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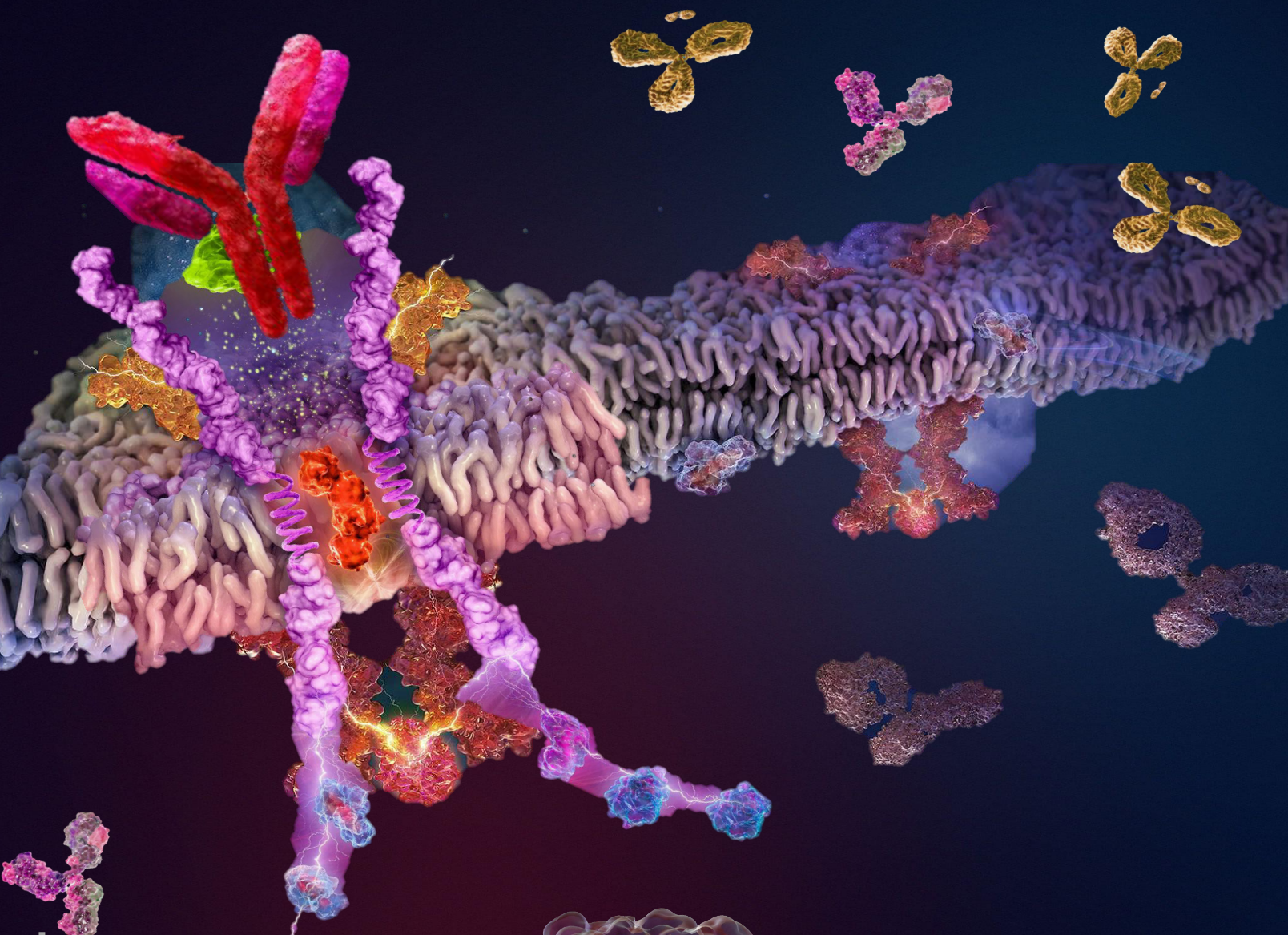

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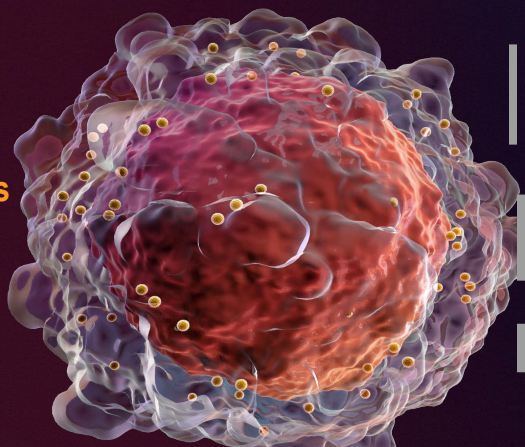

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KCJ REVIEW ARTICLE

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Optimal Duration of Therapy in Metastatic RCC: Exploring Treatment-Free Survival with Checkpoint Inhibitors

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ABSTRACT

The optimal duration of treatment for patients with metastatic renal cell carcinoma (mRCC) on dual immune checkpoint inhibitor (ICI) therapy remains unknown. However, there is evolving evidence that a portion of patients who achieve a complete or partial response will have a durable response, even after therapy discontinuation, leading to a prolonged treatment free survival (TFS). TFS with dual ICI is a phenomenon not seen with targeted agents and has the potential to improve patient reported outcomes and quality of life, without altering overall survival (OS). Despite this understanding, treatment of mRCC remains lifelong, as there has yet to be a prospective, randomized control trial to evaluate this key question. In this review, we analyze available studies in patients with mRCC on dual ICI therapy and propose considerations for early treatment discontinuation. Additionally, we discuss vital questions and next steps to help physicians and patients navigate these challenging treatment decisions.

KEYWORDS: Treatment-Free Survival; Complete Response; Partial Response; Immune Checkpoint Inhibitor; Renal Cell Carcinoma; Kidney Cancer.

INTRODUCTION

Each year there are approximately 79,000 new cases of kidney cancer in the United States[1]. This number has steadily risen since early 1990s, at least in part due to more sensitive imaging techniques. Over the last 10 years the number of new kidney and renal pelvis cases have increased by 0.6%, though death rates over this period have fallen by 1.6% [2]. Nevertheless, despite our diagnostic and therapeutic advances, kidney cancer ultimately results in about 13,920 deaths per year in the United States 1. Over the last 20 years, treatment of metastatic renal cell carcinoma has drastically changed resulting in prolonged survival. Systemic therapeutic options now include immune checkpoint inhibitors (ICI) and targeted therapies (TT) in combination or in sequence based on Phase III clinical trials demonstrating an overall survival advantage. Most of these studies were designed for treatment to continue indefinitely, until disease progression or unacceptable toxicities. Historically, this approach made sense since most patients progressed or developed unacceptable toxicities by year two. However, in the setting of immune checkpoint inhibitors, a substantial percentage of patients tolerate therapy without disease progression for several years. By protocol, these patients should continue therapy indefinitely, but is that necessary? To date, few if any studies have been designed to address this question.

Prognosis and Phases of Overall Survival

As we continue to investigate novel biomarkers to help predict how patients may respond to therapy, many other factors, both patient- and disease-specific, should be examined to help determine optimal treatment duration. Overall survival is considered the gold standard when evaluating new therapeutics in RCC. However, in patient centric oncologic care, other end points are also important to consider. Overall survival can be broken down into three distinct phases: time on therapy, treatment-free survival (TFS), time on subsequent therapy or death (Figure 1). In the targeted therapy era, monotherapies were typically sequenced, with little TFS, since outcomes were linked to dose-intensity; however, in the ICI era there may be an opportunity for meaningful TFS without compromising OS[3]. Critically evaluating these intervals are of the upmost importance when determining the optimal treatment strategy. Median overall survival for intermediate/poor risk mRCC has dramatically improved with the

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FIGURE 1 | Three Phases of Overall Survival *(not to scale)*

use of combination therapy, with OS approaching 47 months with dual ICI and 37.7 months with nivolumab plus cabozantinib[4, 5]. Despite these significant advancements, a large majority of this time is spent in clinic, between lab draw, scans, provider visits and infusion appointments. This does not account for any unplanned hospital admissions to address severe adverse events. Time spent interacting with the healthcare system, in addition the potential for a wide spectrum of side effects, limits quality of life(QOL). Identifying a finite treatment duration, without reducing OS, would provide patients with the needed balance between maintaining an adequate QOL outside of the hospital while continuing to battle their disease.

Immunotherapy for mRCC

The systemic treatment landscape for metastatic renal cell carcinoma has been dramatically changed by the advent of immunotherapy, initially with nivolumab (N), a PD-1 inhibitor and later with combination therapy including PD-(L)1 inhibitors with TKI as well as dual immune checkpoint inhibitor therapy. Based on the groundwork laid by CheckMate 025, 016 and 214, ipilimumab (I) and nivolumab (N) are currently the only combination immunotherapies approved in the metastatic, treatment naïve intermediate and poor-risk (I/P) setting. However, optimal duration of maintenance therapy with N has yet to be elucidated. This vital piece of information is critical, yet there is no robust data to predict who will respond to treatment and when to consider treatment discontinuation.

CheckMate 025 was the first phase III study to evaluate single agent nivolumab versus everolimus in patients with previously treated metastatic RCC. Nivolumab demonstrated an improved in OS and toxicity profile when compared to everolimus [6]. Given the benefits seen with ICI monotherapy, CheckMate 016, a phase I study, evaluated the efficacy and safety of dual ICI with ipilimumab and nivolumab (I+N) in the first line setting. Patients were randomized into three treatment arms to evaluate varying dosing schema, ultimately concluding that N at 3 mg/kg plus I at 1 mg/kg provided similar ORR and 2 year-OS to other dosing regimens, while minimizing toxicity[7]. Based on these results, a larger, randomized phase III multicenter placebo control study, CheckMate 214, began enrolling patients with previously untreated, I/P, metastatic RCC[8]. Patients were randomized to either N at 3 mg/kg plus I at 1 mg/kg every 3 weeks for 4 d oses followed by N at 3mg/kg every 2 weeks (I+N) or sunitinib (S), continued until disease progression or unacceptable toxicity. Notably, a protocol amendment was made 3 years into data collection, which allowed for nivolumab discontinuation at 2 years in the absence of progression or toxicity. Initial 18 month follow up demonstrated improved median progression free survival (PFS), overall response rate (ORR), treatment-free survival (TFS), medial overall survival (OS) and patient reported outcomes (PRO) in those treated with I + N vs S [8].

Treatment with dual immune check point inhibitor (ICI) therapy has improved overall survival for patients with metastatic RCC, with about 10% of patients achieving a durable complete response (CR), and another 28% achieving a partial response (PR) with varying degree of tumor shrinkage[8]. There are many theories as to why patients have such a heterogenous response to ICIs, with two possibilities involving the "cancer-immune set point" and tumor microenvironment (TME). The "cancer-immune set point" is defined as the equilibrium between anti-tumor immunity promotors and suppressors. A certain threshold must be surpassed for a patient to optimally respond to immunotherapy. This "set-point" is felt to vary widely between patients, and likely contributes to the heterogenous treatment responses[9]. This equilibrium can wax and wane overtime, reflecting the tumor's development of novel resistance patterns. In such cases, the continued priming of the immune system with ongoing therapy may be vital to maintain a durable response. Varying dosing schema are currently under investigation[10,11]. The presence of immune cell infiltration in the tumor and the surrounding microenvironment are also thought to be necessary, though not sufficient, to achieve a response to ICI. Checkpoint inhibitor therapy is known to decrease T cell exhaustion and promote the conversion to effector and memory T cells, which is likely necessary to achieve a durable treatment response despite treatment discontinuation[9]. This unique durable response has not been seen with other cancer

directed therapies and has allowed physicians to consider treatment discontinuation; allowing patients to benefit from a prolonged treatment-free survival.

Definition of Treatment-free Survival and Key Questions

Treatment-free survival (TFS) is an important metric to understand how patients live with their cancer. TFS is defined as the time from treatment discontinuation until the start of subsequent therapy or death. While overall survival is the gold standard to determine optimal therapy, treatment-free survival should not be overlooked, as it almost certainty leads to improved financial, physical, and psychological burdens that come along with chronic monthly infusional therapy. The key question is, what treatment-free interval is meaningful to patients? If overall survival is similar, would a prolonged treatment-free survival be appealing, or would it simply promote increased anxiety and fear of recurrence? These important questions will need to be explored further in subsequent studies to help physicians and patients make important treatment decisions.

TFS in CheckMate 214

The treatment-free survival has been evaluated as a secondary endpoint in numerous studies. One such study included work by Regan et. al, who sought to evaluate the TFS following the discontinuation of therapy in patients with I/P risk disease treated on CheckMate 214. Treatment-free survival and overall survival were evaluated at 42 months. At time of evaluation 20% of patients treated with dual immune checkpoint inhibitor (ICI) compared to 9% treated with sunitinib were treatment-free. Over the 42-month period, the mean TFS and OS for patients with I/P risk mRCC was significantly longer when treated with I+N vs S, 6.9 (22.9% of OS) and 30.1 months versus 3.1 months (11.9% of OS) and 25.9 months respectively (Figure 2). In the favorable risk population, TFS was even longer, 11.0 months vs 3.7 months[12]. When TFS was further broken down, it was significantly longer for patients who had an objective response to therapy and even longer in those who achieved a CR, a median (range) of 23.5 months and 34.6 months (0.5-49.7 months) respectively[13, 14]. Ongoing studies across risk groups are aimed at predicting who are most like to objectively respond to treatment.

The median treatment duration reported in the 42 month analysis in the I/P risk population was 14.1 months on I+N versus 10.8 months on S. Responders remained on therapy longer, with a median duration of treatment of 20.6 months (17.7-23.2) and 21.2 months (18.9-24.4) for the I+N and S cohorts respectively [8, 12, 15]. Despite differing time on protocol therapy, the median time between treatment discontinuation until death was similar, at 16 months on I+N vs 15.1 months on S; but the differences were seen in the percentages of patients reaching a TFS, with 43% vs 20% of patients recording a TFS for I+N vs S respectively (Figure 2). When critically evaluating the TFS in patients treated on CheckMate 214, one must take into consideration that the initial protocol did not allow discontinuation of therapy until disease progression or TRAE until an amendment almost 3 years into trial. Presumably, there are a portion of patients with CR/PR who could have stopped therapy at 2 years, or earlier, if protocol allowed, which would have further prolonged the treatment-free survival [12].

Since the initial publication of CheckMate 214, updated analyses have been performed. At 4 years since randomization (median follow up 55 months), 53 (10%) of 547 patients in I+N arm and 15 (3%) of 535 patients in S arm were continued on therapy. The median OS in I/P risk groups was an impressive 48.1 months with I+N vs 26.6 months for sunitinib (HR 0.65; 95% CI, 0.54-0.78). Dual ICI demonstrated a fouryear OS probability of 50%, vs 35.8% with

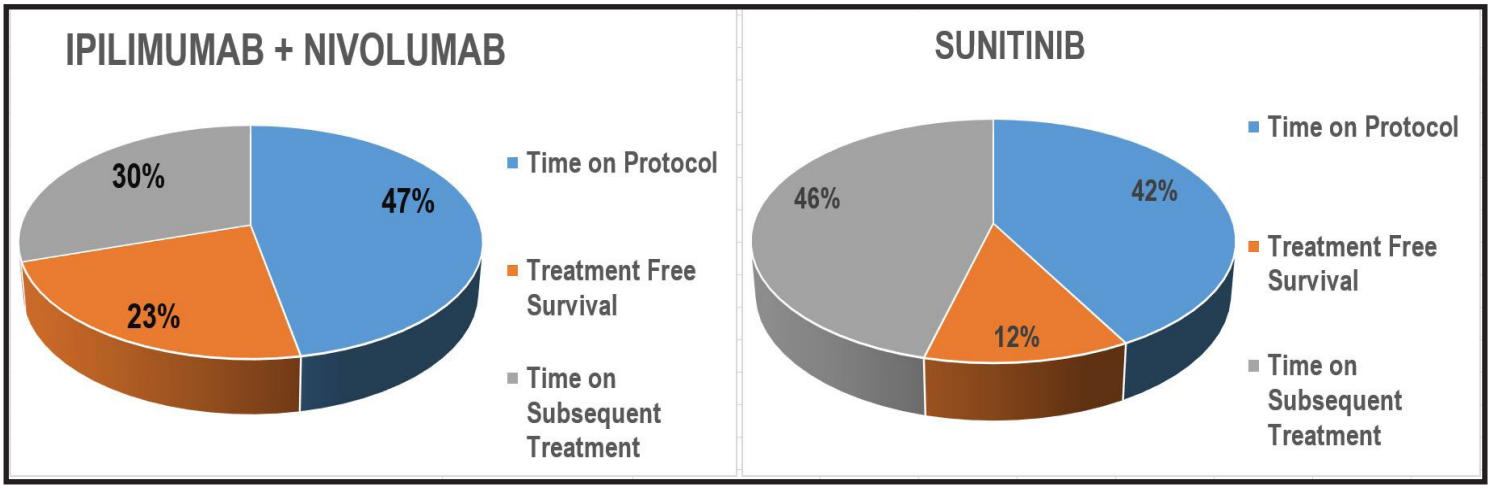

FIGURE 2 | Adapted from Regan *et al* [12]. Percent of OS Spent in Each Phase: Time on Protocol Therapy, Treatment-Free Survival and Time on Subsequent Therapy based on treatment in patients with I/P risk metastatic RCC. OS was 30.1 months with I+N and 25.9 months with S at this 42-month analysis, and patients on the I+N arm had a longer treatment free survival (orange).

	Ipilimumab + Nivolumab *	Sunitinib#
No. Patients with CR	59 (10.7%)	14(2.6%)
On Treatment	19 (32.2%)	3 (21.4%)
Ongoing Response	*18/19 (94.7%)*	*3/3 (100%)*
Off Treatment	27 (45.7%)	3 (21.4%)
Ongoing Response	*25/27 (92.5%)*	*2/3 (66.6%)*
Subsequent Treatment	13 (22%)	8 (57.1%)
Ongoing Response	*12/13 (92.3%)*	*7/8 (87.5%)*

TABLE 1 | TFS in patients on CheckMate 214 who achieved CR at 4 years [4]
*547 patients treated with Ipilimumab + Nivolumab;
#535 patients treated with sunitinib

sunitinib (53.4% vs 43.3% in the ITT population)[4]. Five-year data was recently published (median follow up 67.7 months), which again confirmed superior OS for I/P risk patients with I+N vs S, median OS 47.0 vs 26.6 months (HR 0.68 and 95% CI 0.58 to 0.81), respectively. Five-year OS probabilities were 43% on I+N versus 31% on S[16, 17]. Responders to I+N appeared to have decreased disease burden and higher PD-L1 expression as compared to nonresponders, with 75% of responders achieving an objective response by 4 months [15].

TFS with Complete Response (CR)

At 4 years, 10.7% (59) of patients achieved a complete response on I+N, with over 75% of these responses occurring by 11.3 months (3.8-15.4). Most converted from a PR (75.9%) or SD (19%), as opposed to achieving a CR at time of initial scan [15]. Of the fifty-nine patients who achieved a CR on I+N, 19 (32.2%) remained on therapy at 4 years. 94.7% (18/19) patients who were continued on I+N had an ongoing response at the time of analysis. 45.8% (27) patients treated with I+N discontinued therapy and did not require additional treatment. 92.5% (25/27) of patients on I+N who discontinued therapy after a CR, had an ongoing response off treatment. This is in stark contrast to only 2.6% (14) patients who achieved a CR on S. Of the 14 patients with a CR, 3 remained on therapy, 3 had treatment discontinued and an additional 8 were started on subsequent therapy with 3 (100%), 2 (66%) and 7(87.5%) patients demonstrating an ongoing response[4, 14].

The percentage of patients with ongoing response on I+N were almost identical for patients who were continued on therapy compared to those who discontinued, 94.7% and 92.5%, respectively. Notably, only 21.4% (3/14) patients on S who had a CR discontinued therapy with 66% (2/3) of patients demonstrating an ongoing response. 22% (13) of patients treated with I+N went on to subsequent therapy after ICI discontinuation, though only 23% (3/13) of these patients had findings of progressive disease. Strikingly, in the favorable risk group treated with I+N, thirteen patients discontinued treatment with 5/13 receiving subsequent therapy despite only 7.6% (1/13) of patients demonstrating evidence of disease progression. Conversely, even after achieving a CR, 57% (8/13) of patients treated with S were started on subsequent therapy with 87.5% (7/8) with an ongoing response (Table 1)[4]. Based on these data, it may be reasonable to conclude that patients who achieve a CR on I+N can safely discontinue therapy with a high likelihood of having a durable response. Discontinuation may be further supported in patients with favorable risk disease who achieve a CR, though notably, combined immunotherapy is not approved in this setting. Further analysis of this group should include time to first response, time to complete response and time on therapy prior to discontinuation. Evaluation of minimal residual disease (MRD), circulating tumor DNA (ctDNA) and other pathologic factors should be investigated further, to help clinicians make educated treatment decisions.

	Ipilimumab + Nivolumab*	Sunitinib#
No. Patients with PR	156* (28.5%)	163# (30.4)
On Treatment	28 (17.9%)	9 (5.5%)
Ongoing Response	*22/28 (78.5%)*	*8/9 (88.8%)*
Off Treatment	67 (42.9%)	39 (23.9%)
Ongoing Response	*46/67 (68.6%)*	*19/39 (48.7%)*
Subsequent Treatment	61 (11.1%)	115 (21.4%)
Ongoing Response	*27/61(44%)*	*58/115 (50%)*

TABLE 2 | TFS in patients on CheckMate 214 who achieved PR at 4 years.
*547 patients treated with Ipilimumab + Nivolumab;
#535 patients treated with sunitinib

TFS with Partial Response (PR)

One-hundred and fifty-six (28.5%) patients achieved a partial response on I+N. 17.9% (28) remained on treatment at 4 years, with 78.5% (22) of these patients demonstrating an ongoing response. In contrast, only 5.5% (9) of patients on S remained on treatment at 4 years, with 88% (8/9) maintaining an ongoing response. 42.9% (67) of patients treated with I+N discontinued therapy without the need for subsequent treatment. 31.3% (21/67) of patients with a PR off I+N eventually progressed, whereas 51.2% (20/39) of patients who discontinued therapy with S eventually progressed (Table 2) [4]. So, in summary, the CheckMate 214 data suggests there is about a 31% chance of disease progression for patients who discontinue I+N after a PR vs 51% chance of disease progression in patients treated with S. This is in comparison to a 21% chance of disease progression in those who remain on therapy after PR compared to 11% of disease progression on S. These odds may give physicians pause when considering therapy discontinuation in patients with a PR. In the future, the Depth of Response (DepOR) should be further evaluated to see if patients who achieve a greater DepOR have improved durable responses aftertreatment discontinuation.

Depth of Response in Contemporary Studies

In the analysis above, patients who achieved a PR were not further separated by their Depth of Response (DepOR). Suarez at al looked at the association between DepOR and clinical outcomes in patients with advanced RCC, treated on CheckMate 9ER. This phase III trial compared cabozantinib plus nivolumab versus sunitinib in patients with advanced, previously untreated RCC. The depth of response was defined as the best percent tumor reduction from baseline. This study concluded that deeper responses led to improved 12-month PFS and 18-month OS rates. Interestingly, patients with a CR and PR1 (≥80% reduction in tumor burden) achieved similar OS[18]. The median time to response was similar across groups, suggesting that time to response may not be as vital. Further analysis should be pursued, to see if patients with varying DepOR can discontinue therapy early.

TFS for Dual ICI Therapy in Context

Based on what we learned from CheckMate 214, when treated with dual check point inhibitors, the TFS appears to be far longer than with targeted therapy alone. Tzeng et al sought to expand this data, performing a systematic review and meta-analysis to evaluate the treatment-free survival in objective responders with mRCC who discontinued ICIs[13]. Sixteen cohorts were analyzed, comprising 1833 patients treated with either ICI monotherapy, dual ICI or an ICI plus targeted therapy. A total of 572 (31.2%) patients had either a partial or complete response and 327 (57%) of those patients discontinued therapy. Interestingly, 85 (26%) patients demonstrated an ongoing response off therapy with TFS of 35%(95% CI 20-50%) and 20% (95% CI 8 to 35%) at 6 and 12 months respectively. However, these 16 studies were extremely heterogenous. Differences in TFS between patients achieving a CR vs PR were not analyzed. When this data was broken down by treatment, the TFS was significantly higher when treatedwith dual immunotherapy as compared to an immunotherapy plus VEGF combination. Six- and 12-month TFS rates were 57% (95% CI, 41-73%) and 50% (95% CI, 32-68) when treated with dual ICI as compared to only 20% (95% CI, 2-45%) and 5% (95% CI 0-17%) when treated with and an ICI plus VEGR TKI combination[13]. This significant difference should be considered when choosing initial therapy for patients whose goal is to achieve a period of TFS.

Correlation of Immune-Related Adverse Events and TFS

The durability of response and treatment-free survival is especially important for patients who have had severe immune related adverse events (irAE), as these are often a driving factor for treatment discontinuation. While some patients have mild irAE and can be restarted on therapy, others develop life-threatening issues mandating that treatment be halted. Treatment related adverse events leading to discontinuation were more common with dual checkpoint inhibitor therapy vs sunitinib, occurring in 22% vs 13% respectively. Patients treated with ICI spent more time off treatment, with two-thirds of this time was without a grade ≥2 treatment-related adverse event (TRAE). Conversely, patients treated with sunitinib had a shorter treatment-free survival with about two-thirds of this time with a grade ≥ 2 TRAE[12].

Understanding the depth and durability of response, as well as the safety of restarting therapy following an irAE, is of upmost importance. A multicenter retrospective review by Alaiwi et. al. evaluated patients with mRCC who required at least a 1 week break on immunotherapy. Sixteen percent (80 patients) of patients required treatment interruptions with 45% able to restart therapy, while 55% percent discontinued treatment permanently. The median treatment break was 0.9 months (0.2-31.6 months). Following retreatment, half experienced a second irAE. Interestingly, only one-third of these patients experienced the same adverse reaction while two-thirds experienced a new side effect with median time to recurrent irAE 2.8 months, which was similar to time of first irAE, 2.7 months[19]. Future studies should investigate if patients who have an irAE have an increased chance of achieving a

durable response. This should be further broken down by degree and type of irAE.

Dosing Strategies to Promote TFS with IO Therapy

While prolonged TFS has the potential to improve QOL, alternative dosing strategies may also improve toxicity profiles and patient reported outcomes, without reducing OS. Intermittent dosing strategies have been under investigation to help answer these questions. Ornstein et al conducted a small phase II trial to evaluate the role of intermittent nivolumab dosing for patients with IMDC I/P risk mRCC, previously treated with antiangiogenic therapy with the hope of gaining additional insights into optimal treatment schedule and duration. Patients were treated with nivolumab monotherapy for twelve weeks at which point disease response was assessed. Patients with < 10% tumor burden reduction were continued on nivolumab monotherapy and reassess at 3-month intervals. However, if patients had ≥10% tumor burden reduction they were placed in a treatment-free observation phase, again with imaging every 3 months. This classification and intervention were continued until RECIST-defined progression of disease (PD). Patients who did not achieve at least 10% tumor burden reduction at 6 months were removed from study and treated with nivolumab standard of care [10].

Fourteen patients were included in the study. ORR was 29%, with 4 patients (29%) achieving a PR, 6 with SD (49%) and 4 with PD (29%) at median follow up of 6 months. Median PFS was 7.97 months. Five out of fourteen (38%) of patients were eligible to stop therapy and all agreed. Four out of the five patients achieved this response after only 12 weeks of treatment. At median follow up of 48 weeks only 1 patient needed to restart therapy. The four remaining patients have had a clinical response for a median of 34 weeks (range 16-54) off therapy and a median tumor burden decrease of 46.5% (38-80%)[10]. This study demonstrates that patients may be interested in less frequent therapy, with the notion that treatment breaks result in decreased cumulative toxicity, with possibility for decreased adverse events along with possibly reduced financial toxicity.

CONCLUSION AND SUMMARY

Systemic treatment of metastatic renal cell carcinoma has dramatically improved in the last 5 years with the use of immune checkpoint inhibitors and targeted therapy. These treatment breakthroughs have led to improved overall survival, though currently, treatment for mRCC remains indefinite.

When it comes to first line treatment, physicians have a variety of therapeutics to choose from including dual ICI and ICI/TT combinations. There are many patient and disease specific factors that can help guide these important treatment decisions. For example, a critically ill patient with the need for a rapid treatment response would likely choose ICI+TT combination over dual ICI. Similarly, a patient with a strong history of autoimmune disorders may choose to forego ICI therapy altogether and begin TT monotherapy. However, for the right patient, dual ICI therapy offers the potential for a more durable response with improved TFS and QOL[8, 12, 13].

Overall survival is the hallmark of effective treatment. However, there are many other factors that should be considered when determining the ideal treatment strategy, including treatment tolerability, risk of TRAE, durability of response and the ability to discontinue therapy in favor of close monitoring. CheckMate 214 and subsequent sub-analyses provided great insight towards answering these questions. Patients treated with dual ICI were noted to have more durable and deeper responses, as compared to ICI/TT combination or TT monotherapy[12, 13]. Overall, TFS was more than two times longer with dual ICI vs S, 6.9 months compared to 3.1 months which represents meaningful time away from the hospital and clinic[12].

Patients treated with dual ICI also had significantly higher chance of achieving a CR, 10.7% as opposed to only 2.6% of patients treated with **S**. In this subset of patients, the

LINGERING QUESTIONS
What is the optimal treatment duration and which patients can safely stop?
• Can time to first response or time to CR help predict who can discontinue therapy early?
• How long following a CR must patient's stay on therapy?
• Do patients who have an irAE have an increased chance of achieving a durable response?
• Do patients with a greater depth of response (DepOR) have improved durable responses?
• Does the type or grade of irAE predict response to therapy?
• Can you use molecular profiling or other biomarkers to determine who may be a good candidate for early discontinuation
What treatment free survival would be considered meaningful to patients?
• If overall survival is similar, would a prolonged treatment free interval be appealing, or would it simply promote increased anxiety and fear of recurrence?
• Will the improved HRQOL with I+N seen in CM 214, persist off therapy?

TABLE 3 | Lingering questions.

mean TFS after dual ICI was 34.6 months (0.5-49.7) with objective responders treated for an average of 20.6 months (17.7-23.2) prior to treatment discontinuation[14, 15]. Secondary analyses noted that patients with lower disease burden and higher PD-L1 status were more likely to achieve this coveted CR, though more robust data is needed to help predict who will best respond to therapy[15].

Ultimately, there are many questions still left unanswered. The optimal treatment duration for patients treated with dual ICI is still unknown. After considering that data presented above, it may be reasonable to consider treatment discontinuation for patients who achieved a CR, in favor of active surveillance. Ongoing response rate after CR were similar regardless of whether therapy was continued or stopped, 94.7% versus 92.5% respectively. However, based on the data currently available, the risk of discontinuing therapy after a PR in the I/P risk population may be too great. Future studies should further evaluate TFS based on the depth of response (DepOR), as patients with a deeper DepOR may also have a prolonged TFS, similar to those with a CR. Additionally biomarkers, such as use of next generation sequencing results, ctDNA and MRD, may prove beneficial to help predict who may best respond to ICI therapy. For example, patients with more favorable mutations, such as PBRM1, may be able to discontinue therapy earlier then patients with BAP1 alterations, which have been traditionally associated with a worse prognosis[20]. Finally, while CheckMate 214 reported improved patient reported outcomes on dual ICI vs S, there is limited QOL data during the treatment-free period. These and other questions must be answered to provide patients with improved treatment strategies and QOL, Table 3.

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A 20-year retrospective: How Kidney Cancer Journal Reflected on Advances in The Therapeutic Strategies

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ABSTRACT

The last two decades of the kidney cancer therapeutic landscape encapsulate the most dramatic advances ever achieved in the management of localized and advanced renal cell carcinoma (aRCC). During these years, Kidney Cancer Journal also published some important pieces of research and provided coverage in the kidney cancer space. Herein, we would like to reflect on the journal's contents that informed key advances in the treatment strategies, milestones, and management of cancer during the last two decades of the KCJ's journey

KEYWORDS: Renal Cell Carcinoma; Immune Checkpoint Inhibitors; IFN-α; VEGF-TKIs; mTOR; Cytoreductive Nephrectomy.

INTRODUCTION

There has been tremendous progress in the treatment landscape of aRCC with the expansion of the therapeutic armamentarium of targeted therapies. The vast knowledge that we have gained in the last few years, at a certain point, led to a qualitative and quantitative leap in the treatment era. Over the last two decades, KCJ disseminated and educated clinicians about groundbreaking research and translational scientific discoveries that served as a touchstone for potential treatment strategies. Our editorial contents have kept clinicians on the leading edge of the evolution in cancer therapy as well as closely reflected on advances in cancer care. The original concept of quarterly publication representing in-depth articles, future perspectives, scientific forums, timely reviews, latest breakthroughs, and conference coverages offered tantalizing previews of practice-changing research updates. In this review, we explore novel first-line treatment strategies and provide an overview of the efficacy and safety of emerging investigational agents in the front-line aRCC setting.

VEGF-targeted therapies

The first-line treatment landscape has transitioned from recombinant cytokines to tyrosine kinase inhibitors (TKI), mammalian target of rapamycin (mTOR) inhibitors, and most recently, immune checkpoint inhibitors (ICI) in recent years. With the improved understanding of the implications of von Hippel–Lindau gene mutations in angiogenic pathways, many VEGF-based tyrosine kinase inhibitors (TKIs) evolved as the de facto choice of first-line systemic therapy[1]. For the favorable-risk disease category. Over the last few years, KCJ provided in-depth coverage on VEGF-TKI-based targeted therapies. In particular, our roundtable discussion provided expert perspectives on cabozantinib in 2015 and 2017[2,3]. Similarly, our roundtable discussions provided coverage for tivozanib monotherapy based trials in 2021 and 2022[4,5] and its combinations[6,7].

Based on the phase III trial outcomes, sunitinib, pazopanib, and bevacizumab/IFN-α angiogenic agents[8-11] were approved by FDA/EMA as a front-line treatment. Sunitinib and pazopanib represent an effective first-line VEGFR TKIs and NCCN Kidney Cancer Panel has listed sunitinib and pazopanib as preferred category I. For more than a decade, sunitinib, an orally administered multi-target TKI remained the standard-of-care targeted therapy and as main comparator in clinical trials as well. The survival benefit of sunitinib was evident in the pivotal randomized phase III trial in which sunitinib treatment resulted in improved PFS as compared with IFN-α in the first-line setting (11.0 vs. 5.0 months)[8]. Although a higher OS in patients treated with sunitinib was observed as compared with those treated with IFN-α (26.4 versus 21.8 months, respectively), it lacked statistical significance[8,9]. In 2006 by the FDA and EMA sunitinib was approved multi-nationally for the first- and second-line treatment of metastatic renal cell carcinoma (mRCC).

Based on a randomized, double-blind, phase III VEG105192

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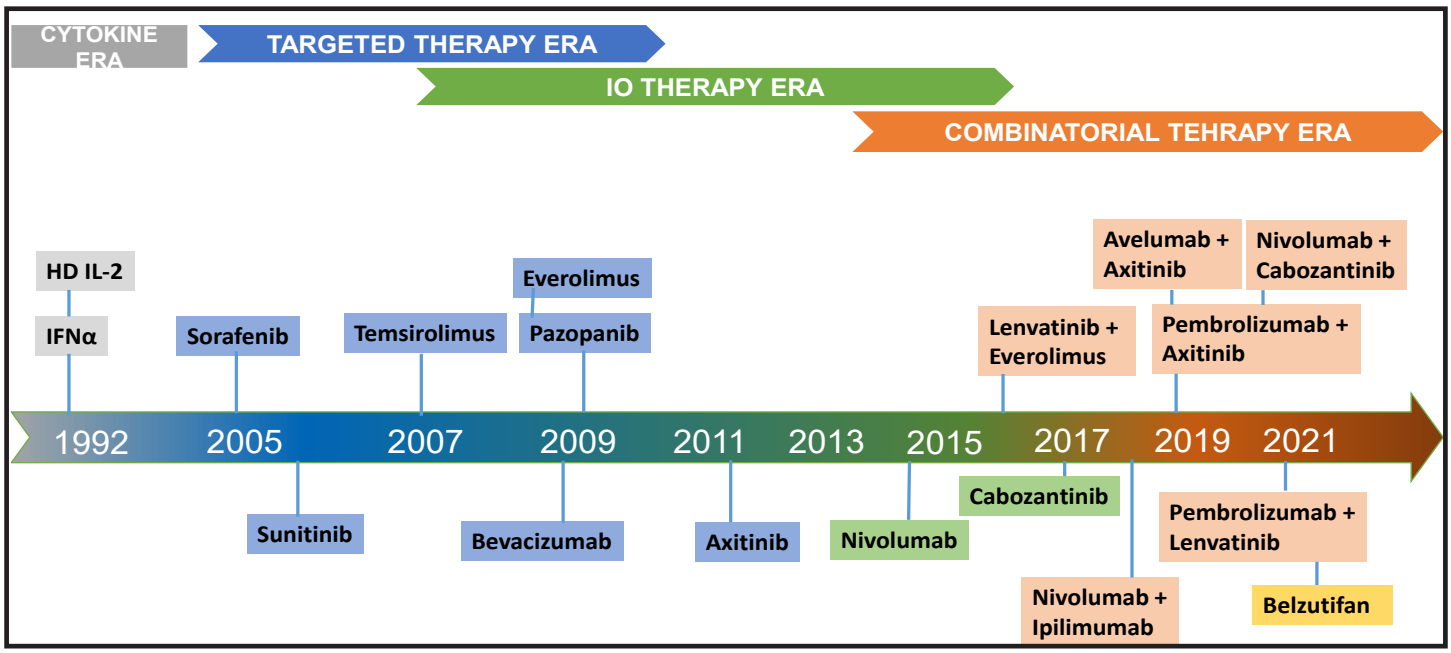

Figure 1 | Advances in Evolving Landscape of First-line Systemic Therapies for Metastatic Renal Cell Carcinoma

study, the FDA approved the use of pazopanib for the treatment of aRCC in 2019 and the EMA approved it for the first-line treatment of aRCC in patients who received prior cytokine therapy for advanced disease in 2010[10]. In a phase 3 AVOREN trial of bevacizumab, a monoclonal antibody directed against the VEGF receptor (VEGFR) plus interferon alfa-2α (IFN) showed significant improvements in PFS (10.2 vs. 5.4 months, p = 0.0001) in contrast to treatment with interferon-α monotherapy in mRCC10. Overall, this AVOREN trial confirms that bevacizumab plus IFN remains the first-line standard of care for patients with mRCC[11]. Multiple phase III randomized studies for eg. TARGET, COMPARZ demonstrated the survival benefits of sorafenib, pazopanib respectively10,12. Altogether these clinical trials validated the use of VEGF targeting agents the first-line standard of care for patients with mRCC.

Cabozantinib is an oral TKI that targets multiple tyrosine kinases, including hepatocyte growth factor (cMet), VEGFRs, and AXL. The randomized, phase 2 CABOSUN trial compared cabozantinib with sunitinib in treatment-naïve patients with intermediate-/poor-risk disease by IMDC. Cabozantinib therapy improved PFS (8.2 vs. 5.6 months) and ORR (46% vs. 18%) and reduced rate of progression or death as compared to sunitinib in treatment-naïve patient[13,14]. Following the encouraging results from the CABOSUN trial, NCCN treatment guideline included cabozantinib as a first-line treatment option for IMDC poor- and intermediate-risk patients (category 2A). Currently, cabozantinib represents a suitable targeted first-line agent, especially among patients who are not eligible to receive immunotherapy. The safety profile of cabozantinib data from the phase III METEOR study was also consistent as seen in CABOSUN, where cabozantinib therapy was associated with significantly improved PFS, OS, and ORR versus everolimus in VEGFR-TKI pretreated patients with aRCC[13,14].

Tivozanib, a highly selective and potent VEGF TKI, has demonstrated single-agent efficacy with minimal off-target toxicities and a favorable adverse event (AE) profile. A randomized controlled TIVO-1 trial has shown that tivozanib, a potent VEGFR-1, VEGFR-2, and VEGFR-3 inhibitor prolongs PFS (12.7 months) as compared with sorafenib (9.1 months) in the prespecified subpopulation of treatment-naive patients15,16. Although, ORR was higher with tivozanib compared with sorafenib per independent review, the sorafenib arm had higher OS. Tivozanib treatment was associated with fewer AE-related dose reductions and dose interruptions compared with sorafanib. Due to the limited benefits from the data, tivozanib monotherapy has not been approved outside of the EU for the treatment of adult patients with relapsed or refractory advanced RCC who have received two or more prior systemic therapies. Later, revised data from the second prespecified analysis of the TIVO-3 trial indicated better survival benefits with a hazard ratio for OS of 0.99 for tivozanib compared with sorafenib15-18. These durable improvements further validated the potential for tivozanib. In KCJ, we closely covered insightful developments of specific targeting agents especially cabozantinib, and

tivozanib[2-5].

mTOR inhibitors

mTOR inhibitors also evolved in parallel to the development of VEGF inhibitors in the mRCC landscape. Currently, both everolimus and temsirolimus are effective mTOR agents for the treatment of aRCC. Temsirolimus, a potent mTOR inhibitor, was approved for first-line treatment of advanced RCC following the favorable outcome obtained from the multicenter, phase 3 ARCC trial (NCT00065468). Temsirolimus monotherapy as compared to temsirolimus plus IFN-α combination significantly prolonged OS compared with IFN-α19. However, superior A more pronounced survival advantage was observed only in patients with non-clear cell histology[19]. Given such modest results and also due to its weekly intravenous injection limitation, temsirolimus is not a widely used therapy in the front-line for patients and its utility has been relegated to second or later lines of therapy for patients with poor risk prognostic features.

Immune Checkpoint Inhibitors

In the last decade, a new avenue of immune checkpoint inhibitors has revolutionized the treatment of patients with advanced renal cell carcinoma, with the potential for dramatic changes in the therapeutic landscape. Owing to their superior and improved overall survival across multiple clinical trials, immune checkpoint-inhibitors (CPIs) such as PD-1 (anti-programmed death receptor 1), PD-L1 (anti-programmed death receptor ligand 1), and CTLA-4 (anti-cytotoxic T lymphocytes antigen 4) have been integrated into the first-line therapeutic landscape for moderate to high-risk mRCC. Since the approval of the CTLA-4 antibody ipilimumab in patients with melanoma in 2011, the footprints of ICIs expanded across the RCC landscape following studies of several PD-1/PD-L1 inhibitors and our coverages in KCJ highlighted the following progress made as well. Nivolumab, an ICI that targets the programmed cell-death protein 1 (PD1), has become the standard treatment for patients with mRCC following progression to single-agent tyrosine kinase inhibitors (TKI)[20]. CheckMate-214 (NCT02231749) evaluated the CTLA-4 blocker (ipilimumab) and PD-1 inhibitor (nivolumab) combination in the IMDC intermediate or high-risk population[21]. The outcomes validated the proof of concept that this combination can deliver better outcomes as compared to the anti-VEGF TKI sunitinib in the first line metastatic RCC setting. Importantly, improved response rates (42%, 9% CR vs 27%, 1% CR), PFS (11.6 mo vs 8.4 mo), and OS (NR vs 26.6 mo) were observed in combination arm as compared to sunitinib. In particular, the addition of ipilimumab to nivolumab resulted in significantly better overall survival and improved ORR as compared to sunitinib. This nivolumab/ip¬ilimumab combination is considered for intermediate-risk disease for patients who cannot receive a TKI, particularly those who are younger (< 65 years) or with tumors having high PD-L1 TPS. PD-L1 expression did not predict treatment response and survival benefit was independent of PD-L1 expression21. IMmotion010 examined the utility of anti-PD-L1 atezolizumab monotherapy as adjuvant therapy in RCC patients at increased risk

Phase III Trial	Treatment arms	# patients	Histology	% PD-L1+ (threshold,%)	ORR	mPFS (months)	OS	Incidence of grade ≥3 AEs	Year
CheckMate 214 (NCT01472081)	Ipilimumab and nivolumab Vs sunitinib	1096	Clear cell	24 (≥1)	42% Vs 27%	11.6 Vs 8.4	At 18 months: 75% Vs 60%	46% Vs 63% Ipi/nivo: 10% elevated lipase, 4% fatigue, 4% diarrhea	2018
Immotion 151 (NCT02420821)	Atezolizumab and bevacizumab Vs sunitinib	915	Clear cell Sarcomatoid allowed	40 (≥1)	37% Vs 33%	11.2 Vs 8.4	Median: 33.6 Vs 34.9	40% Vs 54% Atez/beva: 14% HTN, 3% proteinuria, 2% diarrhea, 2% arthralgia	2019
KEYNOTE-426 (NCT02853331)	Pembrolizumab and axitinib Vs sunitinib	1062	Clear cell	60.5 (≥1)	59.3% Vs 35.7%	15.1 Vs 11.1	At 18 months: 82.3% Vs 72.1%	75.8% Vs 70.6% Pembro/axi: 22.1% HTN, 13.3% elevated ALT, 9% diarrhea, 7% elevated AST	2019
JAVELIN Renal 101 (NCT02684006)	Avelumab and axitinib Vs sunitinib	886	Clear cell	63.2 (≥1)	51.4% Vs 25.7%	13.8 Vs 8.4	At 12 months: 85.7% Vs 83.1%	71.2% Vs 71.5% Avel/axi: 25.6% HTN, 6.7% diarrhea, 6% elevated ALT, 3.9% elevated AST	2019
CheckMate-9ER (NCT03141177)	Nivolumab & cabozantinib Vs Sunitinib	651	Clear cell Sarcomatoid allowed	33.7 (≥1)	55.7% vs. 27.1%	16.6 Vs. 8.3	85.7% Vs 75.6%	60.6% Vs 50.9: 6.9% diarrhea, 7.5% Palmar–plantar erythrodysesthesia, 12.5% HTN	2021
CLEAR (NCT02811861)	lenvatinib & pembrolizumab Vs lenvatinib & everolimus Vs Sunitinib	1069	Clear cell Sarcomatoid allowed	47.6 (≥1)	71% vs. 53.5% vs. 36.1%	23.9 Vs 14.7 Vs 9.2	OS not reached	82.4% Vs 83.1% Vs 71.8%; 9.7 diarrhea, 27.6% HTN, 5% hypothyroidism	2021

TABLE 1 | Summary of phase III front-line combination trials in Renal Cell Carcinoma.

of recurrence after resection. Atezolizumab adjuvant therapy did not improve clinical outcomes as compare to placebo after resection in the ITT population22. Median INV-DFS was 57.2 mo for atezo and 49.5 mo (47.4, NE) for placebo. Safety analysis offered manageable profile for atezolizumab; grade 3/4 adverse events occurred in 27% (106/390) and 21% (81/383) of pts receiving atezo or placebo, respectively; Grade 5 AEs occurred in <1% (1/390) and <1% (3/383) [22,23].

The 30-month follow-up of phase III KEYNOTE-564 trial showed a continued disease-free survival benefit with adjuvant pembrolizumab vs placebo in patients with clear cell renal cell carcinoma who are at increased risk of disease recurrence. Updated results support the use of adjuvant pembrolizumab monotherapy as a standard of care for participants with renal cell carcinoma with an increased risk of recurrence after nephrectomy[24]. At 30 months, the cumulative incidence of local recurrence was 3.8% in the pembrolizumab group vs 7.6% in the placebo group, and distant metastasis–free survival rates were 77.3% vs 68.8[24]. Recently, results from the CheckMate 914 trial examining the role of adjuvant nivolumab and ipilimumab were presented at ESMO2022[25]. This study did not meet the primary endpoint of DFS over a median follow-up of 37.0 months. In patients treated with nephrectomy for localized renal cell carcinoma (RCC) at a high risk of relapse, median DFS was not reached among patients who received nivolumab and ipilimumab and was 50.7 months among those who received placebo[25].

ICIs in combination with VEGF-TKI

Emerging data validate the synergistic effect of ICI agents in combination with anti-VEGF targeted agents that gaining momentum as the first-line treatment landscape of aRCC. The ongoing phase 3 COSMIC-313 trial evaluates the combination of cabozantinib, nivolumab and ipilimumab versus the combination of nivolumab and ipilimumab in patients with previously untreated advanced intermediate- or poor-risk RCC. In the COSMIC-313 study[26], cabozantinib was predicted to synergize with nivolumab plus ipilimumab CPI combination, as a triplet regimen for the first-line standard-of-care treatment in patients with advanced RCC of intermediate or poor risk. At a median follow-up of 20.2 months, patients who received the triplet had a 27% lower risk for progression or death compared with those receiving the checkpoint inhibitor doublet. Median progression-free survival, the primary endpoint, was not reached in the triplet group, versus 11.3 months with the doublet. Overall response rates were 43% and 36%, respectively, with complete responses achieved in 3% of patients in each group26. The disease control rates were 86% and 72%; the incidence of progressive disease as the best response was just 8% in the triplet therapy arm and 20% in the control arm. Rates of grade 3 or 4 treatment-related adverse events were higher with the TKI added, at 73% versus 41% without it. Rates of discontinuation of all treatment components were 12% with the triplet and 5% without it[26].

The CLEAR trial is the latest of the IO-TKI studies examining the first-line treatment of patients with advanced clear cell RCC. The outcome data continues to show a clinically meaningful benefit from lenvatinib and pembrolizumab and reinforces this as a first-line treatment option for people with non–clear cell renal cell carcinoma (RCC)[27]. After 8.2 months of follow-up, 47.6% responded to treatment with three complete responses (3.7%) and 36 partial responses (43.9%). The disease was controlled in 79.3% of patients[27]. In phase III, randomized keynote-426 trial (NCT03075423), treatment with pembrolizumab plus axitinib resulted in significantly longer OS and PFS, as well as a higher ORR, than treatment with sunitinib among patients with previously untreated advanced renal-cell carcinoma. After a median follow-up of 12.8 months, the combination resulted in better OS (median not reached) as compared to therapy with sunitinib (35.7 months) and superior PFS (median 15.4 vs 11.1 months)16. This study validated the benefit of pembro + axi combination therapy[28]. The benefit of pembro/axi was observed across all IMDC risk groups, regardless of PD-L1 expression.

In another randomized phase III JAVELIN Renal 101 (NCT02684006) trial, investigators evaluated the efficacy of axitinib and avelumab combination in treatment-naive RCC patients29. Avelumab plus axitinib therapy resulted in prolonged PFS and a significantly higher objective response rate than those who received sunitinib monotherapy. The mPFS in the combination arm was 13.8 months versus 8.4 months in sunitinib arm, and the ORR and CR rate were 55% and 4% in the combination arm versus 26% and 2% in the sunitinib arm respectively[29]. In CheckMate 9ER study, nivolumab plus cabozantinib combination had significant benefits over sunitinib in terms of PFS and OS in patients with treatment naïve aRCC. The mPFS was 16.6 months with nivolumab plus cabozantinib and 8.3 months with sunitinib30. The probability of OS at 12 months was 85.7% with the combination arm and 75.6% with sunitinib. An OR occurred in 55.7% of patients in the combination arm versus 27.1% in sunitinib arm (P<0.001). Efficacy benefits with nivolumab plus cabozantinib were consistent across subgroups30. In a non-randomized Phase Ib/II study, tivozanib plus nivolumab combination was assessed in patients previously treated with one oral TKI (NCT03136627). The combination of tivozanib with nivolumab prolonged disease control (median PFS of 18.9 months) and also showed a tolerable

AE profile in both treatment-naïve and previously treated metastatic RCC[31]. The ORR was 56%, with one patient achieving a complete response.

Patients with the favorable-risk disease tend to have highly angiogenic tumours, and results from IMmotion151 support the notion of superior clinical benefits from VEGFR TKIs in this setting. The phase 3 IMmotion 151 study compared atezolizumab/bevacizumab with sunitinib[32]. The combination was favored over sunitinib for PFS in PD-L1+ patients. The PFS benefit was maintained in the ITT population and across subgroups of clinical interest in the PD-L1+ population, including patients with liver metastases, sarcomatoid subtype, or favorable-risk disease. Safety analysis indicated that atezolizumab/bevacizumab combination was well tolerated as patients receiving the combination had fewer treatment-related AEs relative to those receiving sunitinib (40% vs 54% for grade ¾)[32]. Although the combination of ICI and antiangiogenics has shown encouraging preliminary antitumor activity for advanced or mRCC, a high incidence of toxicity along with a less favorable tolerability profile may compromise the benefits in patients. For instance, in the phase I study CheckMate 016 (NCT01472081), the efficacy and safety of nivolumab in combination with antiangiogenic tyrosine kinase inhibitors or ipilimumab for the treatment of mRCC. The addition of sunitinib or pazopanib to nivolumab resulted in a high incidence of high-grade toxicities, limiting its scope in future trials[33]. Given the possibility that long-term cumulative adverse effects from the antiangiogenic and ICI combination may accumulate over time to outweigh the benefits, such combinatorial therapies warrant close monitoring to avoid unprecedented risks. In phase 3 PIVOT-09 trial, investigators sought to evaluate the combination efficacy of bempegaldesleukin plus nivolumab compared to sunitinib or cabozantinib as the first-line therapy for advanced renal cell carcinoma (RCC)[34]. This combination did not improve outcomes vs the investigator's choice of TKI in first line treatment of advanced/metastatic clear-cell RCC. Among patients with intermediate or poor risk disease, the ORR was 23.0% for combination arm vs 30.6% for the TKI arm. The complete response rates and clinical benefit rates were higher in the TKI arm. However, among responders, the duration appeared somewhat longer in the combination arm[34].

Other novel approaches

Belzutifan, a highly selective hypoxia-inducible factor inhibitor (HIF-2α), offers a novel approach, taking a different path than commonly used to treat RCC. Most recently, the open-label study 004 (NCT03401788) has validated the efficacy and safety of belzutifan in patients with VHL-associated RCC[35]. Treatment with belzutifan resulted in an ORR of 49%. Based on these data, FDA approved belzutifan for adult patients with von Hippel-Lindau (VHL) disease who require therapy for RCC and other tumors[36]. The LITESPARK-003 trial (NCT03634540) evaluated the synergistic effect of adding belzutifan to cabozantanib therapy in patients with aRCC who previously received immunotherapy at 24.6 months of follow-up[37]. Results showed that the overall ORR in the intention-to-treat population (N = 52) was 31%. The ORR was 27% and 32% among patients with favorable-risk disease (n = 11), and intermediate/poor-risk disease (n = 41) respectively37. Trial recruitment is underway for the phase 3 LITESPARK-011 trial (NCT04586231) assessing belzutifan plus lenvatinib vs cabozantinib in patients who previously had anti–PD-1/PD-L1 therapy.

Surgical management

Even in the era of targeted therapy, we have been continuously providing coverages on the latest updates in the surgical management of kidney cancer, including a recent article in KCJ that reported the Latinx disparity in surgical approach for kidney cancer. Despite revolutionary advances in targeted systemic therapies, durable responses remain rare. Currently, cytoreductive nephrectomy (CN) is the only opportunity for the cure at an early stage. Therefore, until systemic agents provide significant curative impact, surgical resection will remain the benchmark for a long-term cure. On the other hand, despite the curative impact of surgical resection, it is estimated that nearly 30% of the patients will experience a relapse of renal cancer. Whereas, the role of CN and metastasectomy of local recurrence in advanced RCC remains unclear in the era of targeted therapies. In a Phase III PROSPER (ECOG-ACRIN EA8143) study[39], investigators compared perioperative nivolumab versus observation in patients undergoing nephrectomy alone. RFS was similar between the arms. The median RFS was not reached. OS was not mature at the time of analysis but was not statistically different between study arms. Similar withdrawal rates occurred in both arms, approximately 12% (48/404 patients in nivo arm vs. 50/415 in the surgery alone arm). 20% of patients treated with nivo experienced at least one Grade 3-4 AE that could be attributable to nivo, compared with 6% in the control arm[39].

CONCLUDING REMARKS

The frontline treatment paradigm in renal cell carcinoma continues to evolve, with the advent of novel ICI or ICI/TKI combinatorial regimens as reflected in the coverages published in the KCJ over the few years. In the future, a deeper understanding of immune checkpoint biology might reveal new therapeutic targets beyond PD-1, PD-L1, and CTLA-4, as well as new combination approaches. However, controversies remain regarding the precise treatment selection, sequencing, and individualized therapeutic strategy, thanks to unmet clinical need

of identifying reliable predictive markers of response to immune agents and absence of head-to-head comparison among the randomized trials. Currently available approaches viz. PD-L1 expression, gene expression signatures, CD8+ T cell density cannot still predict treatment response to ICIs and/or TKIs. Importantly, validated biomarkers are essential to match patients to single-agent treatment with TKIs or immunotherapy, or combinations of immunotherapies with TKIs or novel agents. As novel treatments come to the clinic, there is a need to develop strategies for sequencing new and established therapies. Once optimized, such strategies will deliver robust survival outcomes while preserving the quality of life and as well the ability to tailor therapy to the individual patient.

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These recommended abstracts from ESMO'22 Annual meeting have been selected by Robert A. Figlin, MD

ABSTRACT 1450MO: Efficacy of a tailored approach with nivolumab and nivolumab/ipilimumab as immunotherapeutic boost in metastatic renal cell carcinoma: Final results of TITAN-RCC *Grimm MO et al.*

METHODS: From OCT 2016 to DEC 2018 207 patients with intermediate/poor risk mRCC started nivo induction (Q2W, 240 mg). Patients with early progressive disease (PD, week 8) or non-responders at week 16 (stable disease [SD]/PD) received 2-4 doses nivo+ipi. Responders to nivo induction (complete/partial response [CR/PR]) continued with nivo maintenance but could receive nivo+ipi for later PD. The primary endpoint was confirmed objective response rate (ORR) per RECIST in 1L and 2L. Secondary endpoints included efficacy of nivo induction, response to boost, progression free (PFS) and overall survival (OS), and safety.

RESULTS: Of the 207 patients, 109 were 1L and 98 2L. Median age was 65 yr, 71 % of patients had intermediate and 25 % poor risk. Confirmed response to nivo induction was 28 % in 1L and 18 % in 2L. After 33.6 months from last patient first treatment and 15.9 months median follow-up, ORR for nivo ± nivo+ipi was 36 % in 1L (significant >25 %, $p<0.05$) and 32 % in 2L. Irrespective of time point, 44% (1L) and 53% (2L) of patients receiving boosts for PD upon nivo improved in best response. PFS was 6.3 months (95 % CI 3.7-10.1) in 1L and 3.7 months (95 % CI 1.8-4.5) in 2L. OS was 32.0 months (95 % CI 22.9-39.4) in 1L and 25.9 months (95 % CI 17.8-33.7) in 2L. No new safety signals emerged. .

CONCLUSIONS: Nivo+ipi boosts improve outcomes compared to nivo monotherapy. Responses were also observed after progression during nivo maintenance suggesting a potential role as rescue strategy. However, overall efficacy of our tailored approach appears to be inferior compared to upfront nivo+ipi treatment.

ABSTRACT LBA8: Phase III study of cabozantinib (C) in combination with nivolumab (N) and ipilimumab (I) in previously untreated advanced renal cell carcinoma (aRCC) of IMDC intermediate or poor risk (COSMIC-313). *Choueiri TK et al.*

METHODS: This global, double-blind, randomized phase III study enrolled previously untreated patients (pts) with clear cell aRCC of IMDC intermediate or poor risk. Pts were randomized to receive C 40 mg QD or matched placebo (P), stratified by region and IMDC risk. Both treatment groups received N (3 mg/kg IV Q3W) + I (1 mg/kg IV Q3W) for 4 cycles followed by N (480 mg IV Q4W); N was administered up to 2 y. The primary endpoint was progression-free survival (PFS) by blinded independent radiology review per RECIST 1.1 in the first 550 randomized pts (PITT population). The secondary endpoint was overall survival (OS) in all randomized pts (ITT population); objective response rate (ORR) and safety were additional endpoints.

RESULTS: From Jun 2019 to Mar 2021, 855 pts were randomized (428, C+N+I; 427, P+N+I); IMDC risk was intermediate for 75% and poor for 25%. The study met the primary PFS endpoint (HR 0.73, 95% CI, 0.57–0.94; p=0.013); median PFS was not reached (NR; 95% CI, 14.0–not estimable) for C+N+I vs 11.3 mo (95% CI, 7.7–18.2) for P+N+I. Prespecified PFS subgroup analyses will be presented. ORR (PITT population) was 43% (95% CI, 37.2–49.2) for C+N+I vs 36% (95% CI, 30.1–41.8) for P+N+I; median duration of response was NR in either treatment group. Grade 3/4 TRAEs occurred in 73% with C+N+I vs 41% with P+N+I; 3 pts (1%) in each arm had grade 5 TRAEs, and a TRAE led to discontinuation of all treatment components in 12% vs 5%.

CONCLUSIONS: C+N+I significantly improved PFS vs P+N+I in previously untreated aRCC of IMDC intermediate or poor risk. Safety was consistent with the known profiles of the treatment components. Follow-up for OS is ongoing.

ABSTRACT 1448O- Phase II KEYNOTE-B61 study of pembrolizumab (Pembro) + lenvatinib (Lenva) as first-line treatment for non-clear cell renal cell carcinoma (nccRCC). *Albiges L et al.*

METHODS: Adults with previously untreated advanced nccRCC and measurable disease per RECIST v1.1 received pembro 400 mg IV Q6W up to 18 cycles (2 y) + lenva 20 mg orally QD. Primary end point was confirmed ORR (CR + PR) per RECIST v1.1 by BICR; secondary end points were DOR, DCR (CR + PR + SD), PFS, OS, and safety. Efficacy was evaluated in treated pts who had the opportunity for ≥24 wk of follow-up. Safety was evaluated in all treated pts.

RESULTS: Of 147 treated pts, 87 (59.2%), 26 (17.7%), and 19 (12.9%) had papillary, chromophobe, and unclassified histology, respectively; 15 pts had translocation (4.1%), medullary (0.7%), or other (5.4%) histology. As of January 31, 2022, median follow-up for pts who had the opportunity for ≥24 wk of follow-up (n=82) was 8.2 mo (range, 5.5-10.5). Of these 82 pts, confirmed ORR was 47.6% (95% CI, 36.4-58.9; 3 CRs [3.7%]; 36 PRs [43.9%]). DCR was 79.3% (95% CI, 68.9-87.4). Median DOR was not reached (range, 1.4+ to 7.2+ mo). ORR and DCR in histologic subgroups are shown in the table. The 6-month PFS rate was 72.3% (95% CI, 60.7-81.0) and the 6-month OS rate was 87.8% (95% CI, 78.5-93.2). In all treated pts (N=147), any grade treatment-related AEs (TRAEs) occurred in 127 pts (86.4%), most commonly hypertension (n=71; 48.3%), diarrhea (n=37; 25.2%), and hypothyroidism (n=37; 25.2%). Grade 3-4 TRAEs occurred in 51 pts (34.7%). No deaths occurred due to TRAEs.

CONCLUSION: In this preliminary analysis, pembro + lenva showed promising antitumor activity and manageable safety in pts with advanced nccRCC. No new safety signals emerged with this combination.

ABSTRACT 1447O: Phase II study of belzutifan plus cabozantinib as first-line treatment of advanced renal cell carcinoma (RCC): Cohort 1 of LITESPARK-003.

METHODS: Treatment-naïve pts with advanced clear cell RCC and ECOG PS of 0/1 received belzutifan 120 mg QD PO plus cabozantinib 60 mg QD PO. The primary end point was confirmed ORR (CR + PR) per RECIST v1.1 by investigator review. Secondary end points were DOR, PFS, OS, and safety.

RESULTS: Of 35 pts enrolled in cohort 1, 10 (29%) discontinued treatment; primarily due to progressive disease (n=8; 23%). Median age was 64 years (range, 33-89) and most pts had an ECOG PS of 0 (n=21; 60%), and IMDC favorable risk (n=21; 60%). Median follow-up was 14.0 mo (range, 0.2-33.0). Confirmed ORR was 57% (2 CRs, 18 PRs) and 13 pts (37%) had a best response of SD. Median DOR was 28.6 mo (range, 1.7+ to 28.6); 13 pts remained in response for ≥6 mo. Median PFS was 30.3 mo (95% CI, 9.4 to not reached); the estimated 12-mo PFS rate was 67%. Median OS was not reached; the estimated 12-mo OS rate was 96%. By IMDC risk category, ORR was 62% in 21 pts with favorable risk and 50% in 14 pts with intermediate/poor risk. In all pts, the most common any grade treatment-related AEs were anemia (n=25; 71%) and diarrhea (n=25; 71%). Grade 3 treatment-related AEs occurred in 13 pts (37%), most commonly hypertension (n=4; 11%) and fatigue (n=3; 9%). There were no grade 4 or 5 treatment-related AEs. 1 pt (3%) discontinued cabozantinib due to an AE (abdominal abscess). No pt discontinued belzutifan due to an AE.

CONCLUSIONS: Belzutifan plus cabozantinib had manageable safety with promising antitumor activity in treatment-naïve pts with advanced clear cell RCC.

ABSTRACT 1464P - The impact of impaired renal function

on the effectiveness of first-line immuno-oncology combination therapies in metastatic renal cell carcinoma (mRCC): Results from the international metastatic RCC database consortium (IMDC) *Navani V et al.*

METHODS: Using the IMDC, a large, multinational, observational cohort study, we identified patients treated with 1L ipilimumab nivolumab (IOIO) or approved PD-1(L1)/vascular endothelial growth factor (IOVE) inhibitor combinations. Baseline characteristics, objective response rate, time to treatment failure and overall survival were captured. Modification of diet in renal disease (MDRD) was used to calculate the estimated glomerular filtration rate (eGFR) at initiation of therapy. IMDC risk group adjusted logistic and Cox regressions were used.

RESULTS: Between Out of 1059 patients with a documented eGFR, 756 (71.4%) received IOIO and 303 (28.6%) received IOVE. Patients with an eGFR <60 (n=513) were more likely to be older (median 65.1 vs 61.3 yrs p<0.0001) and undergone a nephrectomy (82.4% vs 50.6% p <0.0001) than those with an eGFR ≥60. However, the eGFR <60 group, was less likely to have poorer prognostic features such as bone mets (27.7% vs 38.6% p=0.0002) and poor risk IMDC risk status (22% vs 36% p<0.0001) than the GFR ≥60 group. An eGFR <60 did not have an impact on objective response (OR 0.93 95% CI 0.70 – 1.23 p=0.49), time to next treatment (HR 1.13 95% CI 0.94 – 1.36 p=0.18) or overall survival (HR 1.24 95% CI 0.96 – 1.59 p=0.09). Sensitivity analyses examining eGFRs of <45 (HR 1.23 95% CI 0.91 – 1.67 p=0.18) and <15 (HR 1.32 95% CI 0.33 – 5.35 p=0.69) found consistent results. Modelling eGFR as a continuous variable found that every 1ml/min drop in eGFR lead to a HR of 0.999 (95% CI 0.995 – 1.002 p=0.5073).

CONCLUSIONS: Baseline renal function does not adversely impact the effectiveness of 1L immuno-oncology combination therapies in mRCC. Clinicians should not restrict access to these therapies based on renal function.

ABSTRACT 1466P: **Efficacy of immune checkpoint inhibitors (ICI) in renal cell carcinoma (RCC) venous tumor thrombus (VTT) shrinkage.** *Thouvenin J et al.*

METHODS: We performed a French multicenter retrospective study of pts with metastatic RCC with a VTT and treated in first line or beyond with ICI. The main objective was to assess the objective response rate (ORR) of ICI on VTT. Radiological assessment was performed by treating physician according to iRECIST criteria

RESULTS: Twenty-five pts were included, between January 2015 and December 2021, at the participating institutions. Median age at diagnosis was 65 years (range 37-88). IMDC risk group was intermediate (14/25; 56%) and poor for 11 pts (44%). Most frequent metastatic sites were lung (88%; 22/25), lymph nodes (56%; 14/25), bone (40%; 10/25) and liver (36%; 9/25). Seventeen pts (68%) were treated with ICI in first line, 7/25 (28%) in 2ndline and 1 pt (4%) in 3rd line. Fourteen pts were treated with anti-PD-L1 in combination with antiCTLA-4 therapy, 10 pts with ICI monotherapy and 1 with ICI in combination with antiangiogenic TKI. At baseline, median VTT diameter was 20 mm (range 7-85) and VTT extension according to Novick's classification was I for 9pts, II for 7pts, III for 4pts, IV for 2 and unknown for 3 pts. After a median duration of treatment of 3 months (range 3-89), ORR was 36% including 3 complete responses (CR) and 6 partial responses (PR).

CONCLUSIONS: These data highlight the efficacy of ICI to shrink VTT even if it seems to have little impact on VTT level of extension. Further studies are needed to assess the role of ICI in neoadjuvant setting.

ABSTRACT 1677P: **Risk factors predicting immune checkpoint inhibitors (ICIs) toxicity using machine learning computer algorithm.** *Holland R et al.*

RESULTS: The study cohort included 1617 patients with solid tumors who received ICIs between the years 2010-2021 in the Division of Oncology in Rambam Health Care Campus. 1104 (68%) were men, mean age was 69 years. 910 (56%) patients developed grade 3&4 irAEs during and after the ICIs treatment. Gender, BMI and pretreatment derived neutrophil-to-lymphocytes ratio (dNLR) were not associated with higher irAEs in the general cohort. Younger age and PDL-1/CTLA-4 combination were found to be associated with higher irARs rates (P=0.001 and P<.001, respectively). In subgroup analysis, young age was found to be associated with hepatotoxicity and hematologic irAEs (P<.001 and P=0.01, respectively), female gender was associated with endocrine toxicity (P=0.024) and high BMI and low dNLR were associated with renal irAEs (P=0.001 and P=0.029, respectively).

CONCLUSIONS: Using ML tools in real-world data setting, several key characteristics were identified to be correlated with high tendency of irAEs.

ABSTRACT 1451MO: **Pembrolizumab (pembro) plus axitinib (axi) versus sunitinib as first-line therapy for advanced clear cell renal cell carcinoma (ccRCC): Analysis of progression after first subsequent therapy in KEYNOTE-426.** *Powles T et al.*

METHODS: Treatment-naive patients with advanced ccRCC, Karnofsky Performance Status Scale score ≥70% and measurable disease per RECIST v1.1 were randomly assigned 1:1 to receive pembro 200 mg IV every 3 weeks for up to 35 doses (~ 2 y) + axi 5 mg orally twice daily or sunitinib 50 mg orally once daily on a 4-wk on/2-wk off schedule. The end point of this exploratory analysis was PFS2, defined as time from randomization to progression after first subsequent therapy or any-cause death. The Kaplan-Meier method was used to estimate PFS2 and hazard ratios were estimated using a Cox regression model.

RESULTS: Of 861 patients, 432 were assigned to receive pembro + axi; 429, to sunitinib. Median time from randomization to the database cutoff date (January 11, 2021) was 42.8 mo (range, 35.6-50.6). Overall, 47.2% of patients (204/432) in the pembro + axi arm and 65.5% of patients (281/429) in the sunitinib arm received ≥1 line of subsequent anticancer therapy. For patients who received subsequent therapy, anti–PD-1/PD-L1 agents were the first subsequent treatment for 11.3% of patients (23/204) in the pembro + axi arm and 54.8% of patients (154/281) in the sunitinib arm. In the pembro + axi arm, 82.8% of patients (169/204) received a VEGF/VEGFR inhibitor as first subsequent therapy, as did 43.4% (122/281) in the sunitinib arm. PFS2 results are displayed in the Table.

CONCLUSIONS: In this exploratory analysis, PFS2 was longer for patients randomized to pembro + axi compared to sunitinib. Results were consistent across IMDC risk groups. These data support use of pembro + axi for the first-line treatment of patients with advanced ccRCC. Clinical trial information: NCT02853331.

ABSTRACT1461P **Impact of first-line (1L) therapy on outcomes of adult patients with metastatic MiT family translocation renal cell carcinomas treated in the contemporary immune checkpoint therapy era** *Thouvenin J et al.*

METHODS: This is an international, multicenter, retrospective study of adult pts with metastatic TRCC treated with systemic therapies at centers in France, Belgium and in the US. The main objective was to identify prognostic factors associated with 1L therapy and to estimate overall survival (OS..

RESULTS: Fifty-six pts with metastatic TRCC treated at 11 participating centers were evaluable. Median age was 38 years (range 16-62). IMDC risk group was favorable (9/56; 16%), intermediate (38/56; 68%), poor (8/56; 14%) and unknown for 1 patient. Twenty-nine pts (52%) presented with metastatic disease at initial diagnosis; 42 pts (75%) had prior nephrectomy (Nx). 1L therapy included VEGFR tyrosine kinase inhibitors (TKI), ICT combinations (either with TKI or ICT), or other regimens in 32 (57.1%), 18 (32.2%) and 6 pts (10.7%), respectively. With a median follow-up of 27.8 months, 30 pts died from disease progression; median OS was 13.5 months (mo) (95% CI: 3.9-NA) for pts treated with ICT combinations in 1L versus 36.2 mo (95% CI: 27.7-NA) for others (p=0.001). By univariable analysis, ICT combinations in 1L [HR: 3.8; 95% CI (1.6-8.9), p=0.002] and poor risk IMDC group [HR:4.2; 95%CI (1.25-14); p=0.02]

were associated with worse OS, while prior Nx was associated with better OS [HR: 0.35; 95% CI (0.16-0.78); p=0.01]. By multivariable analysis, 1L ICT combinations [HR: 3.6; 95% CI (1.4-9.5); p=0.009] and IMDC poor risk group [HR: 4.6; 95%CI (1.05-19.9); p=0.04] were retained as independent variables associated with inferior OS.
CONCLUSION: These data suggest that some TRCC patients might not derive benefit from a 1L ICT combinations and highlight the variability of this rare subtype of RCC compared to clear-cell RCC. Further collaborative research efforts are needed to elucidate the biology underpinning these findings and to develop more effective therapies for TRCC1.

ABSTRACT 1453P **Phase II study of belzutifan plus cabozantinib for previously treated advanced renal cell carcinoma (RCC): Update from cohort 2 of LITESPARK-003.** *McDermott D et al.*
METHODS: Pts with advanced clear cell RCC and had previously received ICI therapy and ≤2 systemic treatment regimens received belzutifan 120 mg QD PO once daily plus cabozantinib 60 mg QD PO. The primary end point was ORR (CR + PR) per RECIST v1.1 by investigator review. Secondary end points were DOR, PFS, OS, and safety.
RESULTS: Of 52 pts enrolled in cohort 2, 42 (81%) discontinued treatment. Most pts had IMDC intermediate/poor risk (n=41; 79%), one prior line of therapy (n=29; 56%), and prior ICI only (n=28; 54%). Median follow-up was 24.6 mo (range, 17.9-39.8). ORR was 31% (1 CR, 15 PRs) and 32 pts (62%) had a best response of SD. Median DOR was 18.6 mo (range, 4.2+ to 22.8); 9 pts remained in response for ≥12 mo. Median PFS was 13.8 mo (95% CI, 9.2-19.4) and median OS was 24.0 mo (95% CI, 20.0-37.4). At 12 mo, PFS rate was 56% and OS rate was 77%. Responses were consistent across subgroups (Table). In all pts, 51 (98%) had a treatment-related AE (TRAE); 34 (65%) had a grade ≥3 TRAE. No pt had a grade 4 TRAE; 1 pt (2%) died due to a TRAE (respiratory failure).
CONCLUSION: With 24.6 mo of follow-up, belzutifan plus cabozantinib had manageable safety and continued to show promising antitumor activity in pts with advanced RCC previously treated with ICIs.

KCJ ESMO2022 - Recommended Abstracts

Dr. Bernard Escudier Received the ESMO Lifetime Achievement Award 2022

During the ESMO Congress 2022 Opening ceremony on 9 September 2022, Prof. Bernard Escudier from Institut Gustave Roussy, France, was awarded the ESMO Lifetime Achievement Award 2022. He received this award in recognition of his lifelong achievements in renal cell carcinoma, immunotherapy, and on development of new therapeutic strategies, as well as for the support provided to fellow oncologists to advance in their professional careers. In particular, Dr. Escudier participated in the development of anti-VEGF and anti-PD-L1 checkpoint inhibitors based on targeted therapies that have quadrupled patient survival and achieved cures.

Dr. Escudier has authored more than 450 publications in peer-reviewed journals and is a member of the ASCO, the AACR, and the ESMO. He is also a member of the board of our *Kidney Cancer Journal*, the *Kidney Cancer Association*, and president of ARTuR. He was the first investigator named to head the inaugural immunotherapy unit at Gustave Roussy in 1992, and he headed the French Group of Immunotherapy from 1992 to 2012. Over the past three decades, Dr. Escudier has been a principal investigator for many phase III trials, including studies of bevacizumab, sorafenib, and nivolumab plus ipilimumab. His work helped pave the way for the FDA's approval of cabozantinib and the European Commission's approval of tivozanib in RCC, both small molecules that inhibit VEGF. Dr. Escudier was coordinator of Genitourinary Cancer ESMO Faculty Group, 2012-2016. He has also been a member of the Editorial Board of Annals of Oncology, 2012-2014; and of the ESMO Educational Committee, 2012-2016. Since 2016, Dr. Escudier has been a member of the ESMO Open Editorial Board.

"The renal cancer community has grown substantially and we have seen tremendous improvements in patient outcomes, with median survival increasing to more than 4 years. This transformation has been driven by the development of therapies targeting VEGF and programmed death-ligand 1 (PD-L1). These two pathways were first described in renal cancer in the early 2000s and have since been implicated in the development of multiple types of cancer" said Prof. Escudier.

"Despite the achievements of the past two decades, we are still in a position where up to 90% of patients diagnosed with renal cancer will ultimately die from metastatic disease. Providing a cure for these patients is vital and to do this I believe we will need to target a third oncogenic pathway in addition to VEGF and PD-L1. We also need to improve treatment options for patients with less common types of renal cancer. For these patients, research is required to understand the underlying tumor pathology and to identify suitable treatment targets. We also currently lack good biomarkers to determine prognosis and predict treatment response in renal cancer. In this respect, our knowledge lags behind other solid tumors, such as lung or breast cancer, which have fairly well-defined biomarkers. This will be an important focus of our research in the coming years", said Dr. Escudier, when asked about key challenges in the management of kidney cancer today.

2022 ESMO: Promise and Pitfalls of Adjuvant Immunotherapy

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Dear Colleagues,

There is never a dull moment at this year's ESMO'2022 as the congress ends with a sign of progress in a few clinical studies but also delivers the negative outcomes in some follow-up studies. About 30,000 participants from more than 150 countries attended the congress to witness nearly 1900 abstracts from various oncology disciplines. Among five important phase III studies presented in the renal cancer space, the highly anticipated results from the "adjuvant trio" - IMmotion010, CheckMate 914, and PROSPER – fell short of the expectation. Results from the CheckMate 914 trial that assessed nivolumab and ipilimumab vs placebo as adjuvant therapy did not meet the primary endpoint of DFS. After 37.0 months of median follow-up, the DFS in the combination arm showed only sub-10% numerical improvements with insignificant p values in patients with localized RCC at high risk of relapse after nephrectomy. While the safety profile was consistent with its known profile in advanced RCC, the rate of discontinuation due to treatment-related AEs was higher with adjuvant NIVO and IPI as compared to placebo in this trial. These findings showed that NIVO + IPI combination is no better than placebo in terms of DFS improvement. Further analyses are underway to assess the role of adjuvant nivolumab monotherapy (part B cohort study). Even though this combination fails to demonstrate clinical and statistical significance in the adjuvant RCC setting, this combination or nivolumab alone have demonstrated clinical benefits in the advanced disease settings.

Similarly, results obtained from PROSPER shown that neoadjuvant nivolumab prior to nephrectomy followed by adjuvant nivolumab did not improve recurrence free survival in RCC patients at high risk for recurrence. OS data remains immature but is not statistically different between arms. Subset analyses including risk stratification by pathologic stage are ongoing. In the phase 3 IMmotion 010 study, authors explored the utility of anti-PD-L1 atezolizumab as adjuvant therapy in RCC patients at increased risk of recurrence after resection. Atezolizumab adjuvant therapy did not improve clinical outcomes vs placebo after resection in the ITT population but had a manageable safety profile. Although there may be some caveats in study design and methodology which led to unsuccessful outcomes in these three trials, researchers are cautiously optimistic that future trials and analyses will provide better outcome as we learn and move forward.

The dilemma that is faced by clinicians and patients is that despite these results we have the Keynote 564 trial that demonstrated clinical benefit in both high-risk resected patients and those with oligometastatic disease treated with Pembro. We need to understand the differences in study populations studied that can help explain why similar drugs succeeded in some patient populations but not in others. We await the presentations of these abstracts in peer-reviewed publications for additional scrutiny.

COSMIC-313 trial (NCT03937219) is the first phase III trial that compares a triplet regimen to IO doublet therapy as a control in aRCC. In this study, investigators sought to assess the impact of combining a third agent (TKI) to the dual checkpoint inhibitor backbone in the poor- and intermediate-risk RCC patient population. Addition of cabozantinib to nivolumab and ipilimumab combination prolongs progression-free survival in patients with intermediate- to poor-risk RCC. However, there are some drawbacks as well; the response rate was only marginally improved in the triplet arm as compared to doublet arm. In both arms, median duration of response was not reached. The safety profile was consistent with known safety profiles for each monotherapy as well as the combination regimens used in this study. Grade 3 or 4 toxicity was higher in the triplet arm possibly due to the overlapping toxicity (73% vs 41%). Another potential limitation comes from the rate of TRAEs leading to discontinuation with almost half of the patients receiving triplet therapy needing some discontinuation of one of the three components. Follow-up data for the overall survival involving the entire study population (855 patients) is ongoing. We have to wait to see if further updates can make the triplet regimen as "practice changing" therapy in the clinical setting. Additionally, although cross-trial comparisons are fraught with complications, one would

like to know how this triplet would deliver as compare to the already published Cabo/Nivo data.

The CLEAR study is the latest of the IO-TKI studies evaluating first-line treatment of patients with advanced clear cell RCC. The outcome data from CLEAR study presented at ESMO22 confirmed the clinically meaningful benefit from lenvatinib and pembrolizumab as a first-line treatment option. The median PFS is 23.3 months in combination arm versus 9.2 months in the control arm. When compared with alternative doublet treatment approaches such as CheckMate 214, KEYNOTE-426, and CheckMate-9ER, outcome data from the CLEAR trial demonstrated better safety/efficacy profile as compare to other trials in terms of median PFS (23.3 months), ORR (71%), and complete response rate (17%) in the experimental arm. For further details of the abstracts mentioned here, please refer *Recommended Abstracts – ESMO2022* section in this issue.

Results from the phase 3 PIVOT-09 trial have shown that the combination of bempegaldesleukin with nivolumab failed to demonstrate a benefit compared to TKI monotherapy, in terms of overall survival, progression-free survival, or objective response rate. Especially, in the intermediate and poor-risk subgroup, ORR was less common (23%) in the bempegaldesleukin plus nivolumab arm than in the TKI arm (30.6%). Given that the ORR of combination arm is lower to single agent nivolumab therapy, addition of bempegaldesleukin is rather providing reversing effect of nivolumab. The interim analysis from the phase 2 of LITESPARK-003 trial (NCT03634540) shown the meaningful survival advantage of HIF inhibitor belzutifan plus cabozanitinib as first-line therapy for patients with intermediate and poor-risk disease in advanced renal cell carcinoma (RCC). Overall objective response rate (ORR) was 57% and the combination had manageable safety.

It is remarkable to be celebrating the 20th anniversary and the incredible journey of our journal for the last two decades. We have reached this important milestone only through unwavering commitment for the cancer community we serve. Over the years, the KCJ has continuously placed itself at the forefront of providing roundtable discussions, webinars, expert perspectives and conference coverages that set the stage for the KCJ to evolve as a voice of the kidney cancer community. Today, our KCJ is more relevant and important than ever as we serve for the last two decades. As a part of our 20th Anniversary series, we provide a retrospective review of advances in the clinical research and therapeutic strategies. I am so proud to have been part of the evolution of KCJ, and I want to thank and recognize the visionary editorial staffs and volunteers. We look forward to our continued reporting of scientific discoveries for the many decades to come!

[continued from Page 87]

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https://doi.org/10.52733/KCJ20n2-jc

An interdisciplinary consensus on the management of brain metastases in patients with renal cell carcinoma. *Hasanov E et al. Cancer J Clin. 2022 Sep;72(5):454-489. doi: 10.3322/caac.21729. PMID: 35708940.*

ABSTRACT: Brain metastases are a challenging manifestation of renal cell carcinoma. We have a limited understanding of brain metastasis tumor and immune biology, drivers of resistance to systemic treatment, and their overall poor prognosis. Current data support a multimodal treatment strategy with radiation treatment and/or surgery. Nonetheless, the optimal approach for the management of brain metastases from renal cell carcinoma remains unclear. To improve patient care, the authors sought to standardize practical management strategies. They performed an unstructured literature review and elaborated on the current management strategies through an international group of experts from different disciplines assembled via the network of the International Kidney Cancer Coalition. Experts from different disciplines were administered a survey to answer questions related to current challenges and unmet patient needs. On the basis of the integrated approach of literature review and survey study results, the authors built algorithms for the management of single and multiple brain metastases in patients with renal cell carcinoma. The literature review, consensus statements, and algorithms presented in this report can serve as a framework guiding treatment decisions for patients.

WHO 2022 landscape of papillary and chromophobe renal cell carcinoma. Histopathology. 2022 Oct;81(4):426-438. doi: 10.1111/his.14700. PMID: 35596618. *Labo J et al. Histopathology. 2022 Oct;81(4):426-438. doi: 10.1111/his.14700. Epub 2022 Jun 10. PMID: 35596618..*

ABSTRACT: 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..

Phase II Trial of Cabozantinib Plus Nivolumab in Patients With Non-Clear-Cell Renal Cell Carcinoma and Genomic Correlates. *Han Lee et al.* 2022 Jul 20;40(21):2333-2341..

RESULTS: A total of 47 patients were treated with a median follow-up of 13.1 months. Objective response rate for cohort 1 (n = 40) was 47.5% (95% CI, 31.5 to 63.9), with median progression-free survival of 12.5 months (95% CI, 6.3 to 16.4) and median overall survival of 28 months (95% CI, 16.3 to not evaluable). In cohort 2 (n = 7), no responses were observed; one patient had stable disease > 1 year. Grade 3/4 treatment-related adverse events were observed in 32% treated patients. Cabozantinib and nivolumab were discontinued because of toxicity in 13% and 17% of patients, respectively. Common mutations included NF2 and FH in cohort 1 and TP53 and PTEN in cohort 2. Objective responses were seen in 10/12 patients with either NF2 or FH mutations.
CONCLUSION: Cabozantinib plus nivolumab showed promising efficacy in most non-clear-cell RCC variants tested in this trial, particularly those with prominent papillary features, whereas treatment effects were limited in chromophobe RCC. Genomic findings in non-clear-cell RCC variants warrant further study as predictors of response.

Nivolumab, nivolumab-ipilimumab, and VEGFR-tyrosine kinase inhibitors as first-line treatment for metastatic clear-cell renal cell carcinoma (BIONIKK): a biomarker-driven, open-label, non-comparative, randomised, phase 2 trial.
Vano YA, et al. Lancet Oncol. 2022 May;23(5):612-624.

METHODS: This biomarker-driven, open-label, non-comparative, randomised, phase 2 trial included patients from 15 university hospitals or expert cancer centres in France. Eligible patients were aged 18 years or older, had an Eastern Cooperative Oncology Group performance status of 0-2, and had previously untreated metastatic clear-cell renal cell carcinoma. Patients were randomly assigned (1:1) using permuted blocks of varying sizes to receive either nivolumab or nivolumab-ipilimumab (ccrcc1 and ccrcc4 groups), or either a VEGFR-TKI or nivolumab-ipilimumab (ccrcc2 and ccrcc3 groups). Patients assigned to nivolumab-ipilimumab received intravenous nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for four doses followed by intravenous nivolumab 240 mg every 2 weeks. Patients assigned to nivolumab received intravenous nivolumab 240 mg every 2 weeks. Patients assigned to VEGFR-TKIs received oral sunitinib (50 mg/day for 4 weeks every 6 weeks) or oral pazopanib (800 mg daily continuously). The primary endpoint was the objective response rate by investigator assessment per Response Evaluation Criteria in Solid Tumors version 1.1. The primary endpoint and safety were assessed in the population who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, NCT02960906, and with the EU Clinical Trials Register, EudraCT 2016-003099-28, and is closed to enrolment.
FINDINGS: Between June 28, 2017, and July 18, 2019, 303 patients were screened for eligibility, 202 of whom were randomly assigned to treatment (61 to nivolumab, 101 to nivolumab-ipilimumab, 40 to a VEGFR-TKI). In the nivolumab group, two patients were excluded due to a serious adverse event before the first study dose and one patient was excluded from analyses due to incorrect diagnosis. Median follow-up was 18·0 months (IQR 17·6-18·4). In the ccrcc1 group, objective responses were seen in 12 (29%; 95% CI 16-45) of 42 patients with nivolumab and 16 (39%; 24-55) of 41 patients with nivolumab-ipilimumab (odds ratio [OR] 0·63 [95% CI 0·25-1·56]). In the ccrcc4 group, objective responses were seen in seven (44%; 95% CI 20-70) of 16 patients with nivolumab and nine (50% 26-74) of 18 patients with nivolumab-ipilimumab (OR 0·78 [95% CI 0·20-3·01]). In the ccrcc2 group, objective responses were seen in 18 (50%; 95% CI 33-67) of 36 patients with a VEGFR-TKI and 19 (51%; 34-68) of 37 patients with nivolumab-ipilimumab (OR 0·95 [95% CI 0·38-2·37]). In the ccrcc3 group, no objective responses were seen in the four patients who received a VEGFR-TKI, and in one (20%; 95% CI 1-72) of five patients who received nivolumab-ipilimumab. The most common treatment-related grade 3-4 adverse events were hepatic failure and lipase increase (two [3%] of 58 for both) with nivolumab, lipase increase and hepatobiliary

disorders (six [6%] of 101 for both) with nivolumab-ipilimumab, and hypertension (six [15%] of 40) with a VEGFR-TKI. Serious treatment-related adverse events occurred in two (3%) patients in the nivolumab group, 38 (38%) in the nivolumab-ipilimumab group, and ten (25%) patients in the VEGFR-TKI group. Three deaths were treatment-related: one due to fulminant hepatitis with nivolumab-ipilimumab, one death from heart failure with sunitinib, and one due to thrombotic microangiopathy with sunitinib.

Telaglenastat plus Everolimus in Advanced Renal Cell Carcinoma: A Randomized, Double-Blinded, Placebo-Controlled, Phase II ENTRATA Trial.
Lee CH et al. Clin Cancer Res . 2022 Aug 2;28(15):3248-3255
PATIENTS AND METHODS: Eligible patients with mRCC, previously treated with at least two prior lines of therapy [including ≥1 VEGFR-targeted tyrosine kinase inhibitor (TKI)] were randomized 2:1 to receive E, plus Tela or Pbo, until disease progression or unacceptable toxicity. Primary endpoint was investigator-assessed progression-free survival (PFS; one-sided <0.2).
RESULTS: Sixty-nine patients were randomized (46 TelaE, 23 PboE). Patients had a median three prior lines of therapy, including TKIs (100%) and checkpoint inhibitors (88%). At median follow-up of 7.5 months, median PFS was 3.8 months for TelaE versus 1.9 months for PboE [HR, 0.64; 95% confidence interval (CI), 0.34-1.20; one-sided P = 0.079]. One TelaE patient had a partial response and 26 had stable disease (SD). Eleven patients on PboE had SD. Treatment-emergent adverse events included fatigue, anemia, cough, dyspnea, elevated serum creatinine, and diarrhea; grade 3 to 4 events occurred in 74% TelaE patients versus 61% PboE.
CONCLUSIONS: TelaE was well tolerated and improved PFS versus PboE in patients with mRCC previously treated with TKIs and checkpoint inhibitors.

Pembrolizumab versus placebo as post-nephrectomy adjuvant therapy for clear cell renal cell carcinoma (KEYNOTE-564): 30-month follow-up analysis of a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial *Powles T et al, Lancet Oncol . 2022 Sep;23(9):1133-1144.*
METHODS: In the multicentre, randomised, double-blind, placebo-controlled, phase 3 KEYNOTE-564 trial, adults aged 18 years or older with clear cell renal cell carcinoma with an increased risk of recurrence were enrolled at 213 hospitals and cancer centres in North America, South America, Europe, Asia, and Australia. Eligible participants had an Eastern Cooperative Oncology Group performance status of 0 or 1, had undergone nephrectomy 12 weeks or less before randomisation, and had not received previous systemic therapy for advanced renal cell carcinoma. Participants were randomly assigned (1:1) via central permuted block randomisation (block size of four) to receive pembrolizumab 200 mg or placebo intravenously every 3 weeks for up to 17 cycles. Randomisation was stratified by metastatic disease status (M0 vs M1), and the M0 group was further stratified by ECOG performance status and geographical region. All participants and investigators involved in study treatment administration were masked to the treatment group assignment. The primary endpoint was disease-free survival by investigator assessment in the intention-to-treat population (all participants randomly assigned to a treatment). Safety was assessed in the safety population, comprising all participants who received at least one dose of pembrolizumab or placebo. As the primary endpoint was met at the first interim analysis, updated data are reported without p values. This study is ongoing, but no longer recruiting, and is registered with ClinicalTrials.gov, NCT03142334.
FINDINGS: Between June 30, 2017, and Sept 20, 2019, 994 participants were assigned to receive pembrolizumab (n=496) or placebo (n=498). Median follow-up, defined as the time from randomisation to data cutoff (June 14, 2021), was 30·1 months (IQR 25·7-36·7). Disease-free survival was better with pembrolizumab compared with placebo (HR 0·63 [95% CI 0·50-0·80]). Median disease-free survival was not reached in either group. The most common all-cause grade 3-4 adverse events were hypertension (in 14 [3%] of 496 participants) and increased alanine aminotransferase (in 11 [2%]) in the pembrolizumab group, and hypertension (in 13 [3%] of 498 participants) in the placebo group. Serious adverse events attributed to study treatment occurred in 59 (12%) participants in the pembrolizumab group and one (<1%) participant in the placebo group. No deaths were attributed to pembrolizumab.

Phase II Study of Nivolumab and Salvage Nivolumab/Ipilimumab in Treatment-Naive Patients With Advanced Clear Cell Renal Cell Carcinoma (HCRN GU16-260-Cohort A). *Meric-Bernstam F, et al.* Clin Cancer Res. 2022 Apr 14;28(8):1540-1548. doi: 10.1158/1078-0432.CCR-21-2972.
RESULTS: One hundred twenty-three patients were enrolled. The objective response rate (ORR) was 34.1% (95% CI, 25.8 to 43.2). ORR by International Metastatic RCC Database Consortium category was favorable-risk 57.1%, intermediate-risk/poor-risk 25.0%, and by sarcomatoid features 36.4%. The ORR was 26.9%, 50.0%, and 75.0% for patients with the tumor PD-L1 expression of 0, 1-20, or > 20%, respectively (trend test P value = .002). The median duration of response was 27.6 (19.3 to not reached) months, with 26 of 42 responders including 17 of 20 with favorable-risk disease remaining progression-free. The 1-year progression-free survival was 34.6% and 75.0% in the PD-L1 = 0% and > 20% categories, respectively (P = .050). Ninety-seven patients with PD or prolonged stable disease were potentially eligible for part B, and 35 were enrolled. The ORR for part B was 11.4%. Grade ≥ 3 treatment-related adverse events occurred in 35% of patients on nivolumab and 43% of those on salvage nivolumab/ipilimumab.
CONCLUSION: Nivolumab monotherapy is active in treatment-naive ccRCC. Although efficacy appears to be less than that of nivolumab/ipilimumab in patients with intermediate-risk/poor-risk disease, favorable-risk patients had notable benefit. Efficacy correlated with tumor PD-L1 status. Salvage nivolumab/ipilimumab was frequently not feasible and of limited benefit.

Safety and efficacy of first-line nivolumab plus ipilimumab alternating with nivolumab monotherapy in patients with advanced renal cell carcinoma: the non-randomised, open-label, phase IIIb/IV CheckMate 920 trial. George DJ et al. BMJ Open. . *2022 Sep 14;12(9):e058396.*
INTERVENTIONS: Patients received NIVO 6 mg/kg plus IPI 1 mg/kg on day 1 of the first week of each 8-week cycle; the combination alternated with NIVO 480 mg monotherapy on day 1 of the fifth week of each 8-week cycle. Treatment continued until disease progression, unacceptable toxicity, withdrawal of consent or study end. The maximum treatment duration was 2 years. The primary endpoint was the incidence of high-grade (grade 3/4 and grade 5) immune-mediated adverse events (IMAEs) within 100 days of the last dose. Select secondary endpoints included time to onset and resolution of high-grade IMAEs, progression-free survival (PFS) and objective response rate (ORR). The incidence of treatment-related adverse events and the overall survival (OS) were the exploratory endpoints.
RESULTS: The most common grade 3/4 IMAEs were diarrhoea/colitis (7.5%) and rash (6.6%) and no grade 5 IMAEs occurred, with a minimum follow-up of 28.5 months. The median PFS was 4.8 (95% CI 3.0 to 8.3) months, the ORR in evaluable patients (n=96) was 34.4% (95% CI 25.0 to 44.8), and the median OS was not reached (95% CI 24.8 months to not estimable).
CONCLUSIONS: While no new safety signals were reported with less frequent, but continual NIVO+IPI dosing in CheckMate 920, the modified regimen was not associated with clinical benefits relative to the approved NIVO+IPI dose. These results support the continued use of the currently approved NIVO+IPI combination dosing schedule for patients with aRCC.

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KCJ ESMO2022 SPECIAL

Dr. Bernard Escudier Received the ESMO Lifetime Achievement Award 2022

During the ESMO Congress 2022 Opening ceremony on 9 September 2022, Dr. Bernard Escudier from Institut Gustave Roussy, France, was awarded the ESMO Lifetime Achievement Award 2022. He received this award in recognition of his lifelong achievements in renal cell carcinoma, immunotherapy, and on development of new therapeutic strategies, as well as for the support provided to fellow oncologists to advance in their professional careers. In particular, Dr. Escudier participated in the development of anti-VEGF and anti-PD-L1 checkpoint inhibitors based on targeted therapies that have quadrupled patient survival and achieved cures.

Dr. Bernard Escudier, during the award lecture at the ESMO Congress

Dr. Escudier has authored more than 450 publications in peer-reviewed journals and is a member of the ASCO, the AACR, and the ESMO. He is also a member of the board of our *Kidney Cancer Journal*, the *Kidney Cancer Association*, and president of ARTuR. He was the first investigator named to head the inaugural immunotherapy unit at Gustave Roussy in 1992, and he headed the French Group of Immunotherapy from 1992 to 2012. Over the past three decades, Dr. Escudier has been a principal investigator for many phase III trials, including studies of bevacizumab, sorafenib, and nivolumab plus ipilimumab. His work helped pave the way for the FDA's approval of cabozantinib and the European Commission's approval of tivozanib in RCC, both small molecules that inhibit VEGF. Dr. Escudier was coordinator of Genitourinary Cancer ESMO Faculty Group, 2012-2016. He has also been a member of the Editorial Board of Annals of Oncology, 2012-2014; and of the ESMO Educational Committee, 2012-2016. Since 2016, Dr. Escudier has been a member of the ESMO Open Editorial Board.

"The renal cancer community has grown substantially and we have seen tremendous improvements in patient outcomes, with median survival increasing to more than 4 years. This transformation has been driven by the development of therapies targeting VEGF and programmed death-ligand 1 (PD-L1). These two pathways were first described in renal cancer in the early 2000s and have since been implicated in the development of multiple types of cancer" said Prof. Escudier.

"Despite the achievements of the past two decades, we are still in a position where up to 90% of patients diagnosed with renal cancer will ultimately die from metastatic disease. Providing a cure for these patients is vital and to do this I believe we will need to target a third oncogenic pathway in addition to VEGF and PD-L1. We also need to improve treatment options for patients with less common types of renal cancer. For these patients, research is required to understand the underlying tumor pathology and to identify suitable treatment targets. We also currently lack good biomarkers to determine prognosis and predict treatment response in renal cancer. In this respect, our knowledge lags behind other solid tumors, such as lung or breast cancer, which have fairly well-defined biomarkers. This will be an important focus of our research in the coming years", said Dr. Escudier, when asked about key challenges in the management of kidney cancer today.

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