at the IKCS: North America meetings each November. This KCA's new humanitarian award recognizes an individual who has made a great impact in highlighting kidney cancer advocacy as well as strides to raise awareness and resources to advance kidney cancer treatment and patient care. Another award known as the *Christopher G. Wood Rising Star* Award, established in memory of Dr. Christopher G. Wood, to commemorate his commitment to the kidney cancer community, was given to the early-career scientist or physician within seven years of an initial faculty appointment who embodies Chris' spirit for community and collaboration.

The utility of adjuvant immunotherapy has been associated with improved overall survival in patients with RCC. Recently, pembrolizumab was approved by the FDA for adjuvant setting in RCC with an intermediate-high or high-risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions based on

results of the KEYNOTE-564 study (NCT03142334). Despite the approval of pembrolizumab in the adjuvant setting, additional questions remain regarding how to treat patients who relapse on or soon after adjuvant therapy. Importantly, there is an unmet need for the optimal treatment strategy for patients with progression of disease on adjuvant therapy or recurrence after completing adjuvant therapy. Also, precise patient selection will be the key to influencing the benefit of adjuvant treatment. The ensuing article in this issue by Berger et al provides an algorithm for the treatment of recurrences in patients with mRCC during or after adjuvant IO, based on the pharmacokinetics/pharmacodynamics (PK/PD) of IO and the efficacy and adverse events. For example, authors recommend single-agent VEGFR TKI therapy for patients who progress while on adjuvant ICI, and for patients with recurrence after completing adjuvant pembrolizumab, authors recommend resumption of ICI with either combination ICI and VEGFR TKI, or dual ICI based on IMDC risk, time from completion of therapy, and patient-specific factors. For patients who did not tolerate adjuvant ICI, the severity of the irAE and time from discontinuation of therapy influence the decision on (ICI with VEGFR TKI versus single agent VEGFR TKI). In this issue, Dr. Matrana provided in-depth coverage for oral and poster abstracts presented at the IKCS2022. For the recommended abstracts section in this issue, I have provided key abstracts picked from the IKCS2022 sessions.

Holiday greetings to everyone!

Sincerely,

Robert A Figlin, MD

Abstracts Highlight Progress in the Fight Against Kidney Cancer - IKCS 2022

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ABSTRACT

The International Kidney Cancer Symposium (IKCS) took place in Austin, Texas November 4-5, 2022, providing an opportunity for kidney cancer researchers, clinicians, patients, and advocates to join together in-person and virtually to explore the latest science and emerging data in the fight again this dreaded disease. Here, we highlight key kidney cancer research updates presented at the meeting. Slides from the meeting's presentations are available on the KCA-IKCS meeting website.

The International Kidney Cancer Symposium (IKCS) took place in Austin, Texas November 4-5, 2022, providing an opportunity for kidney cancer researchers, clinicians, patients, and advocates to join together in-person and virtually to explore the latest science and emerging data in the fight against this dreaded disease.

Dr. David McDermott served as the conference's keynote speaker in a session moderated by Dr. Tian Zhang. Dr. McDermott's talk, entitled "Making Remissions More Common in Kidney Cancer," began with a focus on the rise of immunotherapies such as IL-2, followed by a decline during the development of targeted therapies, and the recent rise of

Figure 1. Oral presentation at the 2022 Kidney Cancer Symposium.

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immunotherapies again with the develop of PD-1/PD-L1 inhibitors. He discussed the importance of appropriate end-points in clinical trials, suggesting that "percent surviving" may provide a clearer picture of both early and late outcomes and a more robust measure of overall success. He ended his talk with a review of strategies being explored to increase immunotherapy effectiveness and elicit more durable remissions in advanced kidney cancers, including novel combination therapies, early work on TIL therapies, novel targets, and vaccines.

A number of oral abstract presentations illustrated knowledge around the basic biologic mechanisms driving kidney cancer. For example, Dr. Allison May presented an abstract that explored the capacity of spatial molecular imaging (SMI) to dissect the tumor immune microenvironment (TiME) and epithelial to mesenchymal transition EMT, specifically in sarcomatoid RCC. It is thought that sarcomatoid renal cell carcinoma (RCC) arises from other forms of the disease, most commonly clear cell RCC via EMT. May and colleagues spatially capture single cell level transcriptomic data from a RCC sample from a responder to immunotherapy and one from a non-responder. Forty fields of view and over 100,000 single cells were captured. They found significant differences in epithelial staining and the immune microenvironment between clear cell and sarcomatoid regions in the sample and unique differences between the immunotherapy responder and non-responder. Although the sample size of this study is too small to draw definitive conclusions, it does demonstrate the utility of this technique in sarcomatoid RCC.

Gemma Davies presented an interesting study of CD200, which along with its receptor CD200R is an immunosuppressive checkpoint which contributes to cancer cell immune evasion. These investigators found that ccRCC CD200 expression contributes to immune evasion by increasing Treg levels and causing activated NK cell dysfunction, apoptosis, and decreased cytotoxic

FIGURE 2. The Keynote speaker Dr. David McDemott delivering an oral talk at IKCS2022

response. They hypothesize that CD200:CD200R checkpoint inhibition may be a potential novel therapeutic target in ccRCC.

Other oral abstracts focused on advancing clinical science of kidney cancer. Dr. Blum presented a biomarker study of 18 patients with renal medullary carcinoma (RMC), in which he and his colleagues evaluated trends among several common biomarkers. They found that the magnitude of both lactic dehydrogenase (LDH) and CA-125 elevation was directly proportional to the total metastatic burden, and that CA-125 levels in widely metastatic patients were more than 200% higher than upper-limit normal. They concluded that biomarkers such as CA-125 may assist in predicting development of metastatic disease, trending treatment response or efficacy, identifying new therapeutic targets in RMC.

Overly stringent clinical trial eligiblity criteria create slow-accruing, lengthy, and expensive trials whose data are not usually generalizable to larger populations. A recent joint statement by the Friends of Cancer Research (FCR) and the American Society of Clinical Oncology (ASCO) has highlighted the need to broaden eligibility criteria in cancer trials to increase patient accrual and enhance the generalizability of study results. Daniela Castro systemically reviewed eligibility criteria in 423 RCC trials in the clinicaltrials.gov database to assess this issue, finding 112 trials that had enough publicly available data to be evaluable. She found that hepatitis, concurrent malignancies, HIV, and brain metastases were among the most frequently cited exclusionary criteria in these studies, and that a substantial proportion of RCC studies incorporated exclusionary criteria deemed by the FCR-ASCO statement to be potentially excessive.

Dr. Causa Andrieu presented a large database study of 25,200 patients who underwent germline analysis to investigate prevalence and features of rare hereditary RCC, including Hereditary Papillary Renal Carcinoma (HPRC), Birt-Hogg-Dube syndrome (BHDS), BAP1 tumor predisposition syndrome (TPDS), and Hereditary Paraganglioma/ Pheochromocytoma syndrome (PGL/PCC). Prevalence of related gene mutations were: MET: 1 mutation (with associated RCC) out of 25,000 (0.004%); FLCN: 17/25000 (0.067%), 23.5% of which had RCC; BAP1: 22/25000 (0.087%), 18.2% with RCC; and SDH: 39/25000 (0.155%), 23.1% with RCC.

Nazli Dizman presented the long-term follow-up results of a randomized phase Ib trial of 29 patients with metastatic RCC treated with nivolumab/ipilimumab (nivo/ipi) with or without CBM588, a bifidogenic live bacterial product. Overall response rate (ORR) was 20% in the control arm and 58% in those receiving CBM588 in addition to immunotherapy. Disease control rate was 79% in the experimental arm, compared to 20% those who did not receive CBM588. . Median progression free survival (PFS) was 36.4 (95% CI 9.4-63.5) months in the CBM588 arm versus 2.5 (95% CI 2.0-2.9) months in those receiving nivolumab and ipilumumab without CMB588. Median duration of response was 36.4 (95% CI 20.6-52.2) months in the experimental arm versus 4.5 (95% CI NA-NA) in the control arm. Median overall survival was not reached in either arm. The study was limited by small sample size, but the impressive results warrant further investigation of gut microbiome modulation in patients receiving immunotherapy for RCC.

Karie Runcie presented results of a trial exploring the ideal timing of holding neoadjuvant cabozantinib and nivolumab prior to nephrectomy, evaluating the safety of 14 days vs 21 days between discontinuation of cabozantinib and surgery. The study concluded that the combination of cabozantinib and nivolumab can be safely administered up to 14 days prior to cytoreductive nephrectomy.

Ritesh Kotecha presented an analysis of genetic ancestry and its molecular correlations within subtypes of RCC. The study analyzed 953 patients and found differences in histology, stage at presentation, rate of poor-risk disease, and genetic alterations among different ethnic groups. These researchers concluded that population-specific variations do exists in patients of different ancestry, however, it is challenging to determine what role genetic and non-genetic (social determinants of health for example) factors might play into creating the disparities seen amongst populations.

In addition to oral abstract sessions, more than 45 abstracts were selected for poster presentations,

amongst these were abstracts that focused on optimizing clinical aspects of kidney cancer management. For example, Dr. Sven Lundstam presented results of a study aimed at exploring the development of end-stage renal disease (ESRD) following treatment for RCC. They identified 215 patients with RCC and subsequent ESRD and compared these to 9,299 patients with RCC without ERSD from the National Swedish Kidney Cancer Register. The incidence of ESRD after diagnosis of RCC was 2.5%, ten times higher than in the control population. Radical nephrectomy compared to partial nephrectomy or tumor ablation was a significant risk factor during the first year following surgery, while male sex, advanced T-stage, diabetes, hypertension, chronic kidney disease were significant risk factors over a 5 year period following surgery.

Similar to exploring risk factors for ERSD in RCC patients, it is equally important to be able to predict which RCC are at higher risk for developing cardiotoxicity. Dr. Hesham Yasin presented a project that used artifacial intelligence (AI) to accurately predict which RCC patients had the highest cardiotoxicity risk. Dr. Yasin and colleagues suggested that integration of such AI models into electronic medical records (EMR) would assist physicians with identifying patients at highest risk and allow for expedited, proactive referrals for cardio-oncology treatment/monitoring.

Several abstracts explored various nuances of cytoreductive nephrectomy (CN), including one by Pranjal Agrawal that non-clear cell RCC histology doesn't negatively impact survival outcomes after CN for metastatic RCC compared to clear cell RCC, and another poster by the same author that showed inferior vena cava (IVC) tumor thrombectomy with concurrent CN is associated with surgical morbidity, but similar survival as compared to who underwent CN without IVC tumor thrombectomy. A poster by Dr. Andrew Hahn explored CN in patients with metastatic sarcomatoid and/or rhabdoid RCC who were treated with immune checkpoint therapy. This study found that CN offered no difference in immunotherapy treatment duration or differences in survival.

A study presented by Dr. Kelly Fitzgerald retrospectively analyzed 173 real-world patients undering first line combination therapy for metastatic clear cell RCC and found a significant difference in depth of response between those receiving combinations of two immunotherapies vs an immunotherapy and a targeted-therapy. More objective responses were seen in those receiving targeted-therapy based combinations (65%) compared to immunotherapy-only combinations (38%).

Several abstracts updated data from large prospective trials, such as the Checkmate 214 study which randomized patients to receive untreated metastatic RCC patients to receive nivolumab and ipilimumab versus sunitinib. At 60-months, treatment free survival (TFS) for favorable-risk patients was 14.4 months in the combination arm 5.5 months in the control arm, while TFS for intermediate/poor-risk patients at 60-months was 10.1 vs. 4.1 months.

An updated analysis from the CLEAR trial showed that metastatic ccRCC patients who completed 2 years of pembrolizumab combined with lenvatinib had an overall survival rate of 94.5%. A long-term analysis of the TIVO-3 study found that PFS was superior with tivozanib compared to sorafenib in second and third line metastatic RCC patients. Mean PFS rates were 12% and 7.6% at 3 and 4-years for those receiving tivozanib compared to 2% and 0% for those on the comparator arms during the same time periods.

Finally, a poster presented by Dr. Stephen Reese described features of NF2-mutated RCC, a lethal unclassified form of kidney cancer, which metastasizes early and is associated with a 18-month survival in this cohort. A number of posters also described trials in progress among other abstracts.

In summary, abstracts from IKCS 2022, continued to show the diverse work being done around the country and around the world in the fight against kidney cancer.

These recommended abstracts from IKCS 2022 Annual meeting have been selected by Robert A. Figlin, MD, Editor-in- Chief of the Kidney Cancer Journal. The chosen abstracts provided here highlight some of the most important trends in ongoing trials and reflect the foremost research and strategies from latest clinical trials that impact the current standard of care in renal cancer.

https://doi.org/10.52733/IKCS22abs

ABSTRACT 1: Spatial molecular imaging to profile the epithelial to mesenchymal transition and immune crosstalk in sarcomatoid renal cell carcinoma. *Allison May et al.*

BACKGROUND: Sarcomatoid renal cell carcinoma (RCC) is thought to arise from an epithelial to mesenchymal transition (EMT) of the parental tumor, most commonly clear cell RCC. These tumors are known to be highly immunogenic. Whether the EMT state impacts the immune milieu and responsiveness to immunotherapy, is unknown. This study explores the capacity of spatial molecular imaging (SMI) to dissect the tumor immune microenvironment (TiME) and EMT in sarcomatoid RCC.

METHODS: Nanostring's SMI platform, CosMx, was used to spatially capture single cell level transcriptomic data in two sarcomatoid RCC specimens, one from a responder to immunotherapy and one from a non-responder. Fields of view within sarcomatoid, clear cell, and transition areas were selected using H&E and further segmented with morphology markers SYTO11, PanCK, CD3, and CD45. We compared regions within each tumor and the two specimens.

RESULTS: Forty fields of view and over 100,000 single cells were captured. Epithelial staining was high in clear cell regions and decreased to near absent in the sarcomatoid regions. Distinct tumor cell clusters and differing immune cell types existed between clear cell and sarcomatoid areas. Clustering revealed shared tumor cell populations between the responder and non-responder as well as unique populations in each. In the sarcomatoid regions, immune infiltrate was dispersed in the non-responder, but clustered in perivascular regions in the responder. CD4+ naïve T cells and myeloid dendritic cells were higher in the responder while CD4+ memory cells, CD8+ naïve T cells, and plasmacytoid dendritic cells were more abundant in the non-responder.

CONCLUSIONS: We identified differences in the TiME between the responder and non-responder tumors that could contribute to immunotherapy responsiveness. Although no conclusions can be drawn due to the limited sample number, these data demonstrate the power of SMI to detect single cell level differences in sarcomatoid RCC in spatial relation to histology and the TiME.

ABSTRACT 3- Critical assessment of eligibility criteria in contemporary renal cell carcinoma (RCC) trials evaluating systemic therapy. *Daniela V. Castro et al.*

BACKGROUND: In a joint statement, the Friends of Cancer Research (FCR) and American Society of Clinical Oncology (ASCO) highlighted the need to broaden eligibility criteria in cancer trials to increase patient accrual and enhance the generalizability of study results (Kim et al., Clin Cancer Res 2021). In this study, we sought to characterize the frequency of exclusionary criteria in RCC trials deemed by the FCR-ASCO statement to be potentially excessive.

METHODS: Using ClinicalTrials.gov, studies with start dates from June 30, 2012 to June 30, 2022 were included. MeSH terms in our query were "(metastatic OR advanced OR stage IV OR unresectable) AND (kidney cancer OR renal cell carcinoma OR renal cell cancer)". Our query identified international studies examining patients age ≥ 18 in phase I-III trials. Pan-cancer studies and trials involving localized treatments, prognostic tools or radiation therapy were excluded from our analysis.

RESULTS: In total, 423 RCC trials were evaluated; of these, 112 (26.5%) had sufficient publicly available data for evaluation. Over one-third 44 (39.3%) of studies evaluated targeted therapy, 18 (16.1%) evaluated immunotherapy, and (48; 42.9%) evaluated combination therapy. The most frequently cited exclusionary criteria were the presence of hepatitis B/C positivity, concurrent malignancies, HIV positivity, and brain metastases, found in 100.0% (91/91), 100.0% (90/90), 98.9% (91/92) and 89.1% (90/101) of studies, respectively. Over the 10-year evaluation period, no significant trend was observed in use of these exclusionary criteria, nor were any significant differences observed in the use of these criteria among trials based on drug class.

CONCLUSIONS: A substantial proportion of contemporary RCC studies incorporate exclusionary criteria deemed by the FCR-ASCO statement to be potentially excessive. Broadening eligibility criteria will ensure that the resulting data is representative of real-world patient populations.

ABSTRACT 4 Delineating Clinical and Radiologic Features of Rare Kidney Cancer Genetic Syndromes *Pamela I. Causa Andrieu et al.*

BACKGROUND: Hereditary RCC accounts for 5%-8% of all malignant renal tumors, and NCCN recognizes 7 syndromes. Clinical-radiological features of 4 are scarcely researched: Hereditary Papillary Renal Carcinoma (HPRC), Birt-Hogg-Dube syndrome (BHDS), BAP1 tumor predisposition syndrome (TPDS), and Hereditary Paraganglioma/ Pheochromocytoma syndrome (PGL/PCC). The aim is to investigate the prevalence of

those syndromes, and prevalence, clinical features, and imaging features of RCC in these syndromes.

METHODS: IRB approved protocol. 25,220 patients with cancer underwent germline analysis, >70 cancer predisposing genes, from 2015 to 2021. We identified patients with germline pathogenic/likely pathogenic mutations in MET, FLCN, BAP1 and SDHx. We analyzed prevalence of germline mutations, and clinical records were reviewed for clinicopathologic characteristics. For patients with RCC, CT/MRI/PET/CT at presentation was reviewed independently by two radiologists for radiologic features.

RESULTS: Imaging features of hereditary RCC were similar to that of sporadic RCC. Mutation: Prevalence; %with RCC; mean age at diagnosis (years); histologic type; %metastasis at diagnosis; other cancers. MET: 1/25000 (0.004%); 100%, 67; Papillary (100%); 0%; none. FLCN: 17/25000 (0.067%); 23.5%; 55; Unclassified (75%), Clear cell (25%); 25%; Colon (17.6%), Lung (11.8%), Breast, Prostate, Oral SCC, endometrial, MMMT, pancreatic, thyroid (5.9%) BAP1: 22/25000 (0.087%); 18.2%; 58%; Clear cell (75%), Papillary (25%); 33%; Skin (40.9%), Mesothelioma (36.3%), Ovarian, cholangiocarcinoma (13.6%), Lung and HCC (9.1%), Colon, breast, oral SCC,xanthoastrocytoma (4.6%) SDH: 39/25000 (0.155%), 23.1%; 48; SDH-deficient (67%), Clear cell (11%), Not biopsied (22%); 14%; GIST (23.1%), Breast (10.3%), Colon (7.7%), Prostate (5.1%), Skin, adrenal, cervical, glioblastoma, Testicular GCT (2.6%)

CONCLUSIONS: These mutations are very infrequent, and RCC prevalence is up to 23% in them. RCC image features are similar to non-hereditary syndromes.

Feature	MET	FLCN	BAP1	SDH
Prevalence	1/25000 (0.004%)	17/25000 (0.067%)	22/25000 (0.087%)	39/25000 (0.155%)
% With RCC	100%	23.5%	18.2%	23.1%
Mean Age at diagnosis (years)	67	55	58	48
Histologic type	Papillary (100%)	Unclassified (75%) Clear cell (25%)	Clear cell (75%) Papillary (25%)	SDH-deficient (67%) Clear cell (11%) Not biopsied (22%)
% Metastasis at diagnosis	0%	25%	33%	14%
Other cancers	None	Colon (17.6%) Lung (11.8%) Breast, Prostate, Oral SCC, endometrial, MMMT, pancreatic, thyroid (5.9%)	Skin (40.9%) Mesothelioma (36.3%) Ovarian, cholangiocarcinoma (13.6%) Lung and HCC (9.1%) Colon, breast, oral SCC, xanthoastrocytoma (4.6%)	GIST (23.1%) Breast (10.3%) Colon (7.7%) Prostate (5.1%) Skin, adrenal, cervical, glioblastoma, Testicular GCT (2.6%)

ABSTRACT 5 - CD200-mediated immune evasion in clear cell renal cell carcinoma Gemma E.. Davies. *Powles T et al.*

BACKGROUND: Interaction of CD200 with its receptor, CD200R, is an immunosuppressive checkpoint which contributes to cancer cell immune evasion. We have shown this interaction can protect CD200+ tumour cells by reducing CD200R+ natural killer (NK) cell cytotoxic activity and causing NK cell apoptosis in other cancer types. Bioinformatic analysis revealed a change in NK phenotype from active to resting with increased CD200 expression in clear cell renal cell carcinoma (ccRCC). We hypothesised that CD200 signalling may contribute to disease progression by promoting immune evasion.

METHODS: Normal kidney (n=30) and ccRCC tissue samples (n=300) were used to determine CD200 expression and immune response (CD4+ T Helper, CD8+ Cytotoxic T, FoxP3+ Treg and NK cells) by frequency and cell density/mm2. Immune response was compared between CD200 weak, moderate and strong expressing tumour samples. Co-culture of NK cells with ccRCC cell lines was used to determine the effect of CD200 on NK cell activation by measuring CD107a expression and tumour cell killing by NK cells. Western blot was used to study apoptotic markers.

RESULTS: Treg density and frequency increased with higher tumour CD200 expression ($p=0.0001$ and $p=0.0034$ respectively), resulting in an immunosuppressive environment. NK cell density and frequency also increased with greater CD200 expression ($p=0.0013$ and $p=0.0004$ respectively), however NK and ccRCC cell co-culture showed a decrease in CD107a expression ($p=< 0.0001$) and ccRCC cell killing. Western blot showed an increase in activated NK cell apoptosis.

CONCLUSIONS: ccRCC CD200 expression contributes to immune evasion by increasing Treg levels and causing activated NK cell dysfunction, apoptosis, and decreased cytotoxic response. Therefore, inhibition of the CD200:CD200R checkpoint may present a novel therapeutic target in ccRCC management

ABSTRACT 12: Outcomes of active surveillance for young and healthy patients with small renal masses.

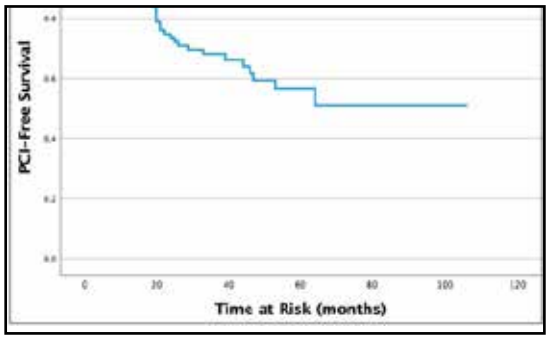
Muammer Altok et al.

BACKGROUND: Reported outcomes for active surveillance (AS) in patients with small renal masses (SRM) are heavily biased towards older and unhealthier patients. The safety, tolerability and rates of delayed intervention (DI) for AS in younger and healthier SRM patients remains largely unexplored. Here we report outcomes at a single center for SRM patients with life expectancy (LE) >20 years managed with AS.

METHODS: From January 2013-March 2019, all patients with non-hereditary SRM presenting to a single urologic oncologist at a National Comprehensive Cancer Network institute were recommended AS if predefined PCI were absent. PCI was defined prospectively as any SRM-related symptoms, unfavorable biopsy histology, cT3a stage, or either of the following without benign neoplastic biopsy histology: longest tumor diameter (LTD) >4 cm; growth rate >5 mm/year for LTD ≤3 cm or >3 mm/year for LTD >3 cm. DI was recommended during AS only upon PCI development. Patients with LE >20 years were retrospectively identified using social security estimates adjusted by age, gender and Charlson Index. 3- and 5-year rates of PCI-freedom and DI-freedom were determined.

RESULTS: Among 90 consecutive SRM patients with LE >20 years (median age 57, IQR 47-61), 89 (99%) patients (101 SRMs) did not meet PCI at presentation and underwent AS. With median follow-up of 44 months, 31/89 (35%) AS patients developed PCI, of whom 21/31 (68%) underwent DI (all surgery). One (1%) AS patient crossed over to DI without PCI development. 3- and 5-year PCI-free rates were 68% and 56%, respectively, and 3- and 5-year DI-free rates were 75% and 67%, respectively. No patient developed metastasis.

CONCLUSIONS: AS using predefined PCI in otherwise unselected SRM patients is well tolerated and allows most SRM patients with >20 years LE to avoid treatment over 5 years. Long-term DI rates and oncologic safety require further study.



ABSTRACT 15: Survival Outcomes Following Adoption of Risk-Adjusted AUA Surveillance Guidelines After Partial Nephrectomy. *Wesley Yip et al.*

BACKGROUND: AUA guidelines for follow-up of clinically localized renal neoplasms in 2013 introduced risk-adjusted follow-up recommendations after partial nephrectomy (PN), with less frequent surveillance imaging in low-risk patients. We sought to evaluate the impact of guideline adherence at our institution on outcomes in affected patient cohorts.

METHODS: 3255 patients underwent PN between January 2000 and March 2017. We used Kaplan-Meier methods to estimate metastasis-free (MFS), cancer-specific (CSS), and overall survival (OS), and multivariable Cox proportional hazard regression for each outcome, with follow-up before or after guideline implementation as the predictor, adjusted for guideline risk [low (pT1, N0/X) vs moderate/high (pT2+)].

RESULTS: The "before" (N=2289) and "after" (N=966) groups showed similar overall tumor characteristics: median tumor size 2.9 cm in both groups; tumor stage pT1 in 79% and 80%; positive surgical margin rates of 5.8% and 5.1%, respectively. 296 patients died from any cause, 24 of whom died from kidney cancer. 47 patients had biopsy-proven metastases (Table 1), with a median follow-up time among survivors of 4.4 years (IQR 2.0, 7.6). The "after" group had significantly better MFS (HR: 0.34; 95% CI 0.13, 0.87; p =0.024) and non-significantly better CSS (HR: 0.28; 95% CI 0.06, 1.20; p = 0.086) and OS (HR: 0.75; 95% CI 0.51, 1.12; p = 0.2).

CONCLUSIONS: Detection of metastases following PN is a rare event, regardless of follow-up regimen. Adoption of the AUA guidelines may increase MFS but does not impact CSS or OS, which supports guideline adherence for risk-adapted follow-up of clinically localized renal neoplasms after PN.

	PN Before Guidelines (N=44)	PN After Guidelines (N=3)
Location		
Lymph Nodes	7	0
Bone	5	0
Pulmonary	15	1
Non-Pulmonary Visceral	7	1
Pulmonary and Non-Pulmonary Visceral	5	1
Other Combination	5	0
Imaging Ordered for Symptoms	16	0
Imaging Ordered on Surveillance Protocol	23	3
Detection Imaging Modality		
CT	36	3
MR	3	0
XR	4	0
Nuclear Medicine	1	0
Initial Therapeutic Outcome		
Observation	8	1
Systemic Therapy	14	2
Surgical Resection	16	0
Radiation Therapy	1	0
Multimodality	5	0

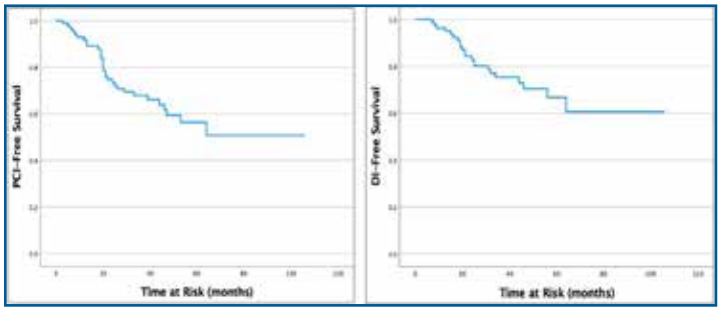
ABSTRACT 21: Short-Term Outcomes of Active Surveillance for Small Renal Masses in Patients With End-Stage Renal Disease and Immunosuppression. *Zoe S. Gan et al.*

BACKGROUND: Renal transplant candidates are often referred to urology for treatment of a small renal mass (SRM) suspicious for a cT1a renal cell carcinoma. Active surveillance (AS) for SRMs may minimize morbidity of treatment, but outcomes of AS in renal transplant candidates and immunocompromised patients have not been established.

METHODS: The multi-institutional Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) prospective registry, including patients with SRMs ≤ 4 cm from 2009 onwards, was reviewed up to December 2021. Patients with end-stage renal disease (ESRD) or immunocompromised status (prior organ transplant, immunosuppressive medications, leukemia or lymphoma, HIV or AIDS) were included. For included patients, the following variables were extracted: follow up period, mass size at diagnosis, mass growth rate, timing and type of intervention if applicable, and development of metastases.

RESULTS: Of 15 patients with ESRD (including 8 transplant candidates), the mean size of the SRM at diagnosis was 2.3 cm, and over a mean follow up period of 2.4 years, the mean SRM growth rate was 0.1 cm/year. Six patients (40%) underwent either intermediate (4 patients) or delayed intervention (2 patients). Of 11 patients (60%) remaining on surveillance, none developed metastases. Of 44 immunosuppressed patients, the mean size of the SRM at initial diagnosis was 1.9 cm, and over a mean follow up period of 3.5 years, the mean SRM growth rate was 0.2 cm/year. Fourteen patients (32%) underwent either immediate (9 patients) or delayed intervention. Of 30 patients (68%) remaining on surveillance, none developed metastases.

CONCLUSIONS: Limited prospective data suggests that ESRD and immunosuppressed patients on AS for SRMs have similar short-term outcomes to those of immunocompetent controls with SRMs of the same size, suggesting promise for the safety of AS in renal transplant recipient candidates.



	FREQUENCY			OVERALL SURVIVAL*	
Depth of response	Overall (N=173)	First-line IO/IO (n=90)	First-line TKI/IO (n=83)	No. of events	24-month survival estimate (95% CI)
CR	20 (12%)	9 (10%)	11 (13%)	1	94% (65, 99)
PR1	21 (12%)	9 (10%)	12 (14%)	1	100%
PR2	18 (10%)	7 (8%)	11 (13%)	5	94% (63, 99)
PR3	29 (17%)	9 (10%)	20 (24%)	8	79% (57, 91)
SD	62 (36%)	36 (40%)	26 (31%)	30	57% (42, 69)
PD	22 (13%)	19 (21%)	3 (4%)	12	52% (29, 71)

*Median follow-up times for survivors is 32 months.

ABSTRACT 24: Depth of response associated with first-line immunotherapy-based combinations in metastatic clear cell renal cell carcinoma. *Kelly N. Fitzgerald et al.*

BACKGROUND: The First-line treatment options for clear cell renal cell carcinoma (ccRCC) include ipilimumab with nivolumab (IO/IO) or several VEGFR-targeted therapies in combination with a PD-1 inhibitor (TKI/IO). Depth of response (DpR) has been proposed as a predictor of sustained benefit from IO-based therapies. Here, we examine the relationship between DpR and OS in patients receiving 1st line IO/IO vs TKI/IO for metastatic ccRCC.

METHODS: A retrospective analysis was performed on patients treated for ccRCC with 1st line IO/IO or TKI/IO at MSKCC between 1/1/2014 and 12/30/2020. DpR is defined as the nadir of tumor shrinkage by RECIST 1.1 criteria. Partial response groups were defined as PR1 (80-99%), PR2 (60-79%), and PR3 (30-59%). Overall survival (OS) from start of 1st line therapy to death or last follow-up is estimated with the Kaplan-Meier method and reported for each DpR group.

RESULTS: One hundred seventy-three patients received 1st line IO/IO (N=90) or TKI/IO (N=83). Differences in the IO/IO group versus TKI/IO include more patients with brain metastases (9% vs 0, p=0.007) and intermediate-poor IMDC risk (88% vs 68%, p=0.007), and fewer with prior nephrectomy (67% vs 86%, p=0.005). Objective response rates for IO/IO and TKI/IO groups were respectively 38% (95% CI: 28, 49) and 65% (95% CI: 54, 75; P< 0.001). Patient distribution across response groups is shown in Table 1; the difference in distribution was significantly different between IO/IO and TKI/IO treatment groups; P=0.002. Twenty four-month survival estimates for response groups are shown in Table 1.

CONCLUSIONS: Patients receiving first-line IO/IO or TKI/IO therapies had a significant difference in the distribution of radiographic DpR groups, with more CR and PR seen in the TKI/IO group and more SD and PD seen with IO/IO. Patients whose best response was CR, PR1, or PR2 had higher 24-month OS than patients with PR3, SD, or PD.

ABSTRACT 34: Characterization of Patients Undergoing Consolidative Nephrectomy after Immunotherapy. *Stephen Reese et al.*

BACKGROUND: There remains uncertainty around how to manage patients who experience complete or partial responses after systemic therapy and then undergo consolidative nephrectomy.

METHODS: We conducted a single-institution (Memorial Sloan Kettering Cancer Center) retrospective analysis of patients treated with immunotherapy with metastatic cancer at the time of treatment (n=23). Patients were stratified based on final surgical pathology given presence of residual disease or pT0. Overall survival (OS) was calculated by the Kaplan-Meier method

RESULTS: All patients had metastatic disease at presentation and almost all had clear cell histology (n=22). All patients who had pT0 at time of surgery were treated with combination ipi + nivo, were on systemic therapy for almost a year prior to surgery and had a significant change in size of primary tumor (-3.75cm). 14 patients (60.87%) had stable mets or were NED after surgery. Median follow-up after surgery was 33 months. Median OS was not reached at time of follow-up, however survival was 52% for patients with residual tumor and 100% for pT0 patients.

CONCLUSIONS: Patients with metastatic disease who demonstrated partial or complete response after immunotherapy and subsequently underwent consolidative nephrectomy had durable overall survival at follow-up, including a sub-set of pT0 patients who were all alive at follow-up.

Table 1. Cohort of patients undergoing consolidative nephrectomy

	Residual Disease (n=17)	pT0 (n=6)	
Patient Characteristics			
Age	61.963 (12.63)	63.783 (9.91)	P=0.21
Gender			P=0.54
Male	17 (94.12%)	6 (100%)	
ASA	3 (0)	3 (0)	P=0.10
Survival Status			
Months Follow-up	33.13 (23.50)	31.30 (57.27)	P=0.57
% OS Survival	9 (52.94%)	6 (100%)	P=0.05
Post-op Clinical Course			P<0.01
Progression	9 (52.94%)	0 (0%)	
Stable Mets	6 (35.29%)	1 (16.67%)	
NED	2 (11.76%)	5 (83.33%)	
Tumor Characteristics			
Stage at Diagnosis			P=1.00
Metastatic (M1)	17 (100%)	6 (100%)	
Size of Primary Tumor at Diagnosis	7.30 (4.4)	7.55 (1.6)	p=0.72
Change In Primary Mass Size from Diagnosis to Surgery	0 (1.80)	-3.75 (1.6)	<0.01
Histology			P=0.54
Clear Cell	16 (94.12%)	6 (100%)	
Unclassified	1 (5.88%)	0 (0%)	
Sarcomatoid Features			P=0.19
Yes	4 (23.53%)	0 (0%)	
Upfront Immunotherapy			P=0.16
IO	2 (11.76%)	0 (0%)	
IO/IO*	11 (64.71%)	5 (83.33%)	
IO/VEGF	4 (23.53%)	0 (0%)	
Interferon	0 (0%)	1 (16.67%)	
Time on Immunotherapy prior to Surgery (years)	0.75 (0.84)	0.88 (1.00)	P=0.79

* All patients received Nivolumab + Ipilimumab as combination IO therapy.

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FRACTION-RCC: nivolumab plus ipilimumab for advanced renal cell carcinoma after progression on immuno-oncology therapy. *Choueiri T et al. 2022. Nov;10(11):e005780.*

Over the past decade, only minor changes have been introduced .The role and sequencing of combination immuno-oncology (IO) therapy following progression on or after first-line IO therapy has not been well-established. The Fast Real-time Assessment of Combination Therapies in Immuno-ONcology (FRACTION) program is an open-label, phase 2 platform trial designed to evaluate multiple IO combinations in patients with advanced renal cell carcinoma (aRCC) who progressed during or after prior IO therapy. Here, we describe the results for patients treated with nivolumab plus ipilimumab. For enrollment in track 2 (reported here), patients with histologically confirmed clear cell aRCC, Karnofsky performance status ≥70%, and life expectancy ≥3 months who had previously progressed after IO (anti-programmed death 1 (PD-1), anti-programmed death-ligand 1 (PD-L1), or anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4)) therapy were eligible. Previous treatment with anti-CTLA-4 therapy plus anti-PD-1/PD-L1 therapy precluded eligibility for enrollment in the nivolumab plus ipilimumab arm. Patients were treated with nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for four doses, followed by nivolumab 480 mg every 4 weeks for up to 2 years or until progression, toxicity, or protocol-specified discontinuation. The primary outcome measures were objective response rate (ORR), duration of response (DOR), and progression-free survival (PFS) rate at 24 weeks. Secondary outcomes were safety and tolerability up to 2 years. Overall survival (OS) was a tertiary/exploratory endpoint. Overall, 46 patients were included with a median follow-up of 33.8 months. The ORR was 17.4% (95% CI, 7.8 to 31.4) with eight (17.4%) patients achieving partial response. Stable disease was achieved in 19 (41.3%) patients, while 14 (30.4%) had progressive disease. Median DOR (range) was 16.4 (2.1+ to 27.0+) months. The PFS rate at 24 weeks was 43.2%, and median OS was 23.8 (95% CI, 13.2 to not reached) months. Grade 3-4 immune-mediated adverse events were reported in seven (15.2%) patients. No treatment-related deaths were reported. Patients with aRCC treated with nivolumab plus ipilimumab may derive durable clinical benefit after progression on previous IO therapies, including heavily pretreated patients, with a manageable safety profile that was consistent with previously published safety outcomes. These outcomes contribute to the knowledge of optimal sequencing of IO therapies for patients with aRCC with high unmet needs.

A Renewal of the TNM Staging System for Patients with Renal Cancer To Comply with Current Decision-making: Proposal from the European Association of Urology Guidelines Panel. *Capitanio U et al. Eur Urol. 2023 Jan;83(1):3-5.*

Over the past decade, only minor changes have been introduced in the TNM staging system for renal cancer. Conversely, many milestones and modifications in management of the disease have been achieved, especially for patients with locally advanced and metastatic cancers. The European Association of Urology guidelines panel proposes a new TNM classification scheme for staging of renal cell carcinoma to reflect these breakthrough clinical improvements.

A multicenter study assessing survival in patients with metastatic renal cell carcinoma receiving immune checkpoint inhibitor therapy with and without cytoreductive nephrectomy.. *Gross EE et al. Urol Oncol. 2023 Jan;41(1):51.e25-51.e31.*

FINDINGS: Between Oct 13, 2016, and July 24, 2019, 355 patients were randomly assigned to the lenvatinib plus pembrolizumab group, 357 to the lenvatinib plus everolimus group, and 357 to the sunitinib group. Median follow-up for HRQOL analyses was 12·9 months (IQR 5·6-22·3). Because of the promising efficacy and safety results of lenvatinib plus pembrolizumab in the first-line setting, we focus the HRQOL results in this report on that combination versus sunitinib. Mean change from baseline in the lenvatinib plus pembrolizumab group compared with the sunitinib group was -1·75 (SE 0·59) versus -2·19 (0·66) for FKSI-DRS, -5·93 (0·86) versus -6·73 (0·94) for EORTC QLQ-C30 global health status/quality of life (GHS/QOL), and -4·96 (0·85) versus -6·64 (0·94) for the EQ-5D visual analogue scale (VAS). Median time to first deterioration in the lenvatinib plus pembrolizumab group compared with the sunitinib group was 9·14 weeks (95% CI 6·43-12·14) versus 12·14 weeks (9·14-15·29; HR 1·13 [95% CI 0·94-1·35], log-rank p=0·20) for FKSI-DRS, 12·00 weeks (7·29-15·14) versus 9·14 weeks (6·29-12·14; 0·88 [0·74-1·05], log-rank p=0·17) for EORTC QLQ-C30 GHS/QOL, and 9·43 weeks (6·43-12·29) versus 9·14 weeks (6·29-12·00; 0·83 [0·70-0·99], log-rank p=0·041) for the EQ-5D VAS. Median time to definitive deterioration in the lenvatinib plus pembrolizumab group compared with the sunitinib group was 134·14 weeks (95% CI 120·00-not estimable) versus 117·43 weeks (90·14-131·29; HR 0·70 [95% CI 0·53-0·92]. No outcomes on any of the instruments significantly favoured sunitinib over lenvatinib plus pembrolizumab. Most HRQOL comparisons of lenvatinib plus everolimus versus sunitinib were similar or favoured sunitinib.

Association of C-reactive protein with efficacy of avelumab plus axitinib in advanced renal cell carcinoma: long-term follow-up results from JAVELIN Renal 101. *Tomita Y. ESMO Open 2022 Oct;7(5):100564.*

RESULTS: In the avelumab plus axitinib and sunitinib arms, respectively, 234, 51, and 108 patients and 232, 36, and 128 patients were categorized into normal, normalized, and non-normalized CRP groups. In respective CRP groups, objective response rates [95% confidence interval (CI)] were 56.0% (49.4% to 62.4%), 66.7% (52.1% to 79.2%), and 45.4% (35.8% to 55.2%) with avelumab plus axitinib and 30.6% (24.7% to 37.0%), 41.7% (25.5% to 59.2%), and 19.5% (13.1% to 27.5%) with sunitinib; complete response rates were 3.8%, 11.8%, and 0.9% and 3.0%, 0%, and 1.6%, respectively. Median progression-free survival (95% CI) was 15.2 months (12.5-21.0 months), not reached (NR) [11.1 months-not estimable (NE)], and 7.0 months (5.6-9.9 months) with avelumab plus axitinib and 11.2 months (8.4-13.9 months), 11.2 months (6.7-13.8 months), and 4.2 months (2.8-5.6 months) with sunitinib; median OS (95% CI) was NR (42.2 months-NE), NR (30.4 months-NE), and 23.0 months (18.4-33.1 months) and NR (39.0 months-NE), 39.8 months (21.7-NE), and 19.1 months (16.3-25.3 months), respectively. Multivariate analyses demonstrated that normalized or non-normalized CRP levels were independent factors for the prediction of objective response rate or OS, respectively, with avelumab plus axitinib.

CONCLUSIONS: In patients with aRCC, CRP levels at baseline and early after treatment may predict efficacy with avelumab plus axitinib.

Temporal Characteristics of Adverse Events of Tivozanib and Sorafenib in Previously Treated Kidney Cancer. *Zengin ZB et al.* Clin Genitourin Cancer. 2022 Dec;20(6):553-557.

MATERIALS AND METHODS: In this open label, randomized, phase 3 TIVO-3 study, previously treated patients with a diagnosis of metastatic renal cell carcinoma and with measurable disease were included. Patients were randomized to receive either tivozanib 1.5 mg orally once daily in 4-week cycles or sorafenib 400 mg orally twice daily continuously. Based on updated safety analysis data (cutoff date of August 15, 2019), time to onset of the most commonly reported TRAEs, duration of toxicity, rate of dose modifications was calculated for each treatment arm.

RESULTS: Overall, 350 patients were randomly assigned to receive tivozanib or sorafenib;173 patients from the tivozanib arm and 170 patients from the sorafenib arm were included in this analysis. Patients received a median of 11.9 cycles (336 days) and 6.7 cycles (192 days) of tivozanib and sorafenib, respectively. Dose reductions, interruptions and treatment discontinuations were

25%, 50%, and 21%, and 39%, 50%, and 30% in the tivozanib and sorafenib arms, respectively, with a longer time to onset of TRAEs in the tivozanib arm.
CONCLUSION: Tivozanib was associated with less TRAEs, fewer dose modifications, a longer time to onset and a shorter duration of TRAEs compared to sorafenib.

Cost-effectiveness of Adjuvant Pembrolizumab After Nephrectomy for High-risk Renal Cell Carcinoma: Insights for Patient Selection From a Markov Model. *Sharma V. J Urol. 2023 Jan;209(1):89-98. PMID: 36067373.*
ABSTRACT: The accumulation of immune-suppressive myeloid cells is a critical determinant of resistance to anti-programmed death-1 (PD-1) therapy in advanced clear cell renal cell carcinoma (ccRCC). In preclinical models, the tyrosine kinase inhibitor sitravatinib enhanced responses to anti-PD-1 therapy by modulating immune-suppressive myeloid cells. We conducted a phase 1-2 trial to choose an optimal sitravatinib dose combined with a fixed dose of nivolumab in 42 immunotherapy-naïve patients with ccRCC refractory to prior antiangiogenic therapies. The combination demonstrated no unexpected toxicities and achieved an objective response rate of 35.7% and a median progression-free survival of 11.7 months, with 80.1% of patients alive after a median follow-up of 18.7 months. Baseline peripheral blood neutrophil-to-lymphocyte ratio correlated with response to sitravatinib and nivolumab. Patients with liver metastases showed durable responses comparable to patients without liver metastases. In addition, correlative studies demonstrated reduction of immune-suppressive myeloid cells in the periphery and tumor microenvironment following sitravatinib treatment. This study provides a rationally designed combinatorial strategy to improve outcomes of anti-PD-1 therapy in advanced ccRCC.

Transcriptomic Correlates of Tumor Cell PD-L1 Expression and Response to Nivolumab Monotherapy in Metastatic Clear Cell Renal Cell Carcinoma. *Denize T et al, Clin Cancer Res. 2022 Sep 15;28(18):4045-4055.*
RESULTS: In both the paired samples and the CM-025 cohort, TC PD-L1 expression was associated with combined overexpression of immune- and cell proliferation-related pathways, upregulation of T-cell activation signatures, and increased tumor-infiltrating immune cells. In the CM-025 cohort, TC PD-L1 expression was not associated with clinical outcomes. A molecular RCC subtype characterized by combined overexpression of immune- and cell proliferation-related pathways (previously defined by unsupervised clustering of transcriptomic data) was enriched in TC PD-L1 positive tumors and displayed longer progression-free survival (HR, 0.32; 95% confidence interval, 0.13-0.83) and higher objective response rate (30% vs. 0%, P = 0.04) on nivolumab compared with everolimus.
CONCLUSIONS: Both TC-extrinsic (immune-related) and TC-intrinsic (cell proliferation-related) mechanisms are likely intertwined in the regulation of TC PD-L1 expression in ccRCC. The quantification of these transcriptional programs may better predict benefit from anti-PD-1-based therapy compared with TC PD-L1 expression alone in ccRCC.

Epidemiology of Renal Cell Carcinoma: 2022 Update. *Bukavina L, et al.* **Eur Urol. 2022 Nov;82(5):529-542.**
CONCLUSIONS: KC incidence and mortality rates vary significantly by geography, sex, and age. Associations of the development of KC with modifiable and fixed risk factors such as obesity, hypertension, smoking, and chronic kidney disease (CKD)/end-stage kidney disease (ESKD) are well described. Recent advances in the genetic characterization of these cancers have led to a better understanding of the germline and somatic mutations that predispose patients to KC development, with potential for identification of therapeutic targets that may improve outcomes for these at-risk patients.

WHO 2022 landscape of papillary and chromophobe renal cell carcinoma. *Lobo J et al. Histopathology. 2022 Oct;81(4):426-438.*
RESULTS: The 5th edition of the WHO Classification of Tumours of the Urinary and Male Genital Systems contains relevant revisions and introduces a group of molecularly defined renal tumour subtypes. Herein we present the World Health Organization (WHO) 2022 perspectives on papillary and chromophobe renal cell carcinoma with emphasis on their evolving classification, differential diagnosis, and emerging entities. The WHO 2022 classification eliminated the type 1/2 papillary renal cell carcinoma (pRCC) subcategorization, given the recognition of frequent mixed tumour phenotypes and the existence of entities with a different molecular background within the type 2 pRCC category. Additionally, emerging entities such as biphasic squamoid alveolar RCC, biphasic hyalinising psammomatous RCC, papillary renal neoplasm with reverse polarity, and Warthin-like pRCC are included as part of the pRCC spectrum, while additional morphological and molecular data are being gathered. In addition to oncocytomas and chromophobe renal cell carcinoma (chRCC), a category of 'other oncocytic tumours' with oncocytoma/chRCC-like features has been introduced, including emerging entities, most with TSC/mTOR pathway alterations (eosinophilic vacuolated tumour and so-called 'low-grade' oncocytic tumour), deserving additional research. Eosinophilic solid and cystic RCC was accepted as a new and independent tumour entity. Finally, a highly reproducible and clinically relevant universal grading system for chRCC is still missing and is another niche of ongoing investigation. This review discusses these developments and highlights emerging morphological and molecular data relevant for the classification of renal cell carcinoma.

5-year outcomes after stereotactic ablative body radiotherapy for primary renal cell carcinoma: an individual patient data meta-analysis from IROCK (the International Radiosurgery Consortium of the Kidney). *Siva S et al. Immunother Cancer. 2022 May;10(5):e004885. doi: 10.1136/jitc-2022-004885.PMID: 35640928.*
METHODS: This study was an individual patient data meta-analysis, for which patients undergoing SABR for primary renal cell carcinoma across 12 institutions in five countries (Australia, Canada, Germany, Japan, and the USA) were eligible. Eligible patients had at least 2 years of follow-up, were aged 18 years or older, had any performance status, and had no previous local therapy. Patients with metastatic renal cell carcinoma or upper-tract urothelial carcinoma were excluded. SABR was delivered as a single or multiple fractions of greater than 5 Gy. The primary endpoint was investigator-assessed local failure per the Response Evaluation Criteria in Solid Tumours version 1.1, and was evaluated using cumulative incidence functions.
FINDINGS: 190 patients received SABR between March 23, 2007, and Sept 20, 2018. Single-fraction SABR was delivered in 81 (43%) patients and multifraction SABR was delivered in 109 (57%) patients. Median follow-up was 5·0 years (IQR 3·4-6·8). 139 (73%) patients were men, and 51 (27%) were women. Median age was 73·6 years (IQR 66·2-82·0). Median tumour diameter was 4·0 cm (IQR 2·8-4·9). 96 (75%) of 128 patients with available operability details were deemed inoperable by the referring urologist. 56 (29%) of 190 patients had a solitary kidney. Median baseline estimated glomerular filtration rate (eGFR) was 60·0 mL/min per 1·73 m2 (IQR 42·0-76·0) and decreased by 14·2 mL/min per 1·73 m2 (IQR 5·4-22·5) by 5 years post-SABR. Seven (4%) patients required dialysis post-SABR. The cumulative incidence of local failure at 5 years was 5·5% (95% CI 2·8-9·5) overall, with single-fraction SABR yielding fewer local failures than multifraction (Gray's p=0·020). There were no grade 3 toxic effects or treatment-related deaths. One (1%) patient developed an acute grade 4 duodenal ulcer and late grade 4 gastritis.

Remembering Dr. Nicholas Vogelzang, MD

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Dr. Nicholas J. Vogelzang, a globally renowned oncology leader, whose generous bedside manner and impressive accessibility to patients made him beloved by those in his care and colleagues, has died at the age of 72. Dr. Vogelzang was known for his pioneering work in kidney cancer and genitourinary oncology space, extraordinary leadership in the field as well as in the development of clinical trials and therapeutics. At the recent IKCS2022 annual meeting, the entire cancer community honored and celebrated Dr. Vogelzang's life and work as we mourn his passing. Here are excerpts from the talks delivered by renowned oncologists Drs. Brian Rini, Sumanta Pal, and Walter Stadler at IKCS2022 Annual conference held in Austin Texas.

Dr. Nicholas Vogelzang

Dr. Brian Rini:

I think we all agree that we could probably spend the whole day talking about Nick (Dr. Nicholas Vogelzang). It's just a joy and a passion he brought to everything he did. When I was on my oncology rotation at the University of Chicago in late 1995, I first met Nick during the last week. We finished talking about patients and he launched into a didactic about chemotherapy and its mechanisms. We learned more from him in that 15 minutes than we had learned from previous attendings.

He brought back an unbridled passion for teaching and mentoring. He is the reason I became an oncologist/GU oncologist. When I see patients with Nick, I would go into the room as a fellow before his arrival. I can always feel that patients wanted to meet Dr. Vogelstein. I start to chat with the patient and then Nick would often come storming into the room and engage with patients with incredible warmth, passion, and kindness. Sometimes, Nick would talk about different mechanisms of drugs and the interesting part is that patients always knew that he was excited for them and he would do anything for them. That is why I think patients loved Nick more than any other physicians I've ever worked with. Because they knew that Nick was by their side through good times and bad times. When I got a call from Nick, I didn't quite realize how sick he was. He said, *"Hey, I just wanted to thank you for everything that you've done for me"*. He is just the kind of gracious guy who sees only good things in people. I just wanted to thank him for putting up with me. For all these years, I kept learning from him. I miss him tremendously. He will always be an influence on me. I hope to make him proud for the rest of my career.

Patients always knew that he was excited for them and he would do anything for them. That is why I think patients loved Nick more than any other physicians I've ever worked with. Because they knew that Nick was by their side through good times and bad times.

Dr. Sumanta Pal:

I met Dr. Nicholas Vogelzang at my first SWOG meeting which had a profound influence on my career. During the meeting, we became good friends and our conversations very quickly extended beyond. I started approaching Nick with key questions and also whenever I had a professional career or industry trial opportunity. Nick would always very graciously send his patients to get second opinions from us, which never made sense to me because he taught me everything I knew about kidney cancer. But having said that, seeing Nick's patients is itself a great learning experience, especially looking through his notes and understanding the rationale for his diagnostic and treatment strategies and also learning how to personally interact with patients. I would say you could learn from his notes and become a better doctor. His notes included so many intricate details including patient's occupation, and the names of their grandkids along with some fun facts like their favorite flavor of ice cream or favorite car etc.

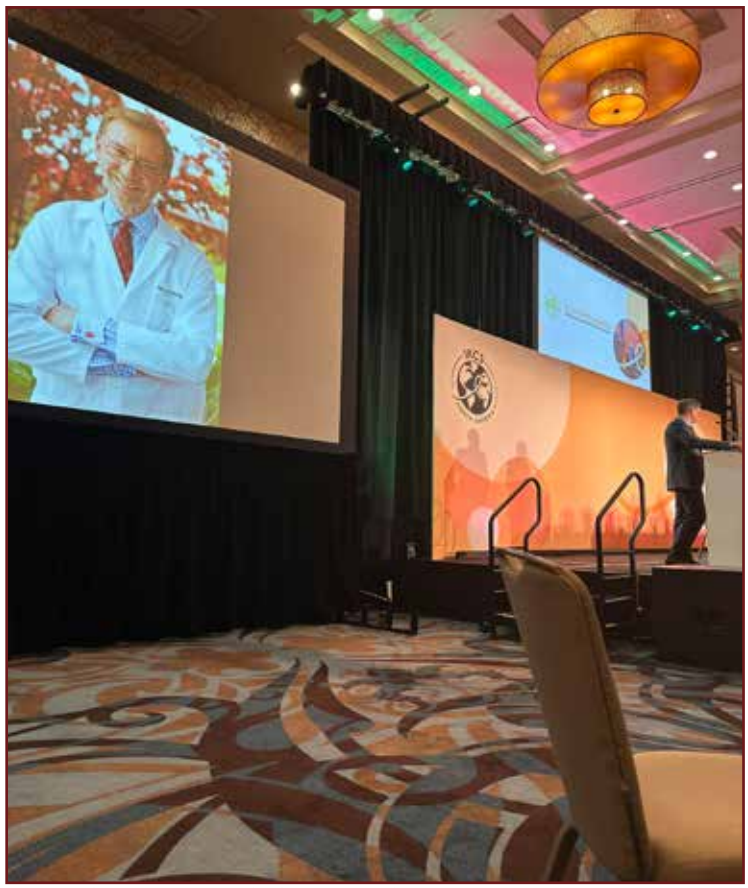
Whenever he saw a clinical design on the screen at the SWOG meeting. He always wanted to see data with the patient's best interest in mind. Nick authored nearly thirty SWOG-related publications. Among those, he neither claimed first-authorship nor senior authorship with one exception. That is just a testimonial to his incredibly selfless professionalism. He always wanted to give the first authorship to junior faculties. This year, SWOG has move forwarded with a memorial fund to honor Nick and sponsor an annual symposium organized by SWOG members. This year's theme is the biomarkers in the bladder. I think that we can carry on Nick's legacy perhaps by carrying on what Nick did in terms of putting patients first and foremost and also by emulating his compassion for trainees, junior faculties, researchers, and colleagues.

Dr. Walter Stadler:

I want to thank everybody for allowing me to say a few words about Nick with whom I have had the longest professional relationship. Frankly, without Nick, I would not be here as a professional and the KCA would not be here successfully.

I think many of his interactions with patients reflected the passion and the beliefs he brought from his family into the clinic. He was also a cancer patient and he understood what it meant to be a patient. He was a mentor. He was a colleague. But most importantly, he was a friend to me.

I, as a trainee clinician, had an opportunity to work with Nick. He would schedule 15 patients for seven slots.



Remembering Dr. Nicholas J. Vogelzang at IKCS2022 Session

Patients were usually ticked, mad, and tired as they were waiting for a long time. However, as soon as Nick enters the room to greet the patient, he directly connects well with patients through their personal lives. It was a skill I've learned so much from and yet I'll never be as good.

` During my rotation days, we, trainees were told to stand up and present an idea that Nick thought just a few minutes ago. But in the end, it taught me to get prepared. It taught me to stand on my feet and it taught me to be analytical. It taught me to be calm and face criticism. I did not realize that he was teaching that to me. Most importantly, he was the patient's advocate. When he and Eugene Schonfeld got together to do something great for patients, they founded KCA. This shows individuals can influence the world. Because of Nick, the KCA organization exists.

He was always thinking of other people. He was always thinking about what they did for him and not the other way around. I just hope that somewhere along the line, I get the wisdom and fortitude to pay it forward. I miss him. Rest in peace.

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