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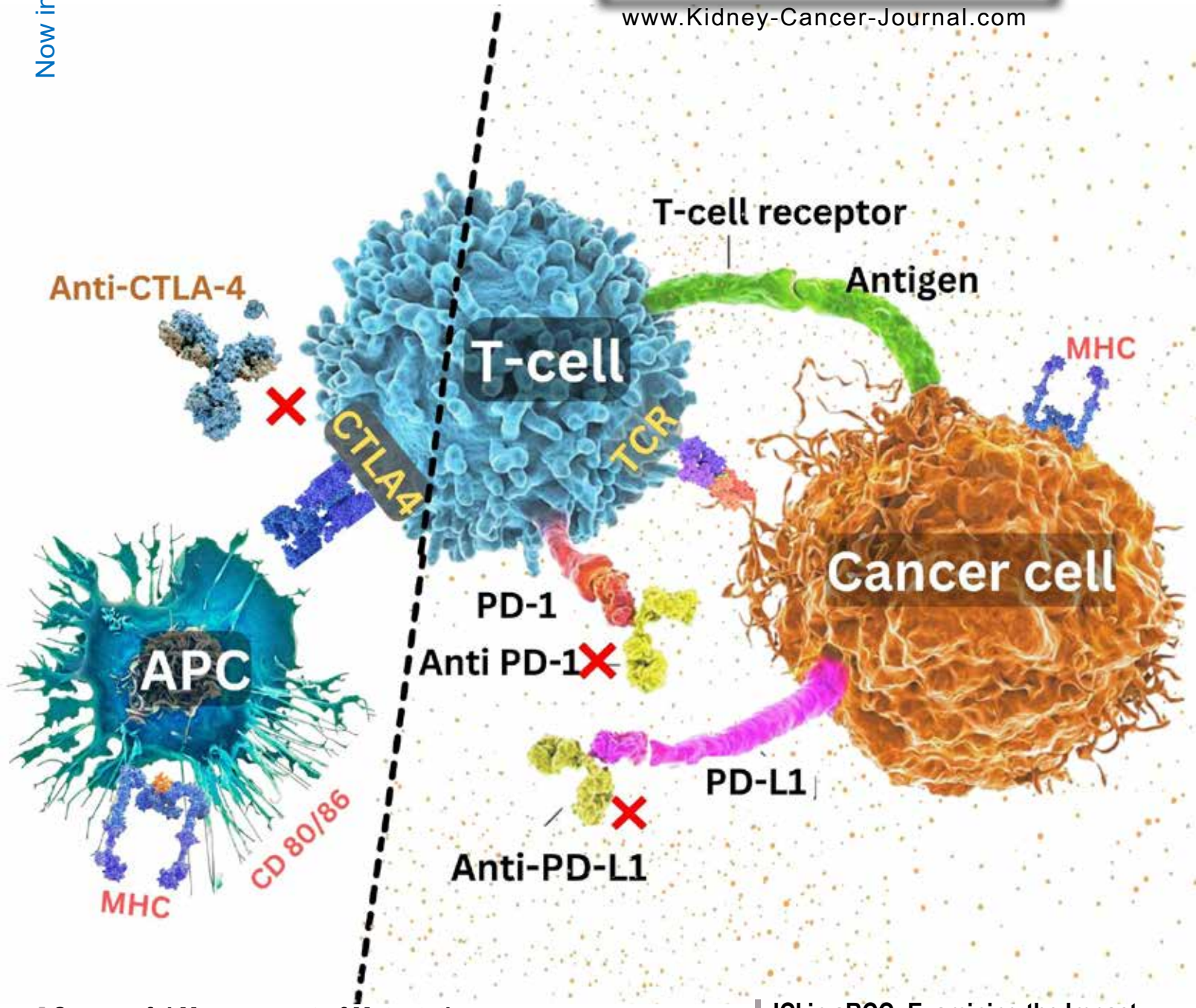

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Successful Management of Metastatic Chromophobe Renal Cell Carcinoma with Nivolumab plus Ipilimumab

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ABSTRACT

Chromophobe renal cell carcinoma (chRCC) is a rare histologic variant that is morphologically and molecularly distinct compared to the more common clear cell renal cell carcinoma (ccRCC). Due to the relatively lower incidence and lack of phase III trials, treatment for metastatic chRCC is often extrapolated from ccRCC. In this case report, we discuss a 58-year-old male with metastatic chRCC who was treated with nivolumab and ipilimumab and achieved a complete response. Though there are no definite predictive biomarkers, tumors that respond to checkpoint inhibitors (CPI) have a high immunogenic gene signature, high PD-L1 expression, MSI instability, or a high tumor mutational burden. Despite a comprehensive genetic profile predicting poor response to CPI, the current patient showed sustained radiologic response over three years. This case challenges the current paradigm of predicted response to CPIs in the setting of chRCC and shows that further biomarker driven research is needed to evaluate the efficacy of these agents in chRCC.

INTRODUCTION

Renal cell carcinoma (RCC) is the eighth most common malignancy in the United States.[1] RCC can be divided into the more common clear cell renal cell carcinoma (ccRCC) and non-clear cell renal cell carcinoma (nccRCC). Chromophobe renal cell carcinoma (chRCC) is the third most common histologic variant of RCC, accounting for 5% of cases.[2] Although computerized tomography (CT) is the preferred imaging modality in diagnosis and staging, histologic and molecular analysis are required to differentiate the histologic variants of RCC. chRCC can be differentiated by its characteristic aneuploidy with the entire loss of chromosomes 1,2,6,10,13, and 17. The high expression of mitochondrial gene mutations and accumulation of abnormal mitochondria suggest that the organelle is important in the pathogenesis of chRCC.[3] ChRCC can also occur in autosomal dominant genetic syndromes such as Birt-Hogg-Dube' and tuberous sclerosis complex.[3]

There is limited evidence regarding the first-line treatment of metastatic chRCC.[2] VEGFR-TKIs (cabozantinib and sunitinib) and mTOR inhibitors (everolimus) have traditionally been utilized in the treatment of nccRCCs due to their proven efficacy in ccRCC.[4] Nivolumab, a PD-L1 inhibitor, has also shown promise in treating ccRCC resistant to VEGFR-TKIs, but there are limited evidence in the current literature addressing their efficacy in the treatment of chRCC.[2,5] We present the case of a patient with cabozantinib-resistant chRCC successfully treated with nivolumab and ipilimumab.

CASE PRESENTATION

The patient is a 58-year-old Caucasian male who initially presented with left flank and lower abdominal wall pain associated with a 30-pound weight loss over one year. Magnetic resonance imaging (MRI) of abdomen showed a large

KEYWORDS: Chromophobe renal cell carcinoma (chRCC), nivolumab, ipilimumab

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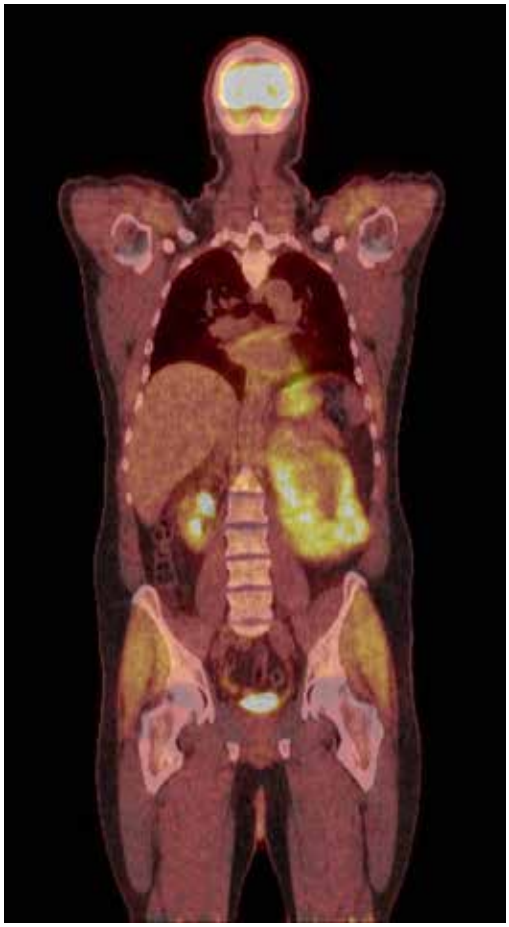

FIGURE 1 | PET-CT at the diagnosis of left-sided chromophobe renal cell carcinoma (April 2018)

left renal mass with invasion of the left renal vein. PET/CT confirmed FDG avid left kidney mass. (**Figure 1**) Biopsy of the mass confirmed chRCC. Subsequently, he underwent left nephrectomy with lymph node dissection and adrenalectomy. Pathology confirmed chRCC with extensive tumor necrosis, lymphovascular invasion, renal sinus and perinephric fat invasion. (**Figure 2A & 2B**) The surgical margins were negative as well as the lymph nodes and adrenal gland were negative for metastatic disease. Reassessment after surgery with CT and bone scan revealed a solitary lytic lesion in the first lumbar vertebrae, and the patient received 30Gy/3fxs stereotactic body radiation to the area.

Subsequent restaging with CT showed disease progression with biopsy-proven liver metastases two months after surgery, and he started first-line systemic therapy with cabozantinib 40 mg daily. Due to the development of severe hand-foot syndrome, the dose of cabozantinib was reduced to 20 mg daily. Despite six months of therapy, the patient continued to have significant disease progression, including new sites of metastases in the lungs. (**Figure 3A & 3B**). At this point in the disease course, therapy was switched to dual checkpoint inhibitor therapy with nivolumab and ipilimumab. Following the fourth cycle of this regimen, reassessment with CT showed partial response with improved liver metastases and resolution of the lung metastases. However, immunotherapy was discontinued after 5 months due to development of an immune-related adverse event (IRAE) in the form of polyneuropathy causing Bell's palsy, dysphagia, and bilateral lower extremity weakness. Brain and spine imaging was negative for metastatic disease or stroke. Cerebrospinal fluid analysis showed an increase in protein levels but was otherwise unremarkable for infection. He was treated with a prolonged tapering dose of high dose prednisone with gradual improvement of symptoms. Despite stopping therapy after 5 months due to IRAEs, he has ongoing complete response in the liver, lung without any evidence of active cancer for over 3 years now (**Figure 4**). Also, he has recovered from the IRAEs.

DISCUSSION

Although localized chRCC can be managed with surgery alone with excellent outcomes, metastatic disease requires the addition of systemic therapy with palliative intent and is generally associated with poor outcomes. The ASPEN phase II randomized control trial of 108 nccRCC patients showed everolimus, when comparable to sunitinib, showed improved overall response rate (33% versus 10% respectively).[4] Within VEGFR-TKIs, cabozantinib has been shown to have improved progression-free survival when compared to sunitinib in randomized controlled trials.[6]

After finding resistance to cabozantinib, we initiated second line therapy with nivolumab plus ipilimumab. In a retrospective analysis of 39 patients with nccRCC treated with nivolumab with or without ipilimumab, only seven patients showed objective response 6 months after therapy initiation.[7] This is in comparison to the phase 3 CheckMate 214 trial that showed objective response rate of 42% in patients with ccRCC treated with nivolumab plus ipilimumab treatment in first line setting. In another review by Bersanelli *et al*, the objective response rates with CPIs as monotherapy or in combination with other TKIs in chRCC ranged anywhere between 0% to 28.5%.[8] The studies evaluating nivolumab plus cabozantinib, atezolizumab plus cabozantinib and pembrolizumab plus lenvatinib showed objective response rates of 0%, 11% and 13.3% respectively.[8] Overall the decreased responses in chRCC when compared to ccRCC can be explained by the unique molecular pathogenesis with lower PD-L1 expression, microsatellite stability, and low tumor mutational burden (TMB) in chRCC.[2] Targeted genomic sequencing with FoundationOne testing which combines DNA and RNA sequencing to identify common genomic alterations and complex nucleic acid fusion events was performed on the patient's tumor specimen. The tumor was also found to be MSI-stable with a TMB of 4 mutations per megabase. PD-L1 immunohistochemical analysis revealed a tumor proportion score of 1%.

Despite the lack of any predictive markers of response to checkpoint inhibitors on the genomic profile, our patient responded well to

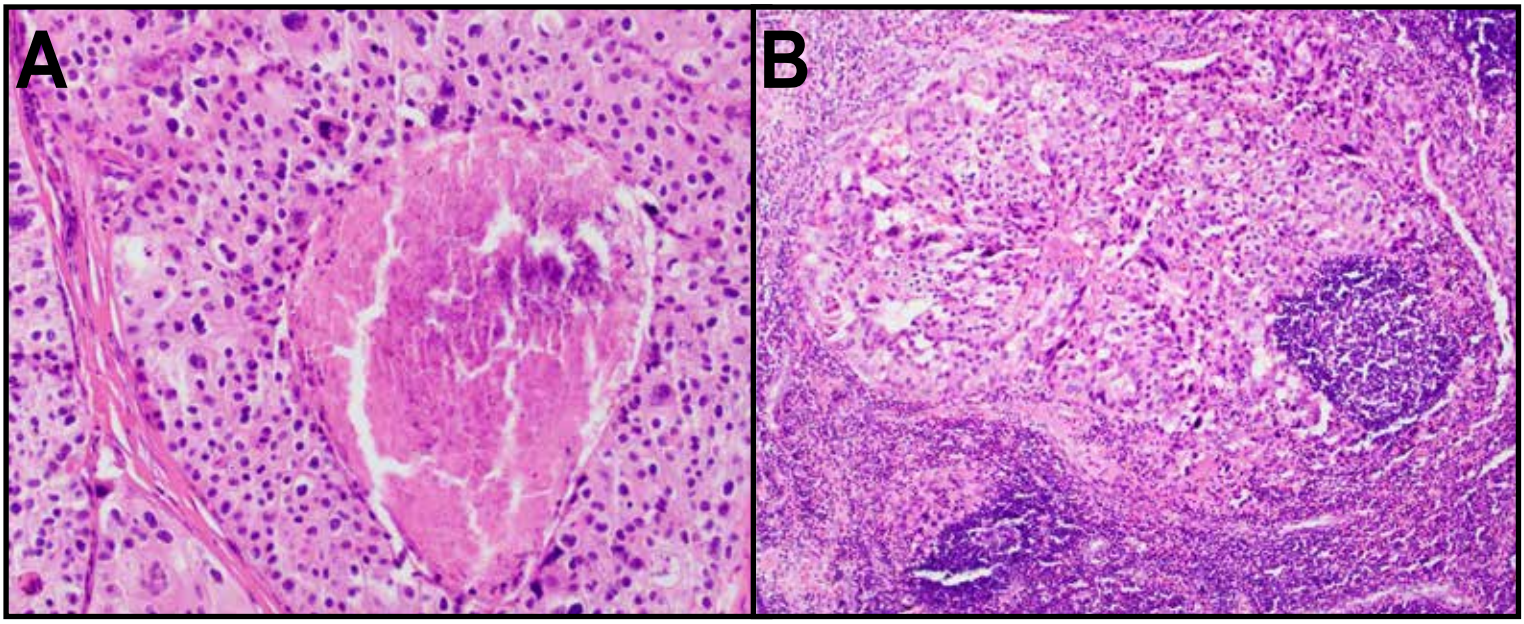

FIGURE 2 | A) Chromophobe renal cell carcinoma, eosinophilic variant with the characteristic eosinophilic tumor cells showing perinuclear halos surrounding irregular raisinoid nuclei. The center of the tumor shows necrosis.
2B) Metastatic chromophobe renal cell carcinoma replacing most of a lymph node.

combination immunotherapy, albeit with serious immune-related adverse events (IRAEs). A couple of retrospective studies in patients with metastatic RCC treated with CPI revealed a correlation between the incidence of IRAEs and improved oncologic outcomes.[9,10] The exact mechanism underlying this association is unclear. One hypothesis is bystander effect of activated cytotoxic T-cells in an organ with low-level inflammation that is potentiated after an IRAE with CPI therapy. In particular, local inflammation caused by IRAEs may activate the immune system and lead to an increased antigen presentation, release of pro-inflammatory cytokines, and recruitment of immune cells to the tumor microenvironment. This could lead to an increased efficacy of the CPI therapy, as the immune system recognizes and responds to the tumor antigens. In a post-mortem study of patients with fulminant myocarditis secondary to CPI, T-cell receptor gene sequencing revealed similar high frequency TCRs in T cells om myocardium and tumor tissue.[11] Another study revealed similar T-cell clones and antigens in the tissue obtained from the site of IRAEs and tumor.[12] Though the onset of IRAE is a potential clinical marker of response to CPI, it is critical to identify those individuals at risk before therapy and understand the underlying mechanism that can aid in enhancing oncologic outcomes

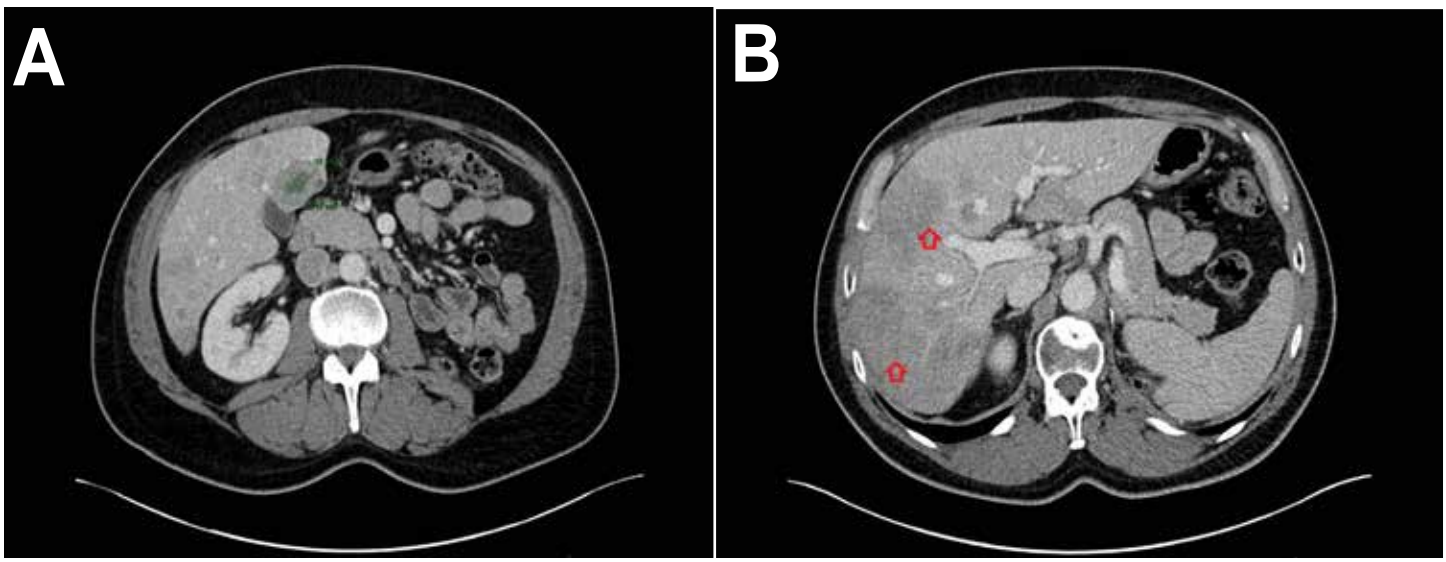

FIGURE 3 | A) A 3.7 cm left liver lobe metastasis after cabozantinib therapy (March 2019).
3B) Multifocal liver hypodensities suggestive of metastases (March 2019)

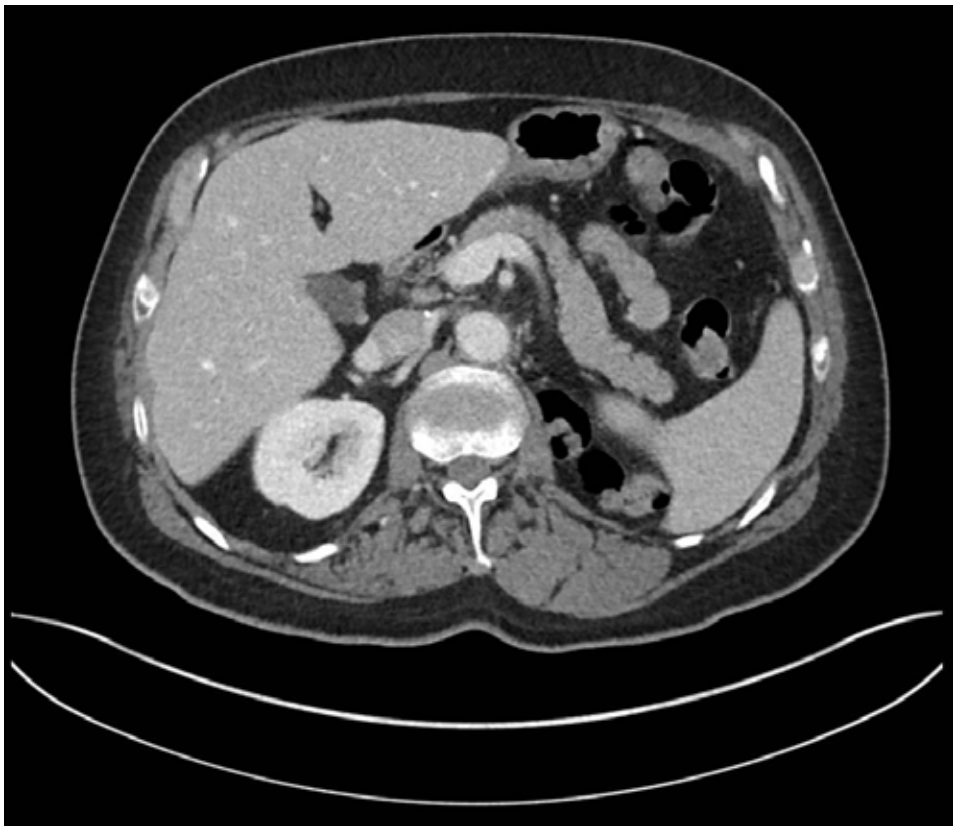

FIGURE 4 | CT scan 3 years after short course therapy with nivolumab and Ipilimumab (October 2022) with complete resolution of liver metastases

while minimizing serious IRAEs.

In summary, while CPIs have shown some promise in the treatment of metastatic chRCC, more biomarker driven research is needed to fully understand their effectiveness in this specific subtype of RCC. Despite having low PD-L1 expression, MSI-stability, and a low TMB, our patient had a durable response with nivolumab and ipilimumab. Additional studies of nivolumab and ipilimumab are needed in a larger cohort of metastatic chRCC, along with further elucidation of mechanisms of IRAEs.

ABBREVIATION

FDG PET: fluorodeoxyglucose (FDG)-positron emission tomography
CTLA-4: cytotoxic T-lymphocyte-associated protein 4
PD-1: programmed cell death protein 1
PD-L1: programmed death ligand 1
mTOR: mammalian target of rapamycin
VEGFR-TKI: vascular endothelial growth factor receptor-tyrosine kinase inhibitors
RCC: renal cell carcinoma
ccRCC: clear cell renal cell carcinoma
nccRCC: non-clear cell renal cell carcinoma
chRCC: chromophobe renal cell carcinoma
CPI: checkpoint inhibitors
MSI: microsatellite instability
TMB: tumor mutational burden

REFERENCE

1. Siegel, R.L., et al., Cancer statistics, 2023. CA: A Cancer Journal for Clinicians, 2023. 73(1): p. 17-48.
2. Garje, R., et al., Comprehensive review of chromophobe renal cell carcinoma. Crit Rev Oncol Hematol, 2021. 160: p. 103287.
3. Davis, Caleb F., et al., The Somatic Genomic Landscape of Chromophobe Renal Cell Carcinoma. Cancer Cell, 2014. 26(3): p. 319-330.
4. Armstrong, A.J., et al., Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): a multicentre, open-label, randomised phase 2 trial. Lancet Oncol, 2016. 17(3): p. 378-388.
5. Vogelzang, N.J., et al., Safety and Efficacy of Nivolumab in Patients With Advanced Non–Clear Cell Renal Cell Carcinoma: Results From the Phase IIIb/IV CheckMate 374 Study. Clinical Genitourinary Cancer, 2020. 18(6): p. 461-468.e3.
6. Campbell, M.T., et al., Cabozantinib for the treatment of patients with metastatic non-clear cell renal cell carcinoma: A retrospective analysis. Eur J Cancer, 2018. 104: p. 188-194.
7. Chahoud, J., et al., Nivolumab for the Treatment of Patients with Metastatic Non-Clear Cell Renal Cell Carcinoma (nccRCC): A Single-Institutional Experience and Literature Meta-Analysis. Oncologist, 2020. 25(3): p. 252-258.
8. Bersanelli, M., et al., Immune checkpoint inhibitors in non-conventional histologies of renal-cell carcinoma. Human Vaccines & Immunotherapeutics, 2023: p. 2171672.
9. Martini, D.J., et al., Immune-Related Adverse Events as Clinical Biomarkers in Patients with Metastatic Renal Cell Carcinoma Treated with Immune Checkpoint Inhibitors. Oncologist, 2021. 26(10): p. e1742-e1750.
10. Verzoni, E., et al., Real-world efficacy and safety of nivolumab in previously-treated metastatic renal cell carcinoma, and association between immune-related adverse events and survival: the Italian expanded access program. J Immunother Cancer, 2019. 7(1): p. 99.
11. Johnson, D.B., et al., Fulminant Myocarditis with Combination Immune Checkpoint Blockade. N Engl J Med, 2016. 375(18): p. 1749-1755.
12. Berner, F., et al., Association of Checkpoint Inhibitor-Induced Toxic Effects With Shared Cancer and Tissue Antigens in Non-Small Cell Lung Cancer. JAMA Oncol, 2019. 5(7): p. 1043-1047.

KCJ REVIEW ARTICLE OPEN ACCESS

Immune Checkpoint Inhibitors in Advanced Renal Cell Carcinoma: Examining the Impact of Nutritional Status, Inflammation, and Body Composition

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ABSTRACT

Renal Cell Carcinoma (RCC) is among the most frequently diagnosed cancers in the United States. One-third of patients present with metastatic disease, and up to another half may progress to metastasis following surgical treatment. Survival rates for metastatic RCC have risen over the past 20 years, an improvement partially attributable to the increased availability of immune checkpoint inhibitors (ICI). However, mRCC remains a fatal genitourinary cancer, with patients often demonstrating both primary and secondary resistance to available immunotherapies. Sarcopenia, inflammation and nutrition have emerged as important prognostic factors in RCC. Recent studies have demonstrated their impact in predicting efficacy and tolerability of ICIs for RCC and other advanced solid malignancies. In this review, we aim to highlight the major milestones in ICI therapy for RCC, and associated mechanisms of action. We also examine how sarcopenia, inflammation and nutrition affect outcomes in RCC, particularly with consideration of the impact on immunotherapy efficacy and toxicity.

KEYWORDS: Kidney Cancer, metastatic renal cell carcinoma, immunotherapy, systemic therapy, sarcopenia, nutrition, inflammation

INTRODUCTION

Renal Cell Carcinoma (RCC) is among the top 10 cancer diagnoses in the United States, with an estimated 79,000 new cases and 14,000 deaths in 2022.[1] The incidence has doubled over the past half-century, likely attributed to improved and more frequent imaging.[2] Nevertheless, one-third of patients present with distant metastatic disease and 20-50% progress to metastasis despite surgical resection.[3] Over the past decade, the 5-year survival rate for metastatic RCC (mRCC) has risen from 12% to 15.3%,[1,3] an improvement at least partially attributed to the increased availability of systemic treatment options. Primary systemic therapy options for RCC include vascular endothelial growth factor (VEGF)-targeted tyrosine kinase inhibitors (TKI) and the more recent introduction of immune checkpoint inhibitors (ICI) such as nivolumab, ipilimumab, pembrolizumab and avelumab. The development of immune checkpoint blockade with antibodies against programmed cell death protein 1 (PD-1), programmed cell death ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) has resulted in significant and durable responses in RCC with acceptable safety.[4–10] Multiple phase III randomized clinical trials comparing ICI monotherapy and combination therapies against targeted therapies for RCC have demonstrated higher median overall survival (OS) and progression-free survival (PFS) with improved objective response rates (ORR).[4–8,11] This has resulted in a major shift towards ICI-based combination therapies as preferred, first-line options for the management of advanced RCC.[12]

However, ICI efficacy and tolerance may be impacted by other factors, such as sarcopenia, inflammation, and nutritional status, which influence survival outcomes in patients with cancer. Sarcopenia is a progressive and generalized

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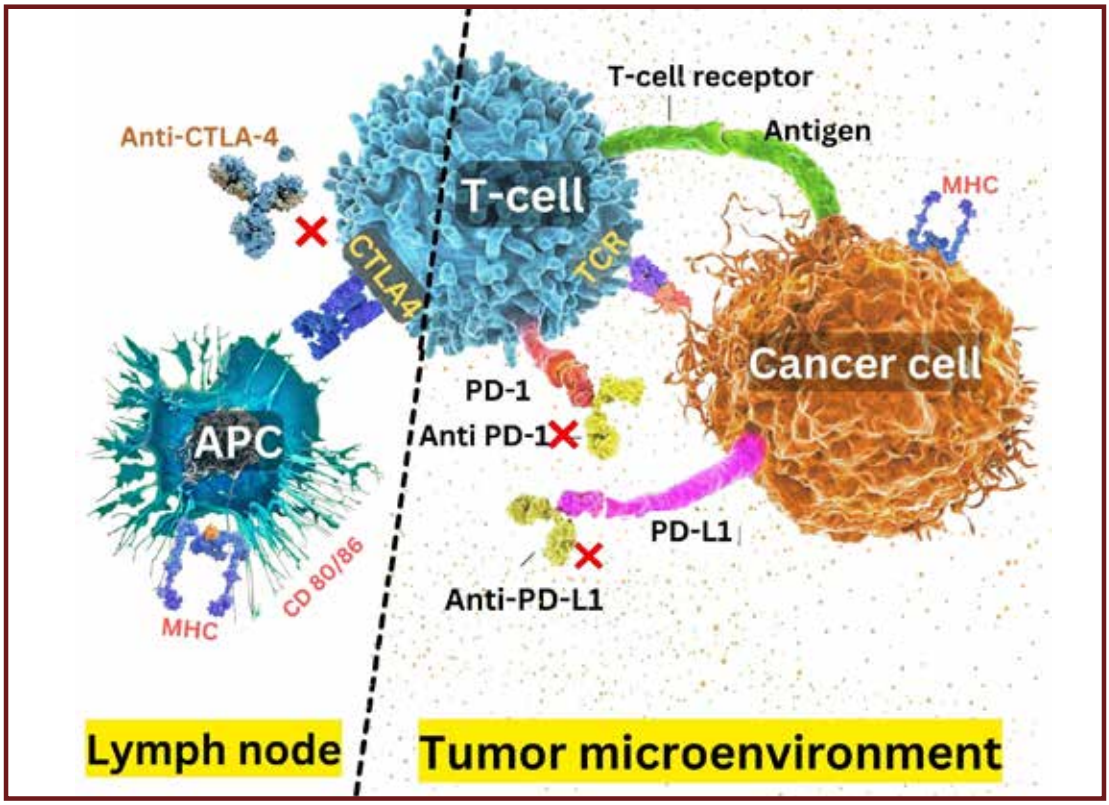

FIGURE 1 | Mechanism of Immune Checkpoint Antibody Blockade in RCC. Abbreviations: Programmed Cell Death Protein 1 (PD-1), Programmed Cell Death Ligand 1 (PD-L1), Cytotoxic T-Lymphocyte-associated Antigen 4 (CTLA-4), T-Cell Receptor (TCR), Antigen Presenting Cell (APC), Major Histocompatibility Complex (MHC), Cluster of Differentiation 80/86 (CD80/86)

skeletal muscle disorder with accelerated loss of muscle mass and function associated with increased risk of falls, frailty, and mortality.[13] Although observed in the context of aging, sarcopenia additionally occurs concurrently or independently in the setting of cancer,[14,15] where there is malignancy-related weight loss and muscle wasting known as cancer cachexia.[16] Sarcopenia and its association with worse survival has been widely reported in patients with RCC, especially in patients with advanced or metastatic disease.[14,17–24] Similarly, markers of malnutrition and inflammation, such as C-reactive protein (CRP), low body mass index (BMI), hypoalbuminemia and neutrophil, lymphocyte, and platelet counts, have also been associated with survival in RCC and other malignancies.[25–29]

In addition to influencing survival in RCC, studies have documented the impact of these factors on the efficacy and tolerability of ICI treatment. Here, we briefly review the major milestones in ICI therapy for advanced RCC and associated mechanisms of action. We focused on data from clear cell RCC as the most commonly encountered histology, recognizing that much of our management of non-clear cell subtypes are extrapolated from this body of work. Then, we examine sarcopenia, inflammation, and malnutrition in RCC and consider its impact on immunotherapy efficacy and tolerance and discuss future considerations for guiding management.

IMMUNE CHECKPOINT INHIBITORS IN ADVANCED RENAL CELL CARCINOMA

Numerous immunotherapies have been studied and received approval for treatment of RCC since 2015. A representative summary of these randomized controlled trials are summarized in **Table 1**. A summary of the mechanism of immune checkpoint inhibition is also represented in **Figure 1**.

History of Immune Checkpoint Inhibitors

The FDA approved the first ICI, ipilimumab (CTLA-4 checkpoint inhibitor), in 2011 for metastatic melanoma.[30,31] Then, in 2014, the FDA approved the first PD-1 checkpoint inhibitor, nivolumab.[30,31] The phase 3 CheckMate 025 trial, published in 2015, compared nivolumab versus everolimus in mRCC following prior treatment, which demonstrated longer median OS (25.0 months [95% confidence interval, 21.8 to not estimable] vs 19.6 months [95% CI, 17.6-23.1]) with less grade 3-4 treatment related adverse events (TRAE), but no difference in progression free survival (PFS, 4.6 [95% CI, 3.7-5.4] vs 4.4 months [95% CI, 3.7-5.5]).4 Nivolumab for the treatment of mRCC after treatment with standard antiangiogenic therapy was then approved. Combination therapy of nivolumab plus ipilimumab versus sunitinib in previously untreated mRCC was studied in the phase III

Clinical Trial	Patient Population	Number of Patients	Treatment Arms	Primary Outcome(s)
CheckMate 025[4]	mRCC following prior treatment	821	1. Nivolumab 2. Everolimus	OS
CheckMate 214[5]	Untreated advanced ccRCC	1096	1. Nivolumab + Ipilimumab 2. Sunitinib	OS, PFS, ORR - among IMDC poor/intermediate risk groups
KEYNOTE-426[11]	Untreated advanced ccRCC	861	1. Pembrolizumab + Axitinib 2. Sunitinib	OS, PFS - in intention-to-treat population
JAVELIN Renal 101[6]	Untreated advanced RCC	886	1. Avelumab + Axitinib 2. Sunitinib	PFS, OS - among PD-L1 positive tumors
CheckMate 9ER[7]	Untreated advanced ccRCC	651	1. Nivolumab + Cabozantinib 2. Sunitinib	PFS
CLEAR[8]	Untreated advanced RCC	1069	1. Lenvatinib + Pembrolizumab 2. Lenvatinib + Everolimus 3. Sunitinib	PFS

TABLE 1 | Summary of Randomized, Open-label, Phase 3 Clinical Trials of FDA-Approved Immunotherapies for RCC

Checkmate 214 trial. This showed significantly longer OS (median OS not reached [95% CI, 28.2 months to not estimable] versus 26.0 months [95% CI, 22.1 to not estimable]), higher objective response rate (ORR, 42% [95% CI, 37-47] vs 27% [95% CI, 22-31], p<0.0001) and complete response rate (CRR, 9% vs 1%), which led to FDA approval as first-line treatment for intermediate to poor-risk advanced RCC in April 2018.[5,31] In the long-term analysis with minimum 42-month follow-up, duration of response was longer, and more patients achieved complete response with nivolumab plus ipilimumab regardless of International mRCC Database Consortium (IMDC) risk group.[32]

Pembrolizumab, another PD-1 checkpoint inhibitor, was first approved in 2014 for advanced melanoma, and showed antitumor activity in untreated mRCC.[33] The KEYNOTE-426 trial comparing pembrolizumab plus axitinib, an anti-VEGF TKI, versus sunitinib for treatment-naive advanced ccRCC showed a 12-month OS benefit (89.9% [95% CI, 86.4-92.4] vs 78.3% [95% CI, 73.8-82.1]) with a longer PFS (15.1 [95% CI, 12.6-17.7] vs 11.1 months [95% CI, 8.7-12.5]) and improved ORR (59.3% [95% CI, 54.5-63.9] vs 35.7% [95% CI, 31.1-40.4], p<0.001). These results were observed across all IMDC risk groups regardless of PD-L1 expression.[11] FDA approval followed soon after in April 2019 as first-line combination immunotherapy for all-risk advanced RCC.

The first PD-L1 checkpoint inhibitor that received approval for mRCC was avelumab with combination axitinib in May 2019. This was supported by the phase III JAVELIN Renal 101 trial of avelumab plus axitinib as compared with sunitinib in patients with previously untreated advanced RCC. Primary endpoints focused on PFS and OS among patients with PD-L1 positive tumors. The median PFS among this cohort was significantly longer for patients that received avelumab plus axitinib (13.8 [95% CI, 11.1 to not estimable] vs 7.2 months [95% CI, 5.7-9.7]), and in the overall population, PFS was also longer (13.8 [95% CI, 11.1 to non estimable] vs 8.4 months [95% CI, 6.9-11.1]).[6]

In 2021, the FDA granted approval to the two remaining frontline combination immunotherapies for advanced RCC treatment: cabozantinib (TKI) plus nivolumab, and lenvatinib (TKI) plus pembrolizumab. The phase III CheckMate 9ER trial comparing nivolumab plus cabozantinib versus sunitinib for advanced RCC showed benefits in median PFS (16.6 [95% CI, 12.5-24.9] vs 8.3 months [95% CI, 7.0-9.7]) and ORR (55.7% [95% CI, 50.1-61.2] vs 27.1% [95% CI, 22.4-32.3], p<0.001). Grade 3 or higher TRAEs were similar, with patients also reporting better health-related quality of life with the combination regiment, demonstrating its acceptable safety profile.[7] In the CLEAR trial comparing lenvatinib plus pembrolizumab or everolimus versus sunitinib for advanced RCC, significant benefits were observed with the immunotherapy-containing regimen in terms of PFS (23.9 [95% CI, 20.8-27.7] vs 9.2 months [95% CI,

Reference	Tumor Type	Treatment	Prognostic Parameters (units)	Primary Outcomes	Results
Loosen et al 2021[72]	NSCLC, Melanoma, UC, GI, Head and Neck, Other	Nivolumab, Pembrolizumab, Nivolumab + Ipilimumab, Others	ΔL3-SMI (mm^2/cm), MMA (HU)	ORR, OS, PFS	OS, PFS significantly lower in ΔSMI <-6.18, ΔMMA <0.4
Herrmann et al 2022[76]	RCC	Nivolumab	SMI (cm^2/m^2), BMI (kg/m^2)	OS, PFS	Median BMI >26, +weight gain associated with longer OS
Martini et al 2020[75]	Melanoma, GI, Lung, Head and Neck, Breast, Other	Immunotherapy-based phase I clinical trials	BMI (kg/m^2); SFI, IFI, VFI (cm^2/m^2)	OS, PFS	SFI ≥73, IFI <3.4, BMI >27 associated with longer OS
Martini et al 2021[74]	RCC	Anti-PD-1 monotherapy, ICI-combination regimen	SMI, SFI, IFI, VFI, TFI (cm^2/m^2)	OS, PFS, CB	BC-poor risk group had shorter OS, PFS, and decreased chance of CB
Ged et al 2022[77]	RCC	Anti-PD1 or Ant-PDL1, Anti-PD1 + Anti-CTLA4, Anti-PD1 + Anti-PDL1	BMI, SMI, multiple adiposity indexes	OS, PFS, ORR	High-BMI had longer OS vs. normal weight
Zahoor et al 2018[80]	RCC	Nivolumab	NLR	OS, PFS, RPD	Higher baseline NLR associated with increased risk of progression
Bilen et al 2018[79]	RCC	Nivolumab	NLR	OS, PFS	NLR >5.5 had median PFS 2.6 months and OS 2.7 months
Bilen et al 2020[78]	Melanoma, GI, Lung, Head and Neck, Breast (results not complete), Other	ICI + experimental combo, Anti-PDL1 monotherapy, Experimental IO	NLR, MLR, PLR; SMI; Combination Risk Grouping	OS, PFS	Low-risk (nonsarcopenic, PLR<242) had significantly longer OS, PFS
Aslan et al 2022[82]	RCC	ICI mono- and combo-therapy	SMI, NLR, Albumin	OS, PFS	CXI<median score had median OS of 7 vs. 48 months, and PFS of 4 vs. 17 months

TABLE 2 | Summary of studies using sarcopenic, inflammatory or nutritional parameters to predict ICI efficacy in advanced malignancies. Abbreviations: Non-small cell lung cancer (NSCLC), urothelial carcinoma (UC), mean skeletal muscle attenuation (MMA), gastrointestinal (GI), subcutaneous fat index (SFI), intermuscular fat index (IFI),visceral fat index (VFI), total fat index (TFI), clinical benefit (CB, defined as stable/improved radiographic disease at ≥6 months) body composition (BC), radiological progressive disease (RPD).

6.0-11.0]), OS at 24 months (79.2% vs 70.4%; hazard ratio [HR] for death, 0.66 [95% CI, 0.49-0.88]; p=0.005), and ORR (71.0% vs 36.1%; relative risk [RR], 1.97 [95% CI, 1.69-2.29]) versus sunitinib.

These immunotherapy regimens represent the approved, first-line and preferred options for the treatment of RCC, with many other immune-checkpoint inhibitor-based combinations or monotherapies currently under investigation or awaiting approval[12,34–38].

Interplay between ICIs and RCC

The tumorigenesis and development of RCC is well documented. Clear cell RCC frequently contains multiple loss-of-function mutations in the tumor suppressor gene Von Hippel-Lindau (VHL). This results in the induction of hypoxia inducible factors (HIF), which promotes cells to express VEGF and other factors that increase tumor angiogenesis and growth.[39] These findings were the basis for anti-angiogenic agents becoming the standard of care for advanced RCC. These drugs demonstrated improvements in OS and PFS, but without significant complete or durable response rates as monotherapies.[40]

It has become better documented how multiple subtypes of RCC share

alterations of specific pathways involving metabolism, hypoxia, and immune checkpoints.[41,42] RCC is notably associated with a highly inflammatory microenvironment with increased frequency of tumor infiltrating lymphocytes.[43] Despite prominent levels of T-cells within tumors, RCC often escapes via immunosuppressive mediators from the microenvironment or tumor cell overexpression of CTLA-4 and PD-L1 which block T-cell responses.[43] This infiltrate is partially composed of regulatory T cells (Treg), which can prevent cancer antigen recognition, and reduce the antitumor activity of lymphocytes present.[44] Markers associated with T-cell exhaustion along with the promotion of Th2 induction have been identified, which can allow for unchecked tumor growth in a state of chronic inflammation.[41,45] These findings support the use and improved benefits associated with immunotherapy in the treatment of RCC. However, many patients may not respond to immunotherapy and durable responses remain an exception, which can reflect the presence of primary and secondary resistance to ICIs.

There are multiple theories that explain resistance including certain patient-intrinsic, tumor cell-intrinsic, and tumor microenvironment factors.[46] One explanation is the tumor cell-induced release of VEGF which promotes abnormal neovascularization, Treg proliferation, and reduces CD8+ T-cell proliferation and penetration into the tumor. This supports the rationale for combining ICIs and anti-VEGFR TKIs as dual therapy for mRCC to target both antitumor processes.[40,47] Other explanations for potential ICI resistance include Wnt/ß-catenin pathway overexpression leading to T-cell exclusion and resistance to anti-PD(L1) and CTLA-4 antibodies along with MAP Kinase alterations that inhibit T-cell recruitment and function.[46] For patients that do respond to ICIs there is often a robust activation of CD8+ T-cells within the microenvironment, along with increased interferon-gamma signaling that promotes acute inflammation.[48] However, over time, evidence suggests an adaptation to increased T-cell checkpoint molecule expression that can lead to immunotherapy resistance.[48] Patient-specific factors, including sarcopenia, systemic inflammation and markers of nutritional status, remain an important barrier to immunotherapy efficacy and can be identified and addressed for improved management of advanced RCC.

SARCOPENIA, INFLAMMATION, AND MALNUTRITION IN ADVANCED RENAL CELL CARCINOMA

Definitions, Epidemiology, Relationships, and Pathophysiology

Sarcopenia is a generalized skeletal muscle disorder defined by 3 main criteria: low levels of muscle strength, muscle quantity and/or quality, and decreased physical performance which can indicate severity.[13,49] Cross-sectional imaging with computed tomography (CT) or magnetic resonance imaging (MRI) is widely prevalent during RCC screening, staging, and follow-up and can additionally be used to evaluate for sarcopenia at the third lumbar vertebra (L3), which correlates well with total skeletal muscle mass.[50–53] Commonly, the skeletal muscle index (SMI, cm2/m2) is calculated by dividing cross-sectional area of skeletal muscle at L3 by the patient's height in meters squared.[54] Then, SMI thresholds are used to define sarcopenia vs. nonsarcopenia; however, it should be noted that there is wide variation in SMI thresholds used to define sarcopenia, which is an important consideration for future incorporation and study interpretation.[55]

There has been further investigation since sarcopenia was first defined to clarify specific categories including primary and secondary forms, acute and chronic sarcopenia, sarcopenic obesity, and malnutrition-associated sarcopenia.[49] Primary sarcopenia refers to age-related changes, where, in addition to hormonal, physical activity, and nutritional changes, a state of chronic low-grade inflammation can contribute to the loss of muscle over time.[49,56] Based on established thresholds for muscle mass, up to 20% of those aged 70-79 and 30% of the population 80 or older meets this criterion for sarcopenia.[57] In addition, studies have demonstrated a high prevalence of weak muscle strength and decreased physical performance in populations aged 65 or older, affecting up to half of all individuals.[57]

Normal aging is associated with elevated levels of pro-inflammatory markers, including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP), often associated with long-standing mitochondrial and immune dysfunction, cellular injury, and increased adiposity.[58] Multiple studies have demonstrated that higher levels of circulating cytokines, including TNF-α and IL-6, are associated with loss of skeletal muscle mass and strength, with an overall increased risk of sarcopenia.[59–61] In a separate meta-analysis, CRP is suggested to be a potential parameter for detecting sarcopenia given its association with higher serum levels in sarcopenic patients.[62] Alterations in pro-inflammatory markers can, directly and indirectly, affect skeletal muscle metabolism by increasing catabolic pathways for muscle breakdown, and preventing appropriate use of proteins for muscle synthesis.[56]

Systemic inflammation is also associated with solid malignancies and can exacerbate typical age-related skeletal muscle mass loss and contribute to worse outcomes. In a meta-analysis of over 80,000 patients with malignant tumors, sarcopenia was identified in 35.3%, and varied between 35-50% in RCC.15 Cancer

and its treatments can increase the risk of developing sarcopenia via the promotion of anorexia, physical inactivity, and pro-inflammatory states, along with treatment related damage to muscle tissue.[63] The development of sarcopenia can also co-occur as a component of cancer cachexia, defined as a progressive, multifactorial syndrome with continuous loss of skeletal muscle mass resulting in functional impairment that cannot be fully reversed.[16] Cancer cachexia arises from a combination of systemic inflammation and negative energy balance and affects ~30% of all cancer patients and close to 80% of patients with metastatic disease to the brain.[64] The diagnosis requires certain changes in overall weight, BMI, and sarcopenic criteria.[16] Furthermore, advanced cancer patients are often affected by nutritional impact symptoms, including anorexia, nausea, vomiting, taste, and smell changes, as a result of chemotherapy, radiotherapy, and even systemic inflammation that can alter hunger/satiety signaling thus preventing compensation for the ongoing negative energy balance.[64]

General Impact of Sarcopenia, Inflammation and Malnutrition on Survival in RCC

Sarcopenia is associated with poor OS and CSS across a wide variety of non-hematological solid tumors.[65] In a systematic review examining treatment-related outcomes for patients undergoing nephrectomy for localized and mRCC, sarcopenia was an independent predictor of mortality, especially following systemic treatment.[66] In patients with non-mRCC treated with radical nephrectomy, Psutka *et al* found sarcopenia as inferior 5-year CSS (79% vs 85%, p=0.05) as well as inferior 5-year OS (65% vs 74%, p=0.005).[19] In a study of mRCC patients, sarcopenia was associated with a 2.5x higher risk of all-cause mortality. and improved the prognostic ability of the MSKCC risk model when included with or substituted for Karnofsky performance status.[21] Similar results have been found in other cohorts of patients with metastatic and nonmetastatic RCC.[18,67]

Increasingly, sarcopenia with other markers of inflammation and nutrition are being considered and have demonstrated an association with increased mortality.[17,18,20,68] Higher modified Glasgow prognostic scores (mGPS), which features CRP and albumin as measures of inflammation and nutrition, have been associated with worse OS, CSS, RFS, and PFS, and have an even greater association when combined with sarcopenia.[18,29,69] Other studies have analyzed the predictive impact of the prognostic nutritional index (PNI) in patients undergoing nephrectomy, as calculated by albumin and lymphocyte levels.[26] Increases in PNI scores have shown a decreased risk of death from RCC.[25] PNI also demonstrated greater prognostic ability for both OS and PFS when compared to other inflammatory measures, such as Neutrophil-to-Lymphocyte (NLR), Platelet-to-Lymphocyte (PLR), and Lymphocyte-to-Monocyte (LMR) ratios.[25,26] On univariate analysis, these indices were associated with shorter OS and PFS, but only PNI was significant on multivariable analysis.[26] Multiple methods of evaluating for sarcopenia, inflammation, and nutritional status exist and demonstrate prognostic utility in localized and advanced RCC.

IMPACT OF SARCOPENIA, MALNUTRITION, AND INFLAMMATION ON IMMUNE CHECKPOINT EFFICACY

Examination of ICI efficacy and toxicity in relation to sarcopenia and other markers of nutrition and inflammation has emerged over the past decade. A representative summary of studies examining these interactions is summarized in **Table 2**.

Sarcopenia

A retrospective analysis of patients with advanced cancer receiving ICIs found sarcopenic patients experienced worse ORR (15.9% vs 30.5%, p=0.095) although this was statistically insignificant.70 However, 1-year PFS (10.8% vs 32%; RR, 1.31; p<0.001) and OS (43% vs 66%; RR 1.71; p<0.001) were significantly lower for the sarcopenic patients.[70] In another group of patients with advanced solid tumors that received ICI monotherapy, sarcopenia prevalence was nearly 50% and a significant predictor of worse OS, PFS, and ORR and not dependent on the type of ICI received.[71]

In addition to baseline muscle measurements, longitudinal change during ICI therapy has additionally exhibited prognostic ability. In one prospective study, [88] patients received either nivolumab (55.7%), pembrolizumab (28.4%), or nivolumab plus ipilimumab (9.1%) for various solid organ malignancies.[72] Although no difference in baseline SMI between responders vs. non-responders was observed, patients that responded to ICI therapy at the 3-month mark experienced an increase in SMI (+1.73 vs -3.20 mm2/cm, p=0.002) and median muscle attenuation (+0.89 vs -1.0 HU, p=0.090), an indicator of muscular fat deposition.72 Furthermore, OS was significantly lower (127 vs 547 days, p<0.001) in patients that experienced a strong decline in SMI (<-6.18 mm2/cm) or muscle attenuation (<-0.4 HU) compared to patients with stable or mild decreases.[72] The progressive loss of muscle mass with increased myosteatosis might reflect increased malignancy-associated inflammation which may negatively influence the antitumor effects of ICIs.[73]

Alternative Body Composition Parameters

In addition to quantified muscle composition, other parameters such as BMI, adipose distribution, and muscle quality may be informative. In an analysis of 79 patients treated with ICI for mRCC, Martini *et al* measured density (as measured via HU) of skeletal muscle, subcutaneous fat, intramuscular fat, and visceral

fat in addition to SMI. Patients were stratified into poor, intermediate, or favorable risk groups based on these measurements, with the poor risk groups experiencing significantly shorter OS, PFS, and lower chance of radiographic response at 6 months compared to the favorable risk group.[74] Furthermore, a lower total fat index was also associated with shorter OS, PFS, and a lower chance of radiographic response.[74] These findings suggest that, in addition to muscle quantification, markers of adiposity and muscle quality (i.e. intramuscular fat) may be informative and predict outcomes for patients with RCC receiving ICI therapy. This aligns with prior studies demonstrating that increased BMI, weight gain, increased subcutaneous fat index, and decreased intermuscular fat index during ICI treatment are associated with prolonged survival or treatment response in patients with cancer,[75] including mRCC.[76,77]

Inflammation

Relationships between inflammation and body composition in patients receiving ICI have also been considered. In 90 patients enrolled in immunotherapy-based phase 1 clinical trials, Bilen et al. risk-stratified patients based on sarcopenia measurements and baseline inflammatory markers (i.e. NLR, MLR, and PLR). A negative correlation was observed between SMI and PLR, and very high-risk (PLR ≥242 and sarcopenic) or intermediate (PLR <242 and sarcopenic) risk groups experienced significantly shorter OS and PFS compared with low-risk patients (PLR <242 and non-sarcopenic).[78] In a separate study of 38 mRCC patients treated with nivolumab, Bilen et al demonstrated that low NLR values were associated with longer median PFS (not estimable vs 2.6 months; HR 0.20 [95% CI, 0.07-0.64; p=0.006]) and OS (not estimable vs 2.7 months; HR 0.06 [95% CI, 0.01-0.55; p=0.012]).[79] These findings were echoed by Zahoor et al, where a higher baseline NLR was associated with an increased risk of progression in mRCC patients treated with nivolumab.[80] It is well documented how both inflammation and sarcopenia contribute to worse outcomes in malignancy and can limit treatment efficacy, but the inclusion of multiple markers for risk stratification may better account for multiple underlying prognostic factors.

Nutritional Status

Advanced RCC patients are often susceptible to malnutrition and resulting cancer cachexia, which can affect ICI efficacy. As previously discussed, higher PNI is associated with better survival. In a series of studies from Asian countries looking at PNI and survival outcomes in advanced cancer patients treated with ICIs, higher PNI was associated with greater ORR and longer OS and PFS.[81] The cachexia index is another combined score of sarcopenic and inflammatory markers used as a prognostic model in cancer patients. This index, based on SMI, NLR, and albumin levels, was used in a retrospective review of 52 mRCC patients who had received ICI as a 2nd-line or later treatment.[82] Below median cachexia index score was found to significantly affect OS (7 vs 48 months; HR 4.5 [95% CI, 1.9-11; p=0.001]) and PFS (4 months vs. 17 months; HR 2.6 [95% CI, 1.3-5.3; p=0.007]) as opposed to the other markers.82 One theory for why the procatabolic and proinflammatory state associated with cancer cachexia may interfere with ICI efficacy is increased clearance and metabolism. A prospective cohort study on the pharmacokinetics of nivolumab used in advanced cancers, including 14 patients (6.3%) with mRCC, showed how increased body-surface area and decreased albumin were associated with increased clearance of the ICI.[83] A clearance-response trend was observed in mRCC where clearance was higher in patients with progressive disease, although this was non-significant.83 However, this trend was significant in NSCLC (n=158; 71.5%), and given the smaller percentage of patients with mRCC, the study may have been underpowered to demonstrate statistical significance in this subgroup.

IMMUNE CHECKPOINT INHIBITOR TOLERANCE

In a series of 8 studies that featured patients with advanced RCC and other metastatic solid tumors, no association between patients with sarcopenia and adverse reactions of any grade were identified.[84] However, in a separate review, an increased risk of AEs with the use of ICIs in sarcopenic cancer patients was observed.[85] In addition to standard TRAEs from systemic therapy, numerous immune-related adverse events (irAE) associated with ICI use that result from upregulation of the host immune system.[86] The most commonly affected organs include the gastrointestinal tract, endocrine glands, skin, and liver.[86] Intriguingly, in a review of 90 patients with ICI-treated RCC, there was a 42% prevalence of irAEs, and this cohort demonstrated improved OS compared to patients without irAEs (35.9 [95% CI, 24.3 to non-estimable] vs 26.5 months [95% CI, 10.2-28.8]; p=0.002).[87] Similar studies have supported the findings of longer OS and PFS in ICI-treated RCC patients reporting greater irAEs.[88,89] In a meta-analysis of patients with advanced solid tumors, researchers analyzed sarcopenia in relation to irAEs, but the findings were mixed: two of the studies found no significant association between sarcopenia and irAEs, however, the 3rd study did identify a higher chance of developing irAEs in the sarcopenic group.[85] An association between sarcopenia and grade 3-4 irAEs may explain the lack of survival benefit in this cohort compared to other studies assessing the prognostic value of irAEs.[90] Although certain studies support sarcopenia as a risk factor for ICI TRAEs, the topic remains controversial and study-dependent. From a pharmacokinetic perspective, susceptibility to TRAEs in sarcopenic patients

makes sense; however, much of the research is limited by sample size, retrospective nature, and inclusion of a wide diversity of tumor types. New prospective studies should be pursued to examine the impact that muscle, inflammation, and nutrition may have ICI-related toxicity in RCC.

CONCLUSIONS

There remains a high prevalence of RCC cases that are either diagnosed at or progress to an advanced stage. ICI-based regimens including ICIs have emerged as first-line treatments for patients with advanced or metastatic disease. Measurements of sarcopenia, inflammation and nutrition hold potential prognostic value for the long-term outcomes of localized and advanced RCC. Strategies aimed for preventing and managing sarcopenia may have significant impact on improving outcomes and quality of life in patients with metastatic RCC.

REFERENCE

1. Cancer of the Kidney and Renal Pelvis - Cancer Stat Facts. SEER. Accessed February 23, 2023. https://seer.cancer.gov/statfacts/html/kidrp.html
2. Bukavina L, Bensalah K, Bray F, et al. Epidemiology of Renal Cell Carcinoma: 2022 Update. Eur Urol. 2022;82(5):529-542.
3. Padala SA, Barsouk A, Thandra KC, et al. Epidemiology of Renal Cell Carcinoma. World J Oncol. 2020;11(3):79-87.
4. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015;373(19):1803-1813.
5. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med. 2018;378(14):1277-1290.
6. Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2019;380(12):1103-1115.
7. Choueiri TK, Powles T, Burotto M, et al. Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2021;384(9):829-841.
8. Motzer R, Alekseev B, Rha SY, et al. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. N Engl J Med. 2021;384(14):1289-1300.
9. Tykodi SS, Gordan LN, Alter RS, et al. Safety and efficacy of nivolumab plus ipilimumab in patients with advanced non-clear cell renal cell carcinoma: results from the phase 3b/4 CheckMate 920 trial. J Immunother Cancer. 2022;10(2). doi:10.1136/jitc-2021-003844
10. Powles T, Plimack ER, Soulières D, et al. Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial. Lancet Oncol. 2020;21(12):1563-1573.
11. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2019;380(12):1116-1127.
12. Motzer RJ, Jonasch E, Agarwal N, et al. Kidney Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2022;20(1):71-90.
13. Cruz-Jentoft AJ, Sayer AA. Sarcopenia. Lancet. 2019;393(10191):2636-2646.
14. Williams GR, Chen Y, Kenzik KM, et al. Assessment of Sarcopenia Measures, Survival, and Disability in Older Adults Before and After Diagnosis With Cancer. JAMA Netw Open. 2020;3(5):e204783.
15. Surov A, Wienke A. Prevalence of sarcopenia in patients with solid tumors: A meta-analysis based on 81,814 patients. JPEN J Parenter Enteral Nutr. 2022;46(8):1761-1768.
16. Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol. 2011;12(5):489-495.
17. Khan AI, Psutka SP, Patil DH, et al. Sarcopenia and systemic inflammation are associated with decreased survival after cytoreductive nephrectomy for metastatic renal cell carcinoma. Cancer. 2022;128(11):2073-2084.
18. Higgins MI, Martini DJ, Patil DH, et al. Sarcopenia and modified Glasgow Prognostic Score predict postsurgical outcomes in localized renal cell carcinoma. Cancer. 2021;127(12):1974-1983.
19. Psutka SP, Boorjian SA, Moynagh MR, et al. Decreased Skeletal Muscle Mass is Associated with an Increased Risk of Mortality after Radical Nephrectomy for Localized Renal Cell Cancer. J Urol. 2016;195(2):270-276.
20. Sharma P, Zargar-Shoshtari K, Caracciolo JT, et al. Sarcopenia as a predictor of overall survival after cytoreductive nephrectomy for metastatic renal cell carcinoma. Urol Oncol. 2015;33(8):339.e17-e23.
21. Fukushima H, Nakanishi Y, Kataoka M, Tobisu KI, Koga F. Prognostic Significance of Sarcopenia in Patients with Metastatic Renal Cell Carcinoma. J Urol. 2016;195(1):26-32.
22. Maurits JSF, Sedelaar JPM, Mulders PFA, Aben KKH, Kiemeney LALM, Vrieling A. Skeletal muscle radiodensity and visceral adipose tissue index are associated with survival in renal cell cancer - A multicenter population-based cohort study. Clin Nutr. 2022;41(1):131-143.
23. Schmeusser BN, Midenberg E, Palacios AR, et al. Clinic friendly estimation of muscle composition: Preoperative linear segmentation shows overall survival correlated with muscle mass in patients with nonmetastatic renal cell carcinoma. Front Oncol. 2022;12:1068357.
24. Watanabe S, Ishihara H, Takagi T, et al. Impact of sarcopenia on post-operative outcomes following nephrectomy and tumor thrombectomy for renal cell carcinoma with inferior vena cava thrombus. Jpn J Clin Oncol. 2021;51(5):819-825.
25. Hofbauer SL, Pantuck AJ, de Martino M, et al. The preoperative prognostic nutritional index is an independent predictor of survival in patients with renal cell carcinoma. Urol Oncol. 2015;33(2):68.e1-e7.
26. Peng D, He ZS, Li XS, et al. Prognostic Value of Inflammatory and Nutritional Scores in Renal Cell Carcinoma After Nephrectomy. Clin Genitourin Cancer. 2017;15(5):582-590.
27. Gu W, Zhang G, Sun L, et al. Nutritional screening is strongly associated with overall survival in patients treated with targeted agents for metastatic renal cell carcinoma. J Cachexia Sarcopenia Muscle. 2015;6(3):222-230.
28. Schmeusser BN, Patil DH, Midenberg E, et al. Data regarding covariates significantly associated with sarcopenia and varying albumin statuses in patients with renal cell carcinoma. Data Brief. 2022;45(108724):108724.
29. Midenberg E, Higgins MI, Schmeusser BN, et al. Prognostic Value of Sarcopenia and Albumin in the Surgical Management of Localized Renal Cell Carcinoma. Urologic Oncology: Seminars and Original Investigations. Published online October 21, 2022. doi:10.1016/j.urolonc.2022.09.020
30. Dobosz P, Dzieciątkowski T. The Intriguing History of Cancer Immunotherapy. Front Immunol. 2019;10:2965.
31. Hargadon KM, Johnson CE, Williams CJ. Immune checkpoint blockade therapy for cancer: An overview of FDA-approved immune checkpoint inhibitors. Int Immunopharmacol. 2018;62:29-39.
32. Motzer RJ, Escudier B, McDermott DF, et al. Survival outcomes and independent response assessment with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma: 42-month follow-up of a randomized phase 3 clinical trial. J Immunother Cancer. 2020;8(2). doi:10.1136/jitc-2020-000891
33. Atkins MB, Plimack ER, Puzanov I, et al. Axitinib in combination with pembrolizumab in patients with advanced renal cell cancer: a non-randomised, open-label, dose-finding, and dose-expansion phase 1b trial. Lancet Oncol. 2018;19(3):405-415.
34. Albiges L, Barthélémy P, Gross-Goupil M, Negrier S, Needle MN, Escudier B. TiNivo: safety and efficacy of tivozanib-nivolumab combination therapy in patients with metastatic renal cell carcinoma. Ann Oncol. 2021;32(1):97-102.
35. Naing A, Gainor JF, Gelderblom H, et al. A first-in-human phase 1 dose escalation study of spartalizumab (PDR001), an anti-PD-1 antibody, in patients with advanced solid tumors. J Immunother Cancer. 2020;8(1). doi:10.1136/jitc-2020-000530
36. Msaouel P, Goswami S, Thall PF, et al. A phase 1-2 trial of sitravatinib and nivolumab in clear cell renal cell carcinoma following progression on antiangiogenic therapy. Sci Transl Med. 2022;14(641):eabm6420.
37. Campbell MT, Matin SF, Tam AL, et al. Pilot study of Tremelimumab with and without cryoablation in patients with metastatic renal cell carcinoma. Nat Commun. 2021;12(1):6375.
38. Tannir NM, Cho DC, Diab A, et al. Bempegaldesleukin plus nivolumab in first-line renal cell carcinoma: results from the PIVOT-02 study. J Immunother Cancer. 2022;10(4). doi:10.1136/jitc-2021-004419
39. Stubbs C, Bardoli AD, Afshar M, et al. A Study of Angiogenesis Markers in Patients with Renal Cell Carcinoma Undergoing Therapy with Sunitinib. Anticancer Res. 2017;37(1):253-259.
40. Brighi N, Farolfi A, Conteduca V, et al. The Interplay between Inflammation, Anti-Angiogenic Agents, and Immune Checkpoint Inhibitors: Perspectives for Renal Cell Cancer Treatment. Cancers . 2019;11(12). doi:10.3390/cancers11121935
41. Ricketts CJ, De Cubas AA, Fan H, et al. The Cancer Genome Atlas Comprehensive Molecular Characterization of Renal Cell Carcinoma. Cell Rep. 2018;23(1):313-326.

e5.
42. Chen F, Zhang Y, Şenbabaoğlu Y, et al. Multilevel Genomics-Based Taxonomy of Renal Cell Carcinoma. Cell Rep. 2016;14(10):2476-2489.
43. Geissler K, Fornara P, Lautenschläger C, Holzhausen HJ, Seliger B, Riemann D. Immune signature of tumor infiltrating immune cells in renal cancer. Oncoimmunology. 2015;4(1):e985082.
44. Itsumi M, Tatsugami K. Immunotherapy for renal cell carcinoma. Clin Dev Immunol. 2010;2010:284581.
45. Chevrier S, Levine JH, Zanotelli VRT, et al. An Immune Atlas of Clear Cell Renal Cell Carcinoma. Cell. 2017;169(4):736-749.e18.
46. Moreira M, Pobel C, Epaillard N, Simonaggio A, Oudard S, Vano YA. Resistance to cancer immunotherapy in metastatic renal cell carcinoma. Cancer Drug Resist. 2020;3(3):454-471.
47. George S, Rini BI, Hammers HJ. Emerging Role of Combination Immunotherapy in the First-line Treatment of Advanced Renal Cell Carcinoma: A Review. JAMA Oncol. 2019;5(3):411-421.
48. Bi K, He MX, Bakouny Z, et al. Tumor and immune reprogramming during immunotherapy in advanced renal cell carcinoma. Cancer Cell. 2021;39(5):649-661.e5.
49. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48(1):16-31.
50. Shen W, Punyanitya M, Wang Z, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. J Appl Physiol. 2004;97(6):2333-2338.
51. Higgins MI, Martini DJ, Patil DH, et al. Quantification of body composition in renal cell carcinoma patients: Comparing computed tomography and magnetic resonance imaging measurements. Eur J Radiol. 2020;132:109307.
52. Khan AI, Reiter DA, Sekhar A, et al. MRI quantitation of abdominal skeletal muscle correlates with CT-based analysis: implications for sarcopenia measurement. Appl Physiol Nutr Metab. 2019;44(8):814-819.
53. Mourtzakis M, Prado CMM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab. 2008;33(5):997-1006.
54. Steele S, Lin F, Le TL, et al. Segmentation and Linear Measurement for Body Composition Analysis using Slice-O-Matic and Horos. J Vis Exp. 2021;(169). doi:10.3791/61674
55. Dent E, Woo J, Scott D, Hoogendijk EO. Sarcopenia measurement in research and clinical practice. Eur J Intern Med. 2021;90:1-9.
56. Dalle S, Rossmeislova L, Koppo K. The Role of Inflammation in Age-Related Sarcopenia. Front Physiol. 2017;8:1045.
57. Dodds RM, Roberts HC, Cooper C, Sayer AA. The Epidemiology of Sarcopenia. J Clin Densitom. 2015;18(4):461-466.
58. Krabbe KS, Pedersen M, Bruunsgaard H. Inflammatory mediators in the elderly. Exp Gerontol. 2004;39(5):687-699.
59. Beyer I, Mets T, Bautmans I. Chronic low-grade inflammation and age-related sarcopenia. Curr Opin Clin Nutr Metab Care. 2012;15(1):12-22.
60. Li CW, Yu K, Shyh-Chang N, et al. Circulating factors associated with sarcopenia during ageing and after intensive lifestyle intervention. J Cachexia Sarcopenia Muscle. 2019;10(3):586-600.
61. Visser M, Pahor M, Taaffe DR, et al. Relationship of interleukin-6 and tumor necrosis factor-alpha with muscle mass and muscle strength in elderly men and women: the Health ABC Study. J Gerontol A Biol Sci Med Sci. 2002;57(5):M326-M332.
62. Bano G, Trevisan C, Carraro S, et al. Inflammation and sarcopenia: A systematic review and meta-analysis. Maturitas. 2017;96:10-15.
63. Williams GR, Dunne RF, Giri S, Shachar SS, Caan BJ. Sarcopenia in the Older Adult With Cancer. J Clin Oncol. 2021;39(19):2068-2078.
64. Law ML. Cancer cachexia: Pathophysiology and association with cancer-related pain. Front Pain Res (Lausanne). 2022;3:971295.
65. Shachar SS, Williams GR, Muss HB, Nishijima TF. Prognostic value of sarcopenia in adults with solid tumours: A meta-analysis and systematic review. Eur J Cancer. 2016;57:58-67.
66. Yuxuan L, Junchao L, Wenya L. The role of sarcopenia in treatment-related outcomes in patients with renal cell carcinoma: A systematic review and meta-analysis. Medicine . 2022;101(43):e31332.
67. Mao W, Wang K, Zhang H, et al. Sarcopenia as a poor prognostic indicator for renal cell carcinoma patients undergoing nephrectomy in China: A multicenter study. Clin Transl Med. 2021;11(1):e270.
68. Medline A, Midenberg E, Patil D, et al. Muscle mass change using linear measurement analysis after nephrectomy for pT3 and pT4 renal cell carcinoma is associated with mortality. JCSM Rapid Communications. 2022;5(2):205-211.
69. Hu X, Wang Y, Yang WX, Dou WC, Shao YX, Li X. Modified Glasgow prognostic score as a prognostic factor for renal cell carcinomas: a systematic review and meta-analysis. Cancer Manag Res. 2019;11:6163-6173.
70. Deng HY, Chen ZJ, Qiu XM, Zhu DX, Tang XJ, Zhou Q. Sarcopenia and prognosis of advanced cancer patients receiving immune checkpoint inhibitors: A comprehensive systematic review and meta-analysis. Nutrition. 2021;90:111345.
71. Takenaka Y, Oya R, Takemoto N, Inohara H. Predictive impact of sarcopenia in solid cancers treated with immune checkpoint inhibitors: a meta-analysis. J Cachexia Sarcopenia Muscle. 2021;12(5):1122-1135.
72. Loosen SH, van den Bosch V, Gorgulho J, et al. Progressive Sarcopenia Correlates with Poor Response and Outcome to Immune Checkpoint Inhibitor Therapy. J Clin Med Res. 2021;10(7). doi:10.3390/jcm10071361
73. Rounis K, Makrakis D, Gioulbasanis I, et al. Cancer Cachexia and Antitumor Immunity: Common Mediators and Potential Targets for New Therapies. Life. 2022;12(6). doi:10.3390/life12060880
74. Martini DJ, Olsen TA, Goyal S, et al. Body Composition Variables as Radiographic Biomarkers of Clinical Outcomes in Metastatic Renal Cell Carcinoma Patients Receiving Immune Checkpoint Inhibitors. Front Oncol. 2021;11. doi:10.3389/fonc.2021.707050
75. Martini DJ, Kline MR, Liu Y, et al. Adiposity may predict survival in patients with advanced stage cancer treated with immunotherapy in phase 1 clinical trials. Cancer. 2020;126(3):575-582.
76. Herrmann T, Mione C, Montoriol PF, et al. Body Mass Index, Sarcopenia, and Their Variations in Predicting Outcomes for Patients Treated with Nivolumab for Metastatic Renal Cell Carcinoma. Oncology. 2022;100(2):114-123.
77. Ged Y, Sanchez A, Patil S, et al. Associations between Pretreatment Body Composition Features and Clinical Outcomes among Patients with Metastatic Clear Cell Renal Cell Carcinoma Treated with Immune Checkpoint Blockade. Clin Cancer Res. 2022;28(23):5180-5189.
78. Bilen MA, Martini DJ, Liu Y, et al. Combined Effect of Sarcopenia and Systemic Inflammation on Survival in Patients with Advanced Stage Cancer Treated with Immunotherapy. Oncologist. 2020;25(3):e528-e535.
79. Bilen MA, Dutcher GMA, Liu Y, et al. Association Between Pretreatment Neutrophil-to-Lymphocyte Ratio and Outcome of Patients With Metastatic Renal-Cell Carcinoma Treated With Nivolumab. Clin Genitourin Cancer. 2018;16(3):e563-e575.
80. Zahoor H, Barata PC, Jia X, et al. Patterns, predictors and subsequent outcomes of disease progression in metastatic renal cell carcinoma patients treated with nivolumab. J Immunother Cancer. 2018;6(1):107.
81. Ni L, Huang J, Ding J, et al. Prognostic Nutritional Index Predicts Response and Prognosis in Cancer Patients Treated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-Analysis. Front Nutr. 2022;9:823087.
82. Aslan V, Kılıç ACK, Sütcüoğlu O, et al. Cachexia index in predicting outcomes among patients receiving immune checkpoint inhibitor treatment for metastatic renal cell carcinoma. Urol Oncol. 2022;40(11):494.e1-e494.e10.
83. Hurkmans DP, Basak EA, van Dijk T, et al. A prospective cohort study on the pharmacokinetics of nivolumab in metastatic non-small cell lung cancer, melanoma, and renal cell cancer patients. J Immunother Cancer. 2019;7(1):192.
84. Li S, Wang T, Lai W, et al. Prognostic impact of sarcopenia on immune-related adverse events in malignancies received immune checkpoint inhibitors: a systematic review and meta-analysis. Transl Cancer Res. 2021;10(12):5150-5158.
85. Guzman-Prado Y, Ben Shimol J, Samson O. Sarcopenia and the risk of adverse events in patients treated with immune checkpoint inhibitors: a systematic review. Cancer Immunol Immunother. 2021;70(10):2771-2780.
86. Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. N Engl J Med. 2018;378(2):158-168.
87. Elias R, Yan F, Singla N, et al. Immune-related adverse events are associated with improved outcomes in ICI-treated renal cell carcinoma patients. J Clin Orthod. 2019;37(7_suppl):645-645.
88. Ishihara H, Takagi T, Kondo T, et al. Association between immune-related adverse events and prognosis in patients with metastatic renal cell carcinoma treated with nivolumab. Urol Oncol. 2019;37(6):355.e21-e355.e29.
89. Paderi A, Giorgione R, Giommoni E, et al. Association between Immune Related Adverse Events and Outcome in Patients with Metastatic Renal Cell Carcinoma Treated with Immune Checkpoint Inhibitors. Cancers . 2021;13(4). doi:10.3390/cancers13040860
90. Liu X, Shi Y, Zhang D, et al. Risk factors for immune-related adverse events: what have we learned and what lies ahead? Biomark Res. 2021;9(1):79.

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Practice-Changing Cancer Trials Take Center Stage at the ASCO GU 2023

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https://doi.org/10.52733/KCJ21n1-e

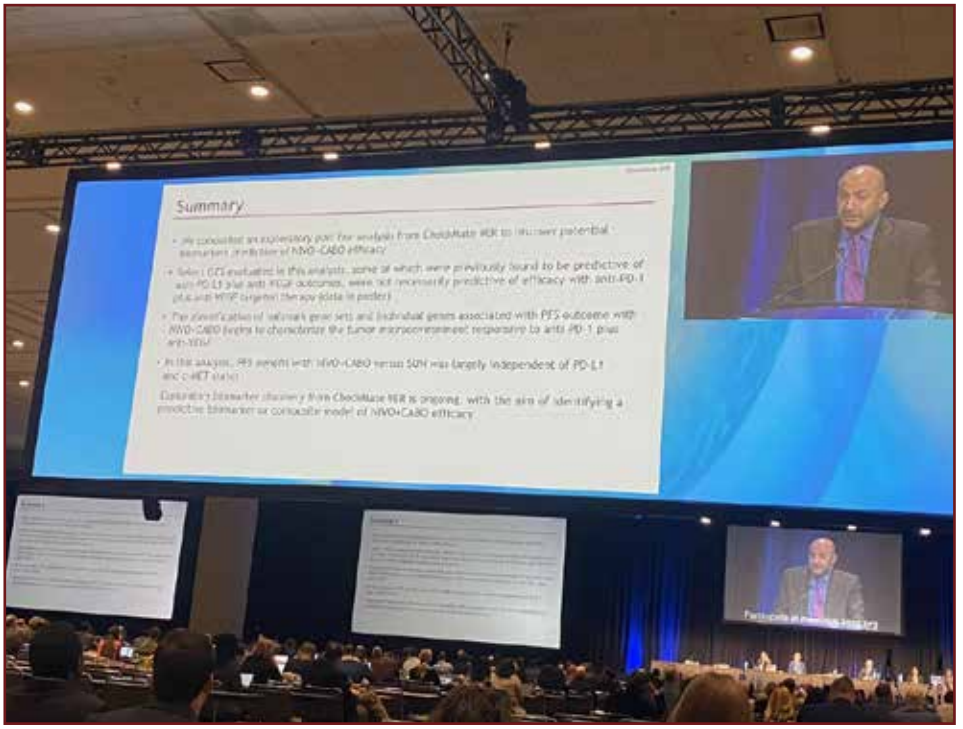
Dear Colleagues,

More than 5,600 clinicians and researchers from 79 countries gathered this February 18-20 at the American Society of Clinical Oncology Genitourinary Cancers Symposium (ASCO GU) in San Francisco to discuss practice-changing research, novel care approaches across the spectrum of GU malignancies. It was exciting to see this year's theme "Today's Science, Tomorrow's Treatment," accurately reflected in practice-changing data, the oral and poster sessions, small group discussions, and thoughtful Q&A sessions at the conference.

This year's keynote session was delivered by Dr. Norman Sharpless, former director of the NCI. In his keynote address entitled "Ending Cancer as We Know It: Predicting Future Cancer Progress" he described the impact of the Cancer Moonshot to accelerate the rate of progress against cancer especially in the context of GU oncology. Dr. Sharpless also shared his insights on how funding allocated to Moonshot 2.0 will impact all attendees. Additionally, he highlighted how the NCI's National Clinical Trials Network can adapt to meet the needs of the oncology community.

Some key abstracts at the conference delivered the groundbreaking results, novel therapies and innovations in the GU oncology space. For example, how artificial intelligence can be exploited to improve digital pathology and radiology as well as the potential for this technology to improve care. Sessions also highlighted new clinical practice approaches to complex care management issues across malignancies. In the kidney cancer space, research presented at the symposium provided follow-up or updated data from pivotal clinical trials including Cosmic-313, COSMIC-021, KEYNOTE-564 and CheckMate 9ER. In the special section of this issue, I have also listed some important kidney cancer abstracts presented at GU ASCO sessions. Here is a quick recap of some of the important findings from ASCO GU 2023.

There is an unmet need for accurate noninvasive techniques to guide patient management. The ZIRCON study



(Abstract LBA 602) evaluated the performance of TLX250-CDx PET/CT for detection of ccRCC in adult patients with IDRM. Results indicated that TLX250-CDx PET/CT is well tolerated and can accurately and noninvasively identify tumors in ccRCC patients with IDRM. Preliminary results from the COSMIC-313 (abstract 605) showed that adding cabozantinib to nivolumab plus ipilimumab significantly increased the time to when the treatment stopped working and progression-free survival in patients with intermediate-risk kidney cancer. The follow-up results from CheckMate-9ER (abstract 603), shows that the combination of cabozantinib plus nivolumab continues to improve survival, control the cancer, and shrink the cancer on scans compared with sunitinib in patients with advanced kidney cancer who had not previously taken any treatment. The exploratory post hoc biomarker analysis (Abstract 608) using the patients from the CheckMate-9ER study indicates that PD-1 biomarker did not predict the progression-free survival and overall survival time outcomes. All the genetic tests did not predict patient outcomes in this study. This suggests that key determinants of response to anti–PD-1 vs anti–PD-L1 therapies may differ.

The latest results from subgroup exploratory analyses (abstract 679) of KEYNOTE-564 study confirmed that adjuvant pembro prolonged DFS compared with pbo for all subgroups in consistent with the results of the ITT population. This further support the use of adjuvant pembro after nephrectomy as standard of care for pts with RCC at increased risk of recurrence. The extended follow-up results of the COSMIC-021 study demonstrates encouraging clinical activity of cabozantinib plus atezolizumab in patients with nccRCC. This follow-up reinforces the encouraging clinical activity of cabozantinib plus atezolizumab in advanced nccRCC with a manageable safety profile. In another study (abstract 604), authors assessed treatment-free survival (TFS) outcomes from the phase II study of nivolumab and salvage nivolumab + ipilimumab in aRCC.

Some reports highlighted emerging trends from the HIF2a inhibitors in combination with other drugs. Abstract TPS748 provided the details about the phase 3 LITESPARK-022 study (NCT05239728) that will evaluate the efficacy and safety of pembro plus belzutifan compared with placebo plus pembro as adjuvant treatment following nephrectomy in pts with ccRCC. The primary end point is disease-free survival. Secondary end points include overall survival, safety, disease recurrence–specific survival, and patient-reported outcomes. In other abstract, (TPS747), authors presented the study design of LITESPARK-024 that investigates the efficacy of HIF-2α inhibitor belzutifan with or without CDK 4/6 inhibitor palbociclib. The primary end point is ORR per RECIST v1.1 by investigator assessment and secondary end points are clinical benefit rate, DOR, PFS, OS, and safety and tolerability.

Overall, the GU ASCO 2023 conference provided valuable insights and updates on the latest research in kidney cancer, which will help in developing more effective treatments for patients with this disease.

Abstracts Highlight Progress in the Fight Against Kidney Cancer - GU ASCO 2023

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ABSTRACT

This year's American Society of Clinical Oncology Genitourinary Cancers (ASCO GU) Symposium was held from 16-18 February 2023, in San Francisco, CA USA. As one of the most renowned conferences focusing on genitourinary cancers, this symposium brought together oncology professionals from around the globe for presentations and discussions surrounding the latest innovative findings in genitourinary cancer treatment, research, and care. Here is the summary of some kidney cancer research presented at the ASCO GU 2023 meeting.

The 2023 ASCO GU Conference brought together leading experts in the field to share the latest developments and insights into the diagnosis, treatment, and management of GU cancers. In this article, we will take a closer look at some of the exciting and promising findings from the 2023 ASCO GU pertaining to renal cell carcinoma (RCC).

The RCC highlights of this year's conference included the ZIRCON study which evaluated radiolabeled 89Zr-DFO-girentuximab (a monoclonal antibody targeting CA IX) for detection of clear cell RCC in patients with indeterminate renal masses. This phase III trial included patients with renal masses (≤7 cm, cT1) who were scheduled to undergo a nephrectomy in 90 days and all patients received a single dose of Radiolabeled 89Zr-DFO-girentuximab (37 MBq ± 10%; 10 mg girentuximab) on Day 0 and underwent PET/CT imaging on Day 5 (± 2 days) prior to surgery. The study met its co-primary end points exceeding the sensitivity and specificity thresholds and confirmed a favorable toxicity profile (Shuch, Pantuck et al. 2023). This study lays the foundation and provides a convenient non-invasive platform for pre-treatment risk stratification of clear cell RCC akin to PSMA in prostate cancer.

Dr. Choueiri presented an exploratory post hoc subgroup analysis of KEYNOTE 564 across the UISS (University of California Los Angeles Integrated Staging System) risk groups and disease stage. The Keynote 564 trial showed an improvement in disease free survival in patients with clear cell RCC with a

Figure 1. Oral presentation at the GU ASCO 2023

high risk of recurrence leading to the FDA approval of pembrolizumab in the adjuvant setting. The UISS is a commonly used prognostic model that predicts the 5-year survival rates following a nephrectomy. In this trial, most patients in both the arms were categorized in the UISS intermediate group (75%) with 5.9% of patients having M1NED disease. Up to 88% of patients had AJCC Stage 3 disease. The results showed that adjuvant pembrolizumab prolonged disease-free survival across subgroups by AJCC Stage, TNM staging, Fuhrman grading and UISS risk compared to placebo. The extent of benefit was most pronounced in patients with M1NED disease (HR: 0.28, 95% CI: 0.11 – 0.73), AJCC stage 3 (HR: 0.68, 95% CI: 0.51 – 0.89) and Stage 4 disease (HR: 0.42, 95% CI: 0.20 – 0.87). This exploratory analysis further supports the use of pembrolizumab in patients with a high risk of recurrence in the adjuvant setting (Choueiri, Tomczak et al. 2023).

Dr. Powles presented an updated analysis of the COSMIC 313 trial which was the first phase 3 trial exploring the triplet combination of cabozantinib along with ipilimumab and nivolumab versus ipilimumab and nivolumab, a contemporary control arm in patients with advanced RCC with intermediate or poor IMDC risk. With an additional follow up of 5 months, the progression free survival (PFS) benefit with the triplet combination was maintained in the overall population with a HR of 0.74 (95% CI 0.61-0.90) and HR of 0.68 (95% CI 0.54-0.86) in the intermediate risk population. Similarly, the objective response rate was also higher with the triplet combination in the intermediate risk group compared to the poor risk group. There were no major differences in the treatment exposure between both the triplet arms that could explain the enhanced efficacy in the intermediate risk group (11.3 months in the intermediate risk population and 10.4 months in the poor risk population). The daily dose of cabozantinib received was also similar in both the groups. Adverse events leading to treatment discontinuation was more common in the intermediate risk population compared to the poor risk group. It is important to note that patients in the poor risk group had significantly fewer nephrectomies compared to the intermediate risk group (40% and 50% in the triplet arm and comparator poor risk group compared to 73% and 69% in the triplet and comparator intermediate risk group respectively) and this could be one of the reasons behind the lower response rates in this patient population. Another likely explanation is that the poor risk group is biologically more immune driven than angiogenesis driven compared to the favorable risk population (Rini, Huseni et al. 2018, Tannir, Signoretti et al. 2021). Overall survival follow up in ongoing (Powles, Motzer et al. 2023) and will be important to consider for regulatory approval of this combination

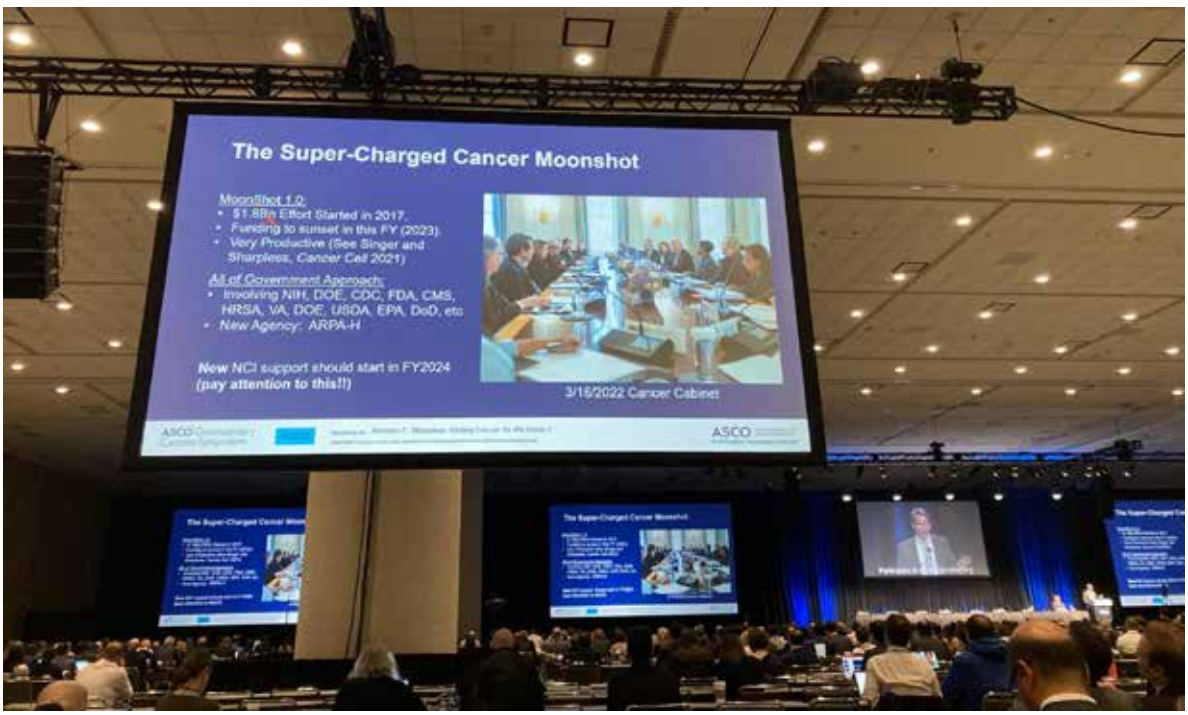


FIGURE 2. Keynote speaker Dr. Norman Sharpless delivering an oral talk at the ASCO GU23

in intermediate and poor risk IMDC risk groups.

Treatment free survival is a meaningful clinical end point that has not been traditionally evaluated as a predefined end point in clinical trials. Dr. Atkins presented the updated analysis of treatment free survival of HCRN GU16-260-Cohort A (Atkins, Jegede et al. 2023). In this study, 128 patients with advanced clear cell RCC received treatment with nivolumab and based on their response they received additional treatment with nivolumab for up to 96 weeks if they had a partial response or a complete response or salvage ipilimumab was added if they had progressive disease or stable disease at 48 weeks. Treatment free survival was defined as the area between the Kaplan Meier curves for time from registration to stopping protocol therapy and time from registration to starting subsequent therapy or death estimated at a mean of 36 months. The response rate in the favorable risk group was 57.9% with the overall response rates being 35.9% at 3 years, 65.6% of patients with favorable risk were alive and treatment free compared to 27.1% of patients with intermediate/poor risk disease. The overall PFS was 14.6%. The 36 month mean treatment free survival was 36% in the favorable risk group which included 4% of patients with TRAE >3 and the treatment free survival was 22% in the intermediate/poor risk group which included 3% of patients with TRAE >3. Based on this study, salvage ipi/nivo in is a viable option in patients who do not respond to nivolumab monotherapy in the front line setting and has a robust treatment free survival with limited toxicity. The maximum benefit was obtained by the favorable risk group like the DFS benefit in favorable risk group in the Checkmate 214 trial supporting the use of this regimen in favorable risk patients (45% vs 36%)

Dr. Albiges presented to interim results of CaboPoint which is a phase II study of cabozantinib in adults with advanced clear cell RCC with progressive disease after front line checkpoint inhibitor therapy. The study consisted of two cohorts: Cohort A including patients with progressive disease after ipilimumab and nivolumab and cohort B including patients with progressive disease on immunotherapy and a VEGFR TKI. Most patients had intermediate risk disease with upfront metastatic disease and did not have a nephrectomy. The ORR in cohort A was 31.7% (95% CI, 20.3-45) and Cohort B was 25% (95% CI, 10.7-44.9). Cabozantinib was effective as a second line treatment option irrespective of the front-line regimen used, with patients with intermediate risk disease having failed ipilimumab and nivolumab seemed to benefit the most with a RR of 40%. The duration of front line therapy also had an impact with patients benefitting more if they received cabozantinib in the primary refractory setting having had progressive disease within 6 months of front line therapy (Albiges, Powles et al. 2023).

The updated results of the BIONIKK trials were also presented (Vano, Phan et al. 2023). This was a randomized phase II trial that prospectively selected patients to receive either nivolumab, nivolumab-ipilimumab or a VEGRF TKI based on the tumor molecular group. They had previously reported high efficacy of VEGFR TKI in CCRCC2 tumors (51%) and high efficacy of nivolumab with ipilimumab in CCRC4 (50%) compared to CCRC1 (39%) tumors. After a follow up of 46.5 months, the median overall survival was not reached for ipilimumab /nivolumab and was 35 months for nivolumab (HR compared to nivo/ipi: 1.56, 95% CI: 0.99 to 2.46) and 45 months for VEGFR TKI (HR compared to nivo/ipi: 1.29, 95% CI: 0.76 to 2.19). When the overall survival was characterized by molecular group, superior survival was observed with the ipilimumab/nivolumab combination compared to nivolumab alone in CCRC1 (HR: 1.44) and CCRC4 (HR: 1.64) groups. There was no difference in survival with treatment with either VEGFR TKI or ipilimumab/nivolumab in the CCRC2 (HR: 1.15) group. About 80% of patients went on to receive second line treatment and most of them received a VEGFR TKI (79%). After a median follow up of 34 months, there was a higher response rate after ipilimumab and nivolumab (33%) than after single agent nivolumab (11%) in the CCRC4 group and the CCRC2 group has the highest response rate of 62% post ipilimumab and nivolumab and 57% post VEGRF TKI. The updated results confirmed the feasibility of biomarker driven trials in RCC and the efficacy of ipililumab/nivolumab in CCRC4 and VEGFR TKI in CCRC2 molecular groups.

Dr. Siva reviewed the use of radiation in oligometastatic kidney cancer. The ASCO guidelines include radiotherapy for management of patients with low volume metastatic disease (Rathmell, Rumble et al. 2022). In a meta-analysis of 28 studies including

1600 patients with almost 4000 treated lesions, the local control rate for both intra cranial and extracranial lesions was 90%. Prospective trials of radiation in oligometastatic RCC have shown that SABR (stereotactic ablative radiation) can be effectively delivered in lieu of systemic therapy. In a single center study of 30 patients with low burden of disease (having 1 median number of metastases) with a median follow up of 17.5 months, the one-year progression free survival was 64%, the median progression free survival was 23 months and importantly, at one year, 82% of patients did not receive any systemic therapy (Tang, Msaouel et al. 2021). Radiation can also be used in the oligoprogressive setting to prolong the efficacy of systemic therapy. In a multicenter trial of 37 patients with oligoprogressive disease, SABR to the oligoprogressive sites resulted in a 93% one-year disease control rate and a progression free survival of 9.3 months. SABR can also be safely delivered with immunotherapy. In the RAPPORT trial, patients received a combination of six months of pembrolizumab with SABR taking advantage of the synergy between radiotherapy and immunotherapy inducing tumor antigen and cytokine release by radiotherapy which can prime the tumor microenvironment and likely transform a cold to hot microenvironment. The median progression free survival was 15 months, and the two-year local control rate was 92% (Siva, Bressel et al. 2022). SABR therefore, provides a safe, non-invasive option of prolonging the efficacy of systemic therapy and has synergy with immunotherapy.

REFERENCES:

1. Shuch, B. M., et al. (2023). "Results from phase 3 study of 89Zr-DFO-girentuximab for PET/CT imaging of clear cell renal cell carcinoma (ZIRCON)." Journal of Clinical Oncology 41(6_suppl): LBA602-LBA602.

2. Choueiri, T. K., et al. (2023). "Adjuvant pembrolizumab (pembro) for renal cell carcinoma (RCC) across UCLA Integrated Staging System (UISS) risk groups and disease stage:Subgroup analyses from the KEYNOTE-564 study." Journal of Clinical Oncology 41(6_suppl): 679-679.

3. Tannir, N. M., et al. (2021). "Efficacy and Safety of Nivolumab Plus Ipilimumab versus Sunitinib in First-line Treatment of Patients with Advanced Sarcomatoid Renal Cell Carcinoma; Clin Cancer Res 27(1): 78-86.

4. Rini, B. I., et al. (2018). "Molecular correlates differentiate response to atezolizumab (atezo) + bevacizumab (bev) vs sunitinib (sun): Results from a phase III study (IMmotion151) in untreated metastatic renal cell carcinoma (mRCC); Annals of Oncology 29: viii724-viii725.

5. Powles, T., et al. (2023). "Outcomes by IMDC risk in the COSMIC-313 phase 3 trial evaluating cabozantinib (C) plus nivolumab (N) and ipilimumab (I) in first-line advanced RCC (aRCC) of IMDC intermediate or poor risk." Journal of Clinical Oncology 41(6_suppl): 605-605.

6. Atkins, M. B., et al. (2023). "Treatment-free survival (TFS) outcomes from the phase II study of nivolumab and salvage nivolumab + ipilimumab in advanced clear cell renal cell carcinoma (aRCC) (HCRN GU16-260-Cohort A)." Journal of Clinical Oncology 41(6_suppl): 604-604.

7. Albiges, L., et al. (2023). "CaboPoint: Interim results from a phase 2 study of cabozantinib after checkpoint inhibitor (CPI) therapy in patients with advanced renal cell carcinoma (RCC)." Journal of Clinical Oncology 41(6_suppl): 606-606.

8. Vano, Y.-A., et al. (2023). "Overall survival (OS) and efficacy results of second-line treatment in patients (pts) with metastatic clear cell renal cell carcinoma (mRCC) treated in the randomized phase II BIONIKK trial." Journal of Clinical Oncology 41(6_suppl): 607-607.

9. Rathmell, W. K., et al. (2022). "Management of Metastatic Clear Cell Renal Cell Carcinoma: ASCO Guideline." J Clin Oncol 40(25): 2957-2995.

10. Siva, S., et al. (2022). "Stereotactic Radiotherapy and Short-course Pembrolizumab for Oligometastatic Renal Cell Carcinoma-The RAPPORT Trial." Eur Urol 81(4): 364-372.

11. Tang, C., et al. (2021). "Definitive radiotherapy in lieu of systemic therapy for oligometastatic renal cell carcinoma: a single-arm, single-centre, feasibility, phase 2 trial." Lancet Oncol 22(12): 1732-1739.

These recommended abstracts from ASCO GU 2023 Annual meeting have been selected by Robert A. Figlin, MD, *Editor-in- Chief* of the *Kidney Cancer Journal.* The chosen abstracts provided here highlight some of the most important trends in ongoing trials and reflect the foremost research and strategies from latest clinical trials that impact the current standard of care in renal cancer.

https://doi.org/10.52733/ASCOGU23abs

ABSTRACT LBA 602: Results from phase 3 study of 89Zr-DFO-girentuximab for PET/CT imaging of clear cell renal cell carcinoma (ZIRCON). *Allison May et al.*

METHODS: ZIRCON was an open-label, multicenter clinical trial. Patients with an IDRM (≤ 7 cm; tumor stage cT1) who were scheduled for partial nephrectomy within 90 days from planned TLX250-CDx administration were eligible. Enrolled patients received a single dose of TLX250-CDx IV (37 MBq ± 10%; 10 mg girentuximab) on Day 0 and underwent PET/CT imaging on Day 5 (± 2 days) prior to surgery. Blinded central histology review determined ccRCC status. The coprimary objectives were to evaluate both the sensitivity and specificity of TLX250-CDx PET/CT imaging in detecting ccRCC in patients with IDRM, using histology as the standard of truth. Key secondary objectives included sensitivity and specificity of TLX250-CDx PET/CT imaging in the subgroup of patients with IDRM ≤ 4 cm (cT1a). Other secondary objectives included positive and negative predictive values, safety, and tolerability. The Wilson 95% confidence intervals (CI) lower bound for sensitivity and specificity had to be > 70% and 68% respectively for ≥ 2 independent readers to declare the study successful. Results: 300 patients received TLX250-CDx; mean age was 62 ± 12 y; 71% were males. Of 288 patients with central histopathology of surgical samples, 193 (67%) had ccRCC, and 179 (62%) had CT1a; Of 284 evaluable patients included in primary analysis, the average across all 3 readers for sensitivity and specificity was 86% [80%, 90%] and 87% [79%, 92%] respectively for coprimary endpoints; and 85% [77%, 91%] and 90% [79%, 95%] respectively for key secondary endpoints. For all readers, the lower boundaries of 95% CI for coprimary and key secondary endpoints were > 75%. For all evaluable patients, positive and negative predictive values were ≥ 91.7% and ≥ 73.7%, respectively. Of 263 treatment-emergent adverse events (TEAEs), 2 TEAEs were treatment related. Conclusions: This study confirms that TLX250-CDx PET/CT is well tolerated and can accurately and noninvasively identify ccRCC, with promising utility for designing best management approaches for patients with IDRM. Clinical trial information: NCT03849118

ABSTRACT 604- Treatment-free survival (TFS) outcomes from the phase II study of nivolumab and salvage nivolumab + ipilimumab in advanced clear cell renal cell carcinoma (aRCC) (HCRN GU16-260-Cohort A). *Michael B. Atkins et al.*

METHODS: Data were analyzed from 128 patients (pts) with clear-cell aRCC treated with first-line nivolumab (NIVO) monotherapy for up to 2 years. As part of the protocol, salvage nivolumab/ipilimumab (NIVO/IPI) for up to 1 year was provided to eligible patients with disease progression at any point or stable disease at 48 weeks (28% of pts). TFS was defined as the area between Kaplan-Meier curves for time from registration to protocol therapy cessation and for time from registration to subsequent therapy initiation or death, estimated from 36-month (mo) mean times. The time on treatment or off treatment with grade 3+ treatment-related adverse events (TRAEs) was also captured. Results: At 36 mos from enrollment, 68.3% of pts were alive: 96.8% of IMDC favorable-risk (FAV) pts and 56.6% of those with intermediate/poor-risk (I/P), respectively. The 36-mo mean time on protocol therapy was 11.5 mos (16.0 mos for FAV pts and 9.6 mos for I/P pts). The 36-mo mean TFS for the whole population was 9.4 mos. For FAV pts the mean TFS was 12.9 mos, of which TFS with grade 3+ TRAEs was 1.5 mos. For I/P pts, the mean TFS was 8.0 mos, of which TFS with grade 3+ TRAEs was 1.0 mos. At 36 mos, 65.6% of FAV pts and 27.1% of I/P pts were alive and second-line treatment-free. Conclusions: NIVO monotherapy with salvage NIVO/IPI in non-responders is an active treatment approach in treatment-naïve pts with aRCC and results in substantial TFS and toxicity-free TFS. TFS was particularly noted in pts with FAV disease, further supporting the use of an immunotherapy-only regimen in this population. Clinical trial information: NCT03117309.

ABSTRACT 608 Biomarker analysis from the phase 3 CheckMate 9ER trial of nivolumab + cabozantinib v sunitinib for aRCC. *Toni K. Choueiri et al.*

METHODS: Progression-free survival (PFS) and overall survival (OS) were evaluated by tumor PD-L1 expression (< 1% or ≥ 1%), CD8% (low, medium, high by tertiles), and CD8 topology phenotype (cold, excluded, inflamed), and

assessed for association using Kaplan–Meier (KM) methods with log-rank test (PD-L1 and CD8), and Cox proportional hazard (Cox PH) models (CD8) (to avoid arbitrary or biased categorization of continuous-valued predictor variables, a potential limitation of KM analyses). Pre-ranked GSEA was performed to assess enrichment for hallmark gene sets using all genes ranked by interaction effect estimates derived using Cox PH regression. Seven GES (Angio, Myeloid, Teff, TIS, Interferon-γ, EMT8, Javelin), including several previously found to be predictive of anti-PD-L1 ± anti-VEGF outcomes, were assessed for association with PFS within treatment arms. Results: At 44 mo median follow-up, median PFS and OS were improved with N+C v S regardless of PD-L1 status. PD-L1 < 1% v ≥ 1% was associated with longer median PFS in the S arm only (P = 0.00045). In KM analyses, higher CD8% was associated with improvements in PFS with N+C, but not S. Of the 410 patients (pts) in the CD8 topology analysis, the predominant CD8 phenotype was inflamed (46.8%), then cold (40.5%) and excluded (12.7%). CD8 topology supported an association between the inflamed phenotype and improved survival outcomes with N+C v S (PFS, P < 0.0001; OS, P = 0.00097). However, these associations were not confirmed in Cox PH models. Common hallmark gene sets with positive (p) or negative (n) enrichment (with false discovery rate < 0.05) in genes associated with longer PFS and OS with N+C v S included oxidative phosphorylation, hypoxia, adipogenesis, P53 pathway (p), and E2F targets (n). Pts receiving N+C had longer median PFS with high Angio GES v medium and low Angio GES (P = 0.019). However, all 7 GES tested, including Angio GES, were not predictive for N+C outcomes in Cox PH models. Conclusions: In this exploratory post hoc analysis, biomarkers previously found to be predictive of anti-PD-L1 ± anti-VEGF outcomes, including established GES, were not predictive of efficacy with anti-PD-1 + anti-VEGF (N+C) using Cox PH models. This suggests that key determinants of response to anti–PD-1 v anti–PD-L1 therapies may differ. Clinical trial information: NCT03141177.

ABSTRACT 614 - Impact of race and payor status on patterns of utilization of partial and radical nephrectomy in patients with localized renal cell carcinoma (RCC).

Powles T et al.

METHODS: iKnowMed EMR was used to identify mRCC pts from USON or Onmark Network, with matched 3rd party insurance claims, that initiated VEGFR TKI treatment between Jan 2015 and Mar 2021. First occurrence of each VEGFR TKI class effect AE was indexed, and associated costs for 90-day (longest median AE duration) follow-up was captured. To assess burden across different TKIs, average per-patient AE management cost was calculated using incidence data from trials supporting FDA approvals, and weight-adjusted to estimated number of commercially insured 3L/4L pts in a 1,000,000-member plan.

METHODS: 5,958 mRCC pts were identified, of which 4,464 were on at least one TKI regimen. Among those, 1,777 experienced an index AE; 1,072 successfully matched to claims data [median 69 years (range 25-94); 55% ECOG PS 0/1; 69% male], accounting for 1,667 unique index AE cases. Most were on cabozantinib (cabo), axitinib (axi), or pazopanib; lenvatinib (len), sunitinib (sun), and sorafenib were also represented. >80% were TKI only, with the rest TKI+IO (18%) or TKI+mTOR (6%). AE costs largely originated from outpatient visits (range 38-77%), excluding renal failure (58% inpatient). Mean cost per AE ranged from $76 (proteinuria) to $1,687 (mucositis/stomatitis). Overall, estimated costs of managing VEGFR TKI class effect AEs in 3L/4L showed lowest resource burden with tivo, and highest with len+everolimus (len+ev; Table). Conclusions: Average VEGFR TKI AE management costs derived from real-world mRCC pts demonstrated differences in healthcare resource burden, with overall anticipated cost dependent on TKI regimen utilized.

ABSTRACT 634: Financial toxicity from first-line TKI plus IO therapies for advanced renal cell carcinoma.

David Joseph Benjamin et al.

BACKGROUND: Since the approval of sunitinib for the treatment of advanced renal cell carcinoma (RCC), the first-line treatment landscape has drastically altered with combination tyrosine kinase inhibitor (TKI) plus immunotherapy (IO) regimens. Despite improvements in survival, it remains unclear if these therapies are cost prohibitive for patients or hospitals compared to prior standard of care sunitinib.

METHODS: Approved TKI plus IO therapies were identified using the US FDA Oncology Announcements website and confirmed with NCCN Guidelines (Version 3.2023). Cost per unit was identified using public data (Lexicomp or manufacturer's website). We calculated the total cost of each treatment regimen using the cost per unit for each therapy and the median duration on treatment as reported in each combination therapy's clinical trial publication. Results: Average PFS benefit from combination TKI plus IO therapies was 8.1 months (range 4-14.7) in comparison with sunitinib. Average cost of TKI plus IO therapy was $443,839.32 compared with $199,541.44 for sunitinib therapy. Conclusions: Average increase in cost of TKI plus IO therapy compared to sunitinib was $244,297.88. For every month of PFS benefit with TKI plus

IO combination therapy, there was on average $30,160.23 cost added per month. These increased costs may be prohibitive for many patients and hospitals, particularly in low- and middle-income countries (LMICs).

Drug(s) Name(s)	Trial Name	Median Duration of Treatment (months)	Cost per Unit	Cycle Length	Cost of Treatment	PFS Benefit (months)
Sunitinib	N/A	11.0	$890.81 (50 mg tablet)	4 weeks on, 2 weeks off	$199,541.44	6
Axitinib plus avelumab	Javelin Renal 101	8.6 avelumab, 9.0 axitinib	$6,314.70 (avelumab 600 mg); $711.04 (axitinib BID)	Avelumab 10 mg/kg every 2 weeks; Axitinib 5 mg PO BID	$113,664.60 + $194,824.96 = $308,489.56	5.4
Axitinib plus pembrolizumab	KEYNOTE-426	10.4	$711.04 (axitinib BID); $10,474.08 (pembrolizumab)	Pembrolizumab 200 mg every 3 weeks; Axitinib 5 mg PO BID	$224,688.64 + $157,111.2 = $381,799.84	4
Lenvatinib plus pembrolizumab	CLEAR	17.0	$426.26 (Lenvatinib 20 mg); $10,474.08 (pembrolizumab)	Pembrolizumab 200 mg every 3 weeks; Lenvatinib 20 mg daily	$220,376.42 + $251,377.92 = $471,754.34	14.7
Cabozantinib plus nivolumab	CheckMate 9ER	13.3	$8,463.84 (nivolumab); $931.50 (cabozantinib 40 mg tablet)	Nivolumab 240 mg every 2 weeks; cabozantinib 40 mg daily	$236,987.52 + $376,326 = $613,313.52	8.3

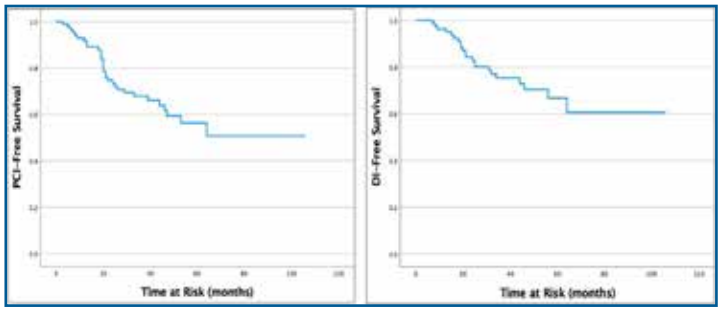
ABSTRACT 647: Cabozantinib in the elderly with metastatic renal cell carcinoma undergoing geriatric G8 screening test: A prospective multicenter observational study (ZEBRA/MEET-URO 9). *Umberto Basso et al.*

BACKGROUND: Cabozantinib (CABO) is an oral tyrosine kinase inhibitor registered for the treatment of metastatic renal cell carcinoma (mRCC) for the first or subsequent lines. Tolerability in real world elderly patients is poorly documented. G8 is a short test for vulnerability gaining increased interest as a screening tool for trials in geriatric oncology. Methods: ZEBRA/MEET-URO 9 was a prospective multicenter study of safety and activity of CABO administered to pts ≥70 years with mRCC, either in the first or subsequent lines of treatment, until progression or unacceptable toxicity. All pts underwent G8 score at baseline, with a cut-off for vulnerability of 14 or below. Data on tolerability and activity were collected prospectively after signature of informed consent. Results: A total of 104 pts started CABO at 13 Italian Centers, 38,5% as first line. Median age was 75.8 yrs (range 70.2-87.4 yrs, 26 pts ≥80 yrs), 73.1% males. IMDC score was good 19.2%, intermediate 53.9%, poor 26.9%. Primary tumor had been removed in 82.7% of pts, histology was clear cell 78.8%, papillary 8.7%, chromophobe 5.8%, unclassified 6.7%. G8 score was ≤14 in 65.4% of pts. Up-front dose reduction of CABO was more frequent in pts with low G8 score (79.4 vs 41.7%, p=0.003), but eventually the majority of pts (91.4%) underwent dose reductions of CABO. After a median treatment of 6.4 months (0.5-26.1 months), 38.4% of pts developed G3-4 toxicities, 22.1% interrupted treatment due to adverse events, 2.8% (3 pts) died due to cardiovascular or thromboembolic events. Median PFS was 7.6 months (95% CI=5.8-12.6 months) in first line, 10.0 months (5.8-15.6) in second or further lines, median OS was 20.1 months (11.1-not reached) and 15.6 months (12.5-not reached), respectively. G8 score ≤14 did not correlate with rate of temporary interruptions >7 days, hospitalization, incidence of G3-5 toxicities, as well as with PFS. Pts with G8 score ≤14 had a trend for reduced OS, but difference was not statistically significant both in the first and further lines of treatment. Conclusions: Screening G8 test was positive in more than a half of pts, underlying the need for detailed geriatric assessment and increased clinical monitoring of such patients. A G8 score ≤14 correlated with up-front dose reduction of CABO but not with G3-5 toxicities probably due to the high rates of dose reductions in the whole cohort. Correlation between low G8 score and OS could not be demonstrated in this population.

ABSTRACT 659: Correlating HLA variants and the emergence of immune-related adverse events (irAEs) from ipilimumab/nivolumab (I/N) in patients (pts) treated on CheckMate 214. *Martin H Voss et al.*

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

METHODS: TheWe analyzed germline HLA + clinical data for 472 pts receiving I/N vs sunitinib (SUT). Based on allelic variants for HLA-A and B pts were categorized into 12 established HLA "Super-Types" (ST), sets of HLA variants with largely overlapping peptide binding specificity. We conducted uni- and multivariate (UV; MV) Cox proportional hazards regression to correlate HLA-ST variables with time to treatment-related AEs (TTrAE, grade 2+) in I/N pts using the Kaplan Meier method. Several MV HLA-ST models were developed on a discovery set (DISC; 2/3 random sample of I/N pts without replacement) and compared using model concordance (c-index) on a validation set (VAL; remaining 1/3). Model coefficients were used to create a "HLA-ST score" that could be computed for individual pts. Results: 235 pts and 237 pts received I/N vs SUT and had available HLA data, respectively. On UV analysis for I/N, HLA-B07 ST had protective association TTrAE (HR= 0.65, 95% CI: 0.46,0.90; p= 0.010), while B62 associated adversely (HR=1.64, 95% CI: 1.12, 2.40; p=0.014). Relevant to the development of our model we identified interactions between several pairs of



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

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

HLA ST. The HLA ST model with best performance in DISC (c-index= 0.606) and VAL (c-index=0.595) integrates B07, B62, A01, B08, and two interactions: B07-B08 and B07-A01. The model-generated HLA-ST score was significantly associated with TTrAE after adjusting for race, BMI, region, PDL1 status, and MSKCC risk score (DISC p<0.001; VAL p=0.028). No association with TTrAE was seen in SUT treated pts (p=0.655), neither in UV nor MV model. I/N-treated patients with HLA-ST score dichotomized >= vs < median had significantly different TTrAE both in DISC (p=0.004) and VAL (p=0.009); again, no difference was observed in the SUT arm (p=0.5). The weighted HLA-ST score had no association with PFS or OS for I/N pts. Conclusions: In this large sample of I/N-treated patients, class I HLA variants were associated with the risk of developing irAEs. We developed a HLA ST based score that correlated with treatment toxicity independent of relevant clinical and demographic features. No association with TTrAE was seen in SUT-treated pts. These results highlight the potential of characterizing germline features to predict immune related toxicity upfront and deserves further study. Clinical trial information: NCT02231749.

ABSTRACT 674: Survival outcomes of metastasis-directed therapy for solitary sites of metastatic clear cell renal cell carcinoma. *Kelly N. Fitzgerald et al.*

BACKGROUND: Metastasis directed therapy (MDT) is associated with improved cancer-specific survival and delay in use of systemic therapy for metastatic clear cell RCC (mccRCC). Although the benefits of MDT may differ based on organ site of metastasis due to differences in disease biology, survival based on site of metastasis remains underexplored. We aim to evaluate survival outcomes of patients who underwent MDT for solitary sites of mccRCC. Methods: The Mayo Clinic Nephrectomy Registry was queried to identify adults undergoing radical or partial nephrectomy for unilateral, sporadic ccRCC from 2000 to 2019 with a single site of metastasis treated with MDT including complete metastasectomy or radiation, in lieu of systemic therapy. Overall and cancer-specific survival were estimated using the Kaplan-Meier method, with the duration of follow-up calculated from the date of metastasis to the date of death or last follow-up. Associations with time to death from RCC were evaluated using Cox proportional hazards regression models and summarized with hazard ratios and 95% confidence intervals (CIs). Results: In this cohort of 207 mccRCC patients, 152 underwent complete metastasectomy and 55 underwent radiation. 133 died at a median of 2.7 years (IQR 1.2-4.7) following metastasis, including 105 who died from RCC at a median of 2.2 years (IQR 1.0-3.9). The median duration of follow-up for the 74 patients who were still alive at last follow-up was 8.1 years (IQR 3.7-12.1). Overall survival rates (95% CI) at 2, 4, 6, 8, and 10 years following metastasis were 73% (69-79), 54% (48-62), 45% (38-52), 37% (30-44), and 32% (26-40), respectively; cancer-specific survival rates were 75% (69-81), 56% (50-64), 47% (41-55), 44% (37-52), and 42% (35-50), respectively. Age, poor performance status, presence of synchronous metastasis and asynchronous metastasis <1 year from nephrectomy, tumor size, and bone metastasis were associated with death from RCC (table). Conclusions: These

Table 1. Cohort of patients undergoing consolidative nephrectomy

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

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

findings provide useful survival benchmarks to patients who are considering MDT as a therapeutic option. In addition, synchronous and asynchronous metastasis <1 year from nephrectomy, poor performance status, and bone metastasis are significantly associated with worse survival from mccRCC.

ABSTRACT 679 Adjuvant pembrolizumab (pembro) for renal cell carcinoma (RCC) across UCLA Integrated Staging System (UISS) risk groups and disease stage: Subgroup analyses from the KEYNOTE-564 study. Toni K. Choueiri, *et al.*

BACKGROUND: Adjuvant pembro prolonged disease-free survival (DFS) for patients (pts) with RCC at increased risk of recurrence after nephrectomy in the phase 3 KEYNOTE-564 study (NCT03142334). This post hoc exploratory analysis evaluated efficacy of adjuvant pembro in pt subgroups based on UISS and disease stage. Methods: Pts with histologically confirmed clear cell RCC (pT2, Grade [G] 4 or sarcomatoid, N0, M0; pT3 or pT4, any G, N0, M0; any pT, any G, N+, M0; or M1 NED) were randomly assigned 1:1 to receive pembro 200 mg IV or placebo (pbo) every 3 weeks for ≤17 cycles (~1 y). DFS was assessed by investigator. UISS risk groups were derived retrospectively from TNM stage, Fuhrman nuclear grade, and ECOG PS. UISS groups were intermediate risk (pT2, G4, N0, M0; pT3, G1, N0, M0; or pT3, G2-4, N0, M0, ECOG 0), high risk (pT3, G2-4, N0, M0, ECOG PS 1; pT4, any G, N0, M0; or N1, M0), or M1 NED. Other subgroups were evaluated based on disease stage. Results: Baseline characteristics were balanced within subgroups. Median follow-up was 30.1 mo (range 20.8-47.5). Of 994 enrolled pts, most had UISS intermediate risk (n = 732, 73.6%; pembro n = 359; pbo n = 373); 195 pts (19.6%; pembro n = 100; pbo n = 95) had UISS high risk, and 58 pts (5.8%; pembro and pbo n = 29 each) had M1 NED. In the UISS intermediate risk group, the hazard ratio (HR) for DFS was 0.65 (95% CI, 0.48-0.88; 24-mo rates, pembro: 81.5%, pbo: 72.4%). In the UISS high-risk group, HR for DFS was 0.77 (95% CI, 0.49-1.20; 24-mo rates, pembro: 65.0%, pbo: 55.9%). In the M1 NED group, HR for DFS was 0.28 (95% CI, 0.12-0.66; 24-mo rates, pembro: 78.4%, pbo: 37.9%). DFS by disease stage is in the Table.

CONCLUSIONS: Consistent with the results of the intention-to-treat (ITT) population, adjuvant pembro prolonged DFS compared with pbo for all subgroups. Results of this exploratory analysis further support the use of adjuvant pembro after nephrectomy as standard of care for pts with RCC at increased risk of recurrence. Clinical trial information: NCT03142334.

ABSTRACT 684 Cabozantinib in combination with atezolizumab in non-clear cell renal cell carcinoma: Extended follow-up results of cohort 10 of the COSMIC-021 study. Toni *Bradley Alexander McGregor, et al.*

BACKGROUND: In the COSMIC-021 phase 1b study (NCT03170960) evaluating cabozantinib plus atezolizumab in advanced solid tumors, this combination therapy demonstrated encouraging clinical activity in patients with advanced non-clear cell renal cell carcinoma (nccRCC) with a median follow-up of 13 mo (Pal. JCO 2021). Results after extended follow-up in nccRCC are presented. Methods: Patients with advanced nccRCC and ECOG PS 0/1 who had ≤1 prior VEGFR-targeting tyrosine kinase inhibitor (TKI) were eligible. Prior treatment with TKIs targeting MET or immune checkpoint inhibitors was not allowed. Patients received cabozantinib 40 mg PO QD plus atezolizumab 1200 mg IV Q3W until unacceptable toxicity or progression; dose reductions of cabozantinib (40 mg QD to 20 mg QD, then to 20 mg QOD) were permitted to manage adverse events. The primary endpoint was objective response rate (ORR) per RECIST v1.1 by the investigator; other endpoints included safety, duration of response (DOR), PFS, and OS. Results: The study enrolled 32 patients with nccRCC (2 from dose escalation phase, and 30 from expansion phase of the study): median age, 62 y; male, 81%; ECOG PS 0/1, 75%/25%; histology, papillary/chromophobe/clear cell/other, 47%/28%/3%/22%; sarcomatoid feature, 13%; IMDC risk favorable/intermediate/poor, 50%/41%/9%; ≥3 tumor sites, 56%; tumor sites, lung/kidney/bone/liver, 50%/25%/16%/16%; prior nephrectomy, 63%; prior VEGFR TKI, 22%; 0/1 lines of prior therapy (locally advanced/metastatic setting), 81%/19%. As of July 21, 2022, median follow-up was 37.2 mo (range 32.1–58.5) with 5 (16%) patients remaining on study treatment. ORR by investigator was 31% (all PRs) and disease control rate was 94% (Table); median

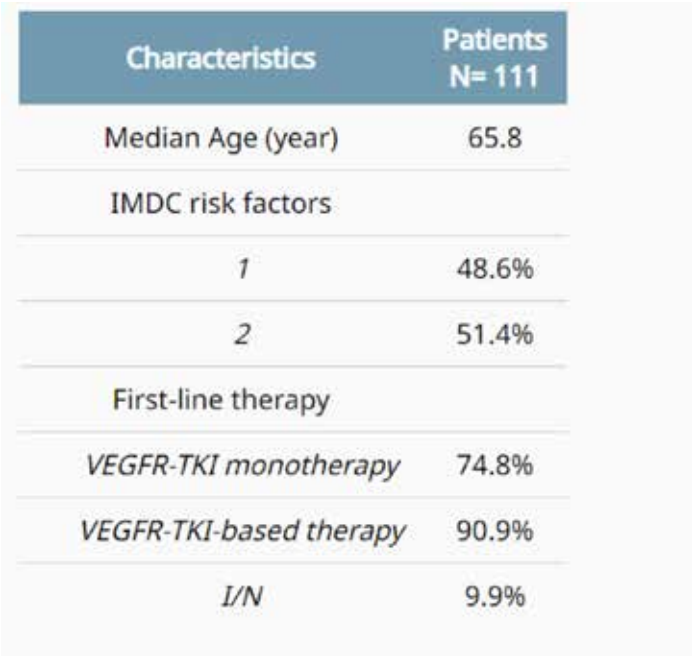
	Advanced nccRCC (N=32)
ORR, % (95% CI)	31 (16–50)
Best response, n (%)	
Confirmed complete response (CR)	0
Confirmed partial response (PR)	10 (31)
Stable disease (SD)	20 (63)
Progressive disease	2 (6)
Disease control rate, % (95% CI)*	94 (79–99)
Median DOR, mo (95% CI)	8.1 (2.4–18.1)

*CR + PR + SD

DOR was 8.1 mo. Median PFS was 9.3 mo (95% CI 5.5–12.3), and median OS was not reached (95% CI 23.0–NE). PFS and OS estimates at 12 mo were 34% and 84%, respectively; 24-mo estimates were 6% and 70%. Treatment-related AEs occurred in 97% (grade 3/4, 53%); the most common AEs included diarrhea (69%), palmar-plantar erythrodysesthesia (50%), fatigue (44%), dysgeusia (41%), hypertension (31%) and nausea (31%). One grade 5 treatment-related AE of pulmonary hemorrhage occurred. Treatment-related AEs leading to discontinuation of both study treatments occurred in 13% of patients. Conclusions: Extended 3-year follow-up reinforces the encouraging clinical activity of cabozantinib plus atezolizumab in advanced nccRCC with a manageable safety profile. Clinical trial information: NCT03170960.

ABSTRACT 714 Evaluation of PBRM1, PD-L1, CD31, and CD4/CD8 ratio as a predictive signature of response to VEGFR-TKI–based therapy in patients with metastatic renal cell carcinoma (mRCC) with IMDC intermediate prognosis: Results from the APAChE-I Study. *Toni K. Choueiri, et al.*

BACKGROUND: Intermediate IMDC group is the largest and most heterogeneous group of mRCC. Current first-line (1L) therapy options for these patients are based on either an anti-angiogenic agent (VEGFR-TKI) combined with immunotherapy(IO),oracomboofIO(ipilimumab+nivolumab [I/N]). No biomarkers (BM) for selecting the most effective regimen have been identified so far. Methods: Immunohistochemical expression of PBRM1, PD-L1, CD31, and CD4/CD8 ratio was evaluated on histological samples of intermediate-risk mRCC pts treated with VEGFR-TKI monotherapy, and then in pts receiving a VEGFR-TKI-based therapy or the immune doublet I/N. PBRM1 positivity score was based on the percentage of positive cells and on the intensity of nuclear expression; PD-L1 positivity was defined as CPS≥10; CD31 high-density had moderate to strong nuclear staining; and the CD4/CD8 ratio cut-off for positivity was >0.2. Cox model was used to assess the correlation between BM and outcomes; PFS and OS were estimated by Kaplan-Meier method. Results: After screening of tumor tissues from 150 pts, a total of 111 were included in the final analysis (Table). In pts treated with VEGFR-TKI monotherapy, a significant correlation with PFS was observed with loss of PBRM1 expression (HR 0.58, p=0.035), PD-L1 negativity (HR 0.44, p=0.048), and high CD4/CD8 ratio (HR 0.62, p=0.073). CD31 density did not significantly correlate with PFS. A profile potentially predictive of angiogenesis (AP+) was defined based on the PBRM1 loss, PD-L1 negative, and high CD4/CD8. In pts treated with VEGFR-TKI monotherapy, tumors with the AP+ (43% of all cases) had a significantly longer median PFS (mPFS 23.8 vs. 11.8 months, p=0.003) and mOS (41.5 vs. 26.9 months, p=0.024) compared to the others. The AP+ retained its significant correlation with PFS (mPFS 23.8 vs. 11.1 months, p<0.001) and OS (41.5 vs. 24.9, p=0.006) in pts receiving VEGFR-TKI-based therapies. The rate of AP+ tumors was 55.6% and 32.7% in pts with one or two IMDC risk factors, respectively (p=0.022). In the small cohort of pts treated with I/N, no differences were observed in PFS (p=0.64) and OS (p=0.75) between AP+ and AP- negative. Conclusions: The AP+ signature (loss of PBRM1, PD-L1 negative, and CD4/CD8 high ratio) was associated with improved clinical outcomes in mRCC pts at IMDC intermediate prognosis treated with VEGFR-TKI-based therapy; this correlation was significant regardless from the addition of IO to VEGFR-TKI monotherapy. Prospective validation of this signature is required for guiding the selection



Characteristics	Patients N= 111
Median Age (year)	65.8
IMDC risk factors	
1	48.6%
2	51.4%
First-line therapy	
VEGFR-TKI monotherapy	74.8%
VEGFR-TKI-based therapy	90.9%
I/N	9.9%

ABSTRACT TPS747 LITESPARK-024: A randomized phase 1/2 study of belzutifan with or without palbociclib in patients with advanced renal cell carcinoma. **Toni K. Choueiri,** *et al.*

BACKGROUND: The combination of immunotherapy with antiangiogenic agents is a well-established first-line treatment option for patients (pts) with advanced renal cell carcinoma (RCC), but many pts develop resistance, and effective second- or subsequent-line options are needed. The von Hippel-Lindau (VHL) gene is inactivated in approximately 90% of RCC cases, which results in the constitutive activation of hypoxia-inducible factor 2α (HIF-2α) signaling. HIF-2α is

involved in angiogenesis, tumor growth, proliferation, and metastasis, and is a key oncogenic driver in RCC. The HIF-2α inhibitor belzutifan has demonstrated promising antitumor activity with manageable safety in pts with heavily pretreated RCC. The cyclin-dependent kinase (CDK) pathway is altered in several cancer types, including RCC, and is associated with poor clinical outcomes. The CDK 4/6 inhibitor palbociclib inhibited cell growth in RCC cell lines, and the antiproliferative effects of CDK 4/6 inhibition were synergistic with HIF-2α inhibition in HIF-2α–dependent VHL -/- clear cell RCC cell lines. We hypothesized palbociclib could potentially enhance the efficacy of belzutifan as combination therapy for previously treated pts with advanced RCC. Methods: LITESPARK-024 (NCT05468697) is an open-label, multicenter, phase 1/2 randomized study of belzutifan + palbociclib versus belzutifan monotherapy in pts with advanced RCC. Pts must have histologically confirmed unresectable stage IV RCC with a clear cell component, received at least 2 prior systemic regimens (both an anti–PD-1/PD-L1 monoclonal antibody and a VEGF receptor–targeted TKI, in sequence or in combination), have measurable disease per RECIST v1.1 by BICR, have KPS score of ≥70%, and have radiographic disease progression on or after the most recent regimen per investigator. Part 1 will evaluate the safety of belzutifan + palbociclib and determine the recommended phase 2 dose (RP2D) for the combination using a modified toxicity probability interval design. Part 2 will evaluate the safety and efficacy of belzutifan + palbociclib versus belzutifan alone. In part 1, ≤30 pts will be enrolled into 3 dose groups and receive belzutifan 120 mg once daily + palbociclib (75, 100, or 125 mg) daily for 21 consecutive days followed by 7 days off. In part 2, approximately 150 pts will be randomly assigned 2:1 to receive belzutifan 120 mg once daily + palbociclib RP2D (21 consecutive days/7 days off) or belzutifan 120 mg once daily. Pts will be stratified by IMDC risk (0 vs 1-2 vs 3-6) and sarcomatoid histology (yes vs no) at randomization in part 2. The primary end point for part 1 is to assess dose-limiting toxicities and adverse events to determine the RP2D of belzutifan + palbociclib. The primary end point for part 2 is ORR per RECIST v1.1 by investigator assessment. Secondary end points for part 2 are clinical benefit rate, DOR, PFS, OS, and safety and tolerability. Clinical trial information: NCT05468697.

ABSTRACT TPS748 Phase 3 LITESPARK-022: Pembrolizumab (pembro) plus hypoxia-inducible factor 2α (HIF-2α) inhibitor belzutifan as adjuvant treatment for clear cell renal cell carcinoma (ccRCC)... Toni K. Choueiri, *et al.*

BACKGROUND: The Treatment with the PD-1 inhibitor pembro produced significant improvement in disease-free survival after surgery for patients (pts) with ccRCC in the phase 3 KEYNOTE-564 trial. Based on these results, pembro was approved by the US Food and Drug Administration and the European Medicines Agency for adjuvant treatment of pts with RCC at increased risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions. Despite advances in the treatment landscape for RCC, more effective adjuvant treatment strategies are needed for pts at risk of recurrence after surgery. HIF-2α is an established oncogenic driver in ccRCC, and promising antitumor activity in advanced ccRCC and von Hippel-Lindau disease–associated RCC has been demonstrated with the HIF-2α inhibitor belzutifan. The multicenter, double-blind, randomized, phase 3 LITESPARK-022 study (NCT05239728) will evaluate the efficacy and safety of pembro plus belzutifan compared with placebo plus pembro as adjuvant treatment following nephrectomy in pts with ccRCC. Methods: Key eligibility criteria include adults with histologically or cytologically confirmed intermediate-high risk, high risk, or M1 with no evidence of disease (NED) RCC with a clear cell component; pts with no prior systemic therapy, nephrectomy, and/or metastasectomy ≤12 weeks before randomization; and pts who are tumor free per computed tomography/magnetic resonance imaging. Approximately 1600 pts will be randomly assigned to receive belzutifan 120 mg orally once daily plus pembro 400 mg intravenously (IV) every 6 weeks (Q6W) for ≤9 administrations (~54 weeks) or oral placebo plus pembro 400 mg IV Q6W for ≤9 administrations (~54 weeks) or until verified disease recurrence by blinded independent central review, start of new anticancer treatment, unacceptable toxicity, or decision to withdraw. Stratification factors are tumor grade (1 or 2 vs 3 or 4) and risk type (intermediate-high risk versus high risk versus M1 NED). Pts will be radiologically evaluated Q12W from randomization through year 2, Q16W in years 3 to 5, and Q24W in years 6 and beyond. Adverse events will be monitored throughout the study and for 30 days following cessation of study treatment (90 days for serious adverse events). The primary end point is disease-free survival. Secondary end points include overall survival, safety, disease recurrence–specific survival, and patient-reported outcomes. Recruitment is underway in Asia, Australia, Europe, North America, and South America.
 This abstract was accepted and previously presented at the 2022 ASCO Annual Meeting. Clinical trial information: NCT05239728.

https://doi.org/10.52733/KCJ21n1-jc

Temporary treatment cessation versus continuation of first-line tyrosine kinase inhibitor in patients with advanced clear cell renal cell carcinoma (STAR): an open-label, non-inferiority, randomised, controlled, phase 2/3 trial. *Janet E Brown et al. Lancet Oncol. 2023 Mar;24(3):213-227*

BACKGROUND: Temporary drug treatment cessation might alleviate toxicity without substantially compromising efficacy in patients with cancer. We aimed to determine if a tyrosine kinase inhibitor drug-free interval strategy was non-inferior to a conventional continuation strategy for first-line treatment of advanced clear cell renal cell carcinoma.

METHODS: This open-label, non-inferiority, randomised, controlled, phase 2/3 trial was done at 60 hospital sites in the UK. Eligible patients (aged ≥18 years) had histologically confirmed clear cell renal cell carcinoma, inoperable loco-regional or metastatic disease, no previous systemic therapy for advanced disease, uni-dimensionally assessed Response Evaluation Criteria in Solid Tumours-defined measurable disease, and an Eastern Cooperative Oncology Group performance status of 0-1. Patients were randomly assigned (1:1) at baseline to a conventional continuation strategy or drug-free interval strategy using a central computer-generated minimisation programme incorporating a random element. Stratification factors were Memorial Sloan Kettering Cancer Center prognostic group risk factor, sex, trial site, age, disease status, tyrosine kinase inhibitor, and previous nephrectomy. All patients received standard dosing schedules of oral sunitinib (50 mg per day) or oral pazopanib (800 mg per day) for 24 weeks before moving into their randomly allocated group.

FINDINGS: Between Jan 13, 2012, and Sept 12, 2017, 2197 patients were screened for eligibility, of whom 920 were randomly assigned to the conventional continuation strategy (n=461) or the drug-free interval strategy (n=459; 668 [73%] male and 251 [27%] female; 885 [96%] White and 23 [3%] non-White). The median follow-up time was 58 months (IQR 46-73 months) in the ITT population and 58 months (46-72) in the per-protocol population. 488 patients continued on the trial after week 24. For overall survival, non-inferiority was demonstrated in the ITT population only (adjusted HR 0·97 [95% CI 0·83 to 1·12] in the ITT population; 0·94 [0·80 to 1·09] in the per-protocol population). Non-inferiority was demonstrated for QALYs in the ITT population (n=919) and per-protocol (n=871) population (marginal effect difference 0·06 [95% CI -0·11 to 0·23] for the ITT population; 0·04 [-0·14 to 0·21] for the per-protocol population). The most common grade 3 or worse adverse events were hypertension (124 [26%] of 485 patients in the conventional continuation strategy group vs 127 [29%] of 431 patients in the drug-free interval strategy group); hepatotoxicity (55 [11%] vs 48 [11%]); and fatigue (39 [8%] vs 63 [15%]). 192 (21%) of 920 participants had a serious adverse reaction. 12 treatment-related deaths were reported (three patients in the conventional continuation strategy group; nine patients in the drug-free interval strategy group) due to vascular (n=3), cardiac (n=3), hepatobiliary (n=3), gastrointestinal (n=1), or nervous system (n=1) disorders, and from infections and infestations (n=1).

INTERPRETATION: Overall, non-inferiority between groups could not be concluded. However, there seemed to be no clinically meaningful reduction in life expectancy between the drug-free interval strategy and conventional continuation strategy groups and treatment breaks might be a feasible and cost-effective option with lifestyle benefits for patients during tyrosine kinase inhibitor therapy in patients with renal cell carcinoma.

Adjuvant nivolumab plus ipilimumab versus placebo for localised renal cell carcinoma after nephrectomy (CheckMate 914): a double-blind, randomised, phase 3 trial *Motzer R et al. Clinical Trial Lancet . 2023 Mar 11;401(10379):821-832.*

BACKGROUND: Effective adjuvant therapy for patients with resected localised renal cell carcinoma represents an unmet need, with surveillance being the standard of care. We report results from part A of a phase 3, randomised trial that aimed to assess the efficacy and safety of adjuvant nivolumab plus ipilimumab versus placebo.

METHODS: The double-blind, randomised, phase 3 CheckMate 914 trial enrolled patients with localised clear cell renal cell carcinoma who were at high risk of relapse after radical or partial nephrectomy between 4-12 weeks before random assignment. Part A, reported herein, was done in 145 hospitals and cancer centres across 20 countries. Patients were randomly assigned (1:1) to nivolumab (240 mg) intravenously every 2 weeks for 12 doses plus ipilimumab (1 mg/kg) intravenously every 6 weeks for four doses, or matching placebo, via an interactive response technology system. The expected treatment period was 24 weeks, and treatment could be continued until week 36, allowing for treatment delays. Randomisation was stratified by TNM stage and nephrectomy (partial vs radical). The primary endpoint was disease-free survival according to masked independent central review; safety was a secondary endpoint. Disease-free survival was analysed in all randomly assigned patients (intention-to-treat population); exposure, safety, and tolerability were analysed in all patients who received at least one dose of study drug (all-treated population). This study is registered with ClinicalTrials.gov, NCT03138512.

FINDINGS: Between Aug 28, 2017, and March 16, 2021, 816 patients were randomly assigned to receive either adjuvant nivolumab plus ipilimumab (405 patients) or placebo (411 patients). 580 (71%) of 816 patients were male and 236 (29%) patients were female. With a median follow-up of 37·0 months (IQR 31·3-43·7), median disease-free survival was not reached in the nivolumab plus ipilimumab group and was 50·7 months (95% CI 48·1 to not estimable) in the placebo group (hazard ratio 0·92, 95% CI 0·71-1·19; p=0·53). The number of events required for the planned overall survival interim analysis was not reached at the time of the data cutoff, and only 61 events occurred (33 in the nivolumab plus ipilimumab group and 28 in the placebo group). 155 (38%) of 404 patients who received nivolumab plus ipilimumab and 42 (10%) of 407 patients who received placebo had grade 3-5 adverse events. All-cause adverse events of any grade led to discontinuation of nivolumab plus ipilimumab in 129 (32%) of 404 treated patients and of placebo in nine (2%) of 407 treated patients. Four deaths were attributed to treatment with nivolumab plus ipilimumab and no deaths were attributed to treatment with placebo.

INTERPRETATION: Adjuvant therapy with nivolumab plus ipilimumab did not improve disease-free survival versus placebo in patients with localised renal cell carcinoma at high risk of recurrence after nephrectomy. Our study results do not support this regimen for the adjuvant treatment of renal cell carcinoma.

Efficacy and safety of nivolumab in bone metastases from renal cell carcinoma: Results of the GETUG-AFU26-NIVOREN multicentre phase II study. *Maud Velev Clinical Trial Eur J Cancer 2023 Mar;182:66-76.*

INTRODUCTION: Bone metastases (BM) in renal cell carcinoma (RCC) are associated with a poor prognosis based on retrospective studies evaluating antiangiogenic agents. Few data are available regarding immune checkpoint inhibitors (ICI) in patients with bone metastatic RCC. NIVOREN is a multicentre prospective study in which patients were treated with nivolumab after the failure of antiangiogenic agents. We aim to assess the impact of BM on prognosis, and the efficacy and safety of nivolumab in patients enrolled in the NIVOREN trial.

MATERIALS AND METHODS: All patients with BM at inclusion were included in our study. The primary endpoint was

overall survival (OS). Secondary endpoints were progression-free survival (PFS), objective response rate (ORR), safety, and skeletal-related events (SRE).
RESULTS: Among 720 patients treated with nivolumab, 194 presented BM at inclusion. The median follow-up was 23.9 months. Median OS was 17.9 months in patients with BM versus 26.1 months in patients without BM (p = 0.0023). The difference was not statistically significant after adjustment (p = 0.0707). The median PFS was shorter in patients with BM even after adjustment (2.8 versus 4.6 months, p = 0.0045), as well as the ORR (14.8% versus 23.3%). SRE occurred for 36% of patients with BM. A post-hoc analysis evaluating the impact of bone-targeting agents (BTA) on SRE incidence showed a significant benefit of BTA on the incidence of SRE (OR = 0.367, CI95% [0.151-0.895]).
CONCLUSION: Nivolumab is associated with shorter PFS, and lower ORR in RCC patients with BM. Our study suggests that BTA in association with immunotherapy decreases the incidence of SRE.

Health-Related Quality of Life Outcomes With Two Different Starting Doses of Lenvatinib in Combination With Everolimus for Previously Treated Renal Cell Carcinoma *Cristiane Bergerot 2023 Jan 18;28(1):59-71. doi: 10.1093/oncolo/oyac142.*
BACKGROUND: Preserving health-related quality of life (HRQOL) is an important goal during renal cell carcinoma treatment. We report HRQOL outcomes from a phase II trial (NCT03173560).
PATIENTS AND METHODS: HRQOL data were collected during a multicenter, randomized, open-label phase II study comparing the safety and efficacy of 2 different starting doses of lenvatinib (18 mg vs. 14 mg daily) in combination with everolimus (5 mg daily), following one prior vascular endothelial growth factor-targeted treatment. HRQOL was measured using 3 different instruments-FKSI-DRS, EORTC QLQ-C30, and EQ-5D-3L-which were all secondary endpoints. Change from baseline was assessed using linear mixed-effects models. Deterioration events for time to deterioration (TTD) analyses were defined using established thresholds for minimally important differences in the change from baseline for each scale. TTD for each treatment arm was estimated using the Kaplan-Meier method.
RESULTS: Baseline characteristics of the 343 participants randomly assigned to 18 mg lenvatinib (n = 171) and 14 mg lenvatinib (n = 172) were well balanced. Least-squares mean estimates for change from baseline were favorable for the 18 mg group over the 14 mg group for the FKSI-DRS and most EORTC QLQ-C30 scales, but differences between treatments did not exceed the minimally important thresholds. Median TTD was longer among participants in the 18 mg group than those in the 14 mg group for most scales.
CONCLUSIONS: Participants who received an 18 mg lenvatinib starting dose had favorable HRQOL scores and longer TTD on most scales compared with those who received a 14 mg starting dose.

RRenal functional and cardiovascular outcomes of partial nephrectomy versus radical nephrectomy for renal tumors: a systematic review and meta-analysis *Mario Ochoa-Arvizo et al. 2023 Mar;41(3):113-124.*
This systematic review and meta-analysis aimed to evaluate the postoperative renal and cardiovascular outcomes of partial nephrectomy (PN) versus radical nephrectomy (RN) for the treatment of renal carcinoma. A systematic literature search was performed on scientific databases including Scopus, Web of Science, MEDLINE, and EMBASE from their inception to September 2021. Studies comparing renal and cardiovascular outcomes between PN and RN in patients with renal cancer were included. The generic inverse variance method with random-effects models was used to determine the pooled hazard ratios and odds ratio for each outcome. Quality Assessment for observational studies was guided by the New-Castle Ottawa Scale. Overall, a total of 31 studies (n=51,866) reported renal outcomes, while 11 studies (n= 101,678) reported cardiovascular outcomes. When compared to PN, RN had a higher rate of new-onset postoperative EGFR <60 mL/min/1.73 m2 (HR 3.39; CI 2.45 - 4.70; I2=93%; P=<0.00001) and EGFR <45 mL/min/1.73 m2 (HR 4.70; CI 2.26 - 9.79; I2=98%; P=<0.0001). No difference was observed in new-onset advanced kidney disease and end-stage renal disease. A 19% reduction in cardiovascular events was observed in the PN group (HR 0.81; CI 0.70 - 0.93, P=0.002). No protective effect of PN was observed in new-onset or worsening hypertension (HR 0.85; CI 0.64 - 1.14, P=0.28) nor myocardial infarction (HR 0.86; CI 0.71 - 1.04, P=0.13). PN was associated with a decreased risk of postoperative early-stage CKD and cardiovascular events compared with RN. However, no benefit of PN over RN was observed in advanced CKD, new-onset or worsening hypertension, myocardial infarction, and cardiovascular mortality.

Comparative risk of acute kidney injury among cancer patients treated with immune checkpoint inhibitors. *Fei Liu et al. Review Cancer Commun (Lond). 2023 Feb;43(2):214-224.*
RESULTS: With the development and introduction of immune checkpoint inhibitors (ICIs) in cancer patients, immune-related side effects have increasingly attracted attention. However, the risks of immune-related renal toxicity are poorly characterized. In this study, we performed a network meta-analysis (NMA) of ICI-related randomized clinical trials (RCTs) to elucidate the comparative risk of acute kidney injury (AKI) in cancer patients receiving different ICIs. We also sought to identify other factors potentially affecting the risk of AKI. PubMed and EMBASE were searched for peer-reviewed trial reports published between January 2000 and May 2021. Eligible studies were RCTs studying ICIs in cancer patients and reporting AKI data. We performed a frequentist NMA to evaluate the risk ratios for grade 1-5 and grade 3-5 AKI between the treatment groups. We also assessed the absolute incidence of AKI in the ICI-containing arm using traditional direct meta-analysis. Once significant heterogeneity was detected in a traditional direct meta-analysis, multivariable meta-regression analysis was applied to identify factors that significantly affected the absolute incidence of AKI. A total of 85 RCTs were included in this study. In the NMA for the risk of grade 1-5 and 3-5 AKI, ipilimumab showed a significantly higher risk than avelumab and durvalumab, whereas 1 mg/kg nivolumab plus 3 mg/kg ipilimumab (N1I3) showed a significantly higher risk than other groups. In terms of treatment ranking, durvalumab ± low-dose tremelimumab and avelumab were consistently among the top three safest treatments for grade 1-5 or 3-5 AKI, whereas N1I3, ipilimumab and tremelimumab were consistently among the top three treatments with the highest risk for grade 1-5 or 3-5 AKI. Compared with other cancers, renal cell carcinoma and urothelial carcinoma showed a significantly higher risk of AKI. The incidence of AKI was significantly higher with ICI+chemotherapy than with ICI monotherapy. In this NMA involving large-scale up-to-date ICI trials, we demonstrated the comparative safety of existing ICI drugs for grade 1-5 and grade 3-5 AKI. Based on data from the ICI arms of these trials, we also revealed several potential risk factors for immune-related AKI, including tumor type and treatment paradigm.
CONCLUSIONS: TelaE and TelaC showed encouraging clinical activity and tolerability in heavily pretreated mRCC patients.