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ASCO 2023 Kidney Cancer Roundup

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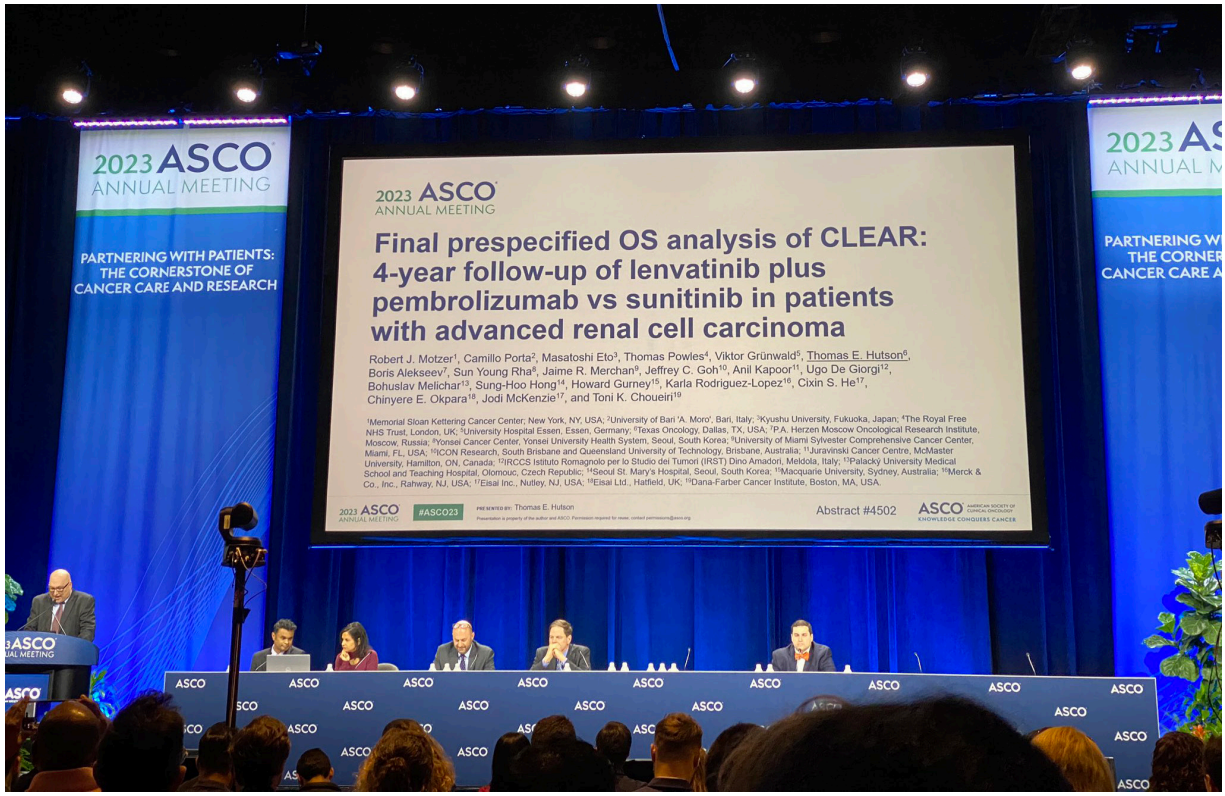
https://doi.org/10.52733/KCJ21n2-e

Dear Colleagues,

The world-leading cancer researchers from more than 125 countries gathered at the 2023 ASCO Annual Meeting from June 2-6, held in Chicago, USA and online to drive conversations on the state-of-the-art treatment modalities, breakthroughs, novel strategies, and ongoing controversies in the field. The sessions were packed with practice-changing results and scientific insights from major phase III trials presented alongside exciting as well as early phase trial results. This year's theme, 'Partnering With Patients: The Cornerstone of Cancer Care and Research', takes a closer look at how interactions between clinicians and patients have changed over the years, and what can be done to make interactions between clinicians and patients better.

Approximately 6,900 abstracts were presented at this year's Annual meeting, with almost 30% of all abstracts related to clinical trials. Of these, more than 70% of referenced phase II trials are currently ongoing. The ASCO features over 120 sessions featuring important and timely research from the clinical oncology landscape topics. Overall, with over 1,100 drugs discussed, ASCO23 highlighted progress on a wide range of established and new therapeutic regimens. One of the key focus areas at ASCO this year is novel immunotherapeutics, checkpoints inhibitors, bispecifics, and vaccines in development. As seen in recent years, Pembrolizumab and Nivolumab (both anti-PD-1 antibodies) remain the top drugs of interest based on the large number of presentations.

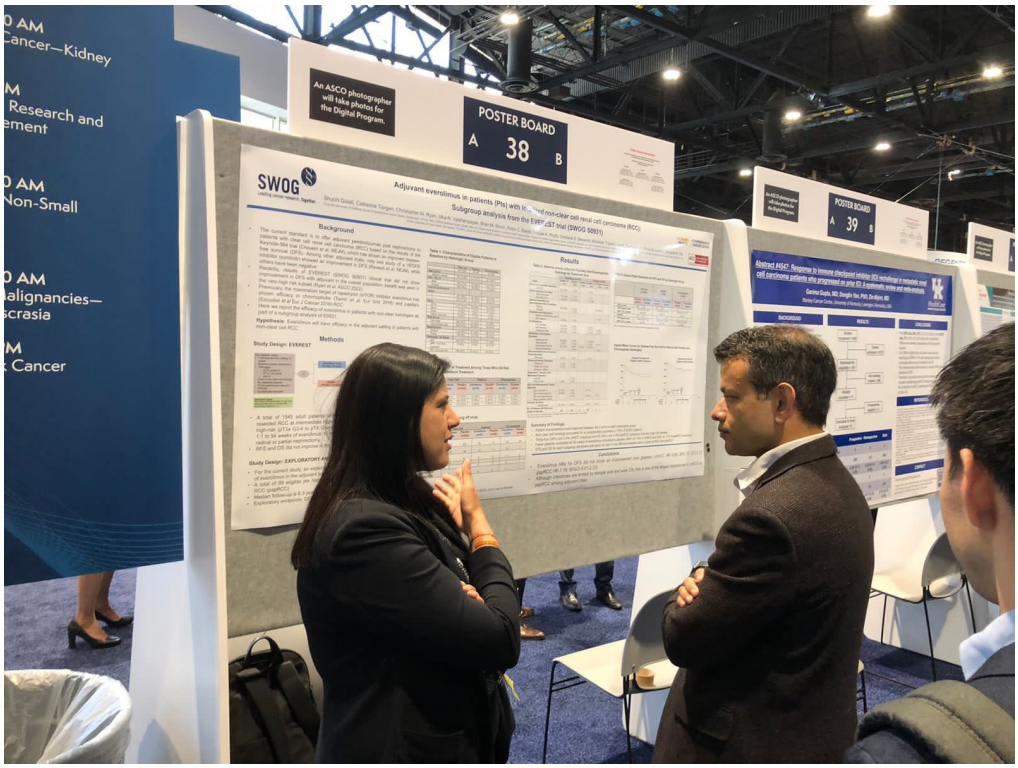
Let's dive into the key developments from some of the highest-profile clinical trials presented in the ASCO23



conference. Primary PFS analysis from the phase III, randomized, open-label CONTACT-03 study (Abstract LBA4500) has shown the atezolizumab plus cabozantinib combination failed to improve primary PFS with IO-TKI in the second-line setting in patients with metastatic RCC. Therefore, using a targeted therapy plus an immunotherapy combination does not outweigh the benefits of targeted therapy alone in patients whose disease has gotten worse on previous treatment. The data reinforce the need for randomized prospective assessment of rechallenge with checkpoint inhibitors and PD-1/PD-L1 inhibitors in patients who experience progression on a PD-1/PD-L1 inhibitor. The extended 4-year follow-up data (Abstract 4502) has shown that the IO-TKI combination - lenvatinib plus pembrolizumab remains superior to sunitinib in all risk groups , as first-line treatment in aRCC, (CLEAR study). Although not practice changing, the updated results from CLEAR reaffirm current practice of using front-line immunotherapy/TKI combination.

This year, there were several studies presented focusing on the treatments for non-clear cell kidney cancer (Abstract 4518, 4537, and 4520 etc). For example, in Abstract 4520, the triple combination of nivolumab, ipilimumab and cabozantinib showed some benefit in patients with non-clear cell kidney cancer, especially when compared to other treatments like nivolumab plus cabozantinib, or lenvatinib plus pembrolizumab. The COSMIC-313 study previously showed a delay in the time to when the cancer regrows in the setting of cabozantinib with two immunotherapy medicines, nivolumab and ipilimumab for patients with advanced clear cell kidney cancer. This triple combination study is still ongoing at various stages of their treatment schedule and yet to be tested in other subtypes.

Abstract 4530 reports about the utility of cabozantinib as a second-line treatment following IO therapy has stopped working as compared to other VEGFR TKIs in the real world. Cabozantinib was effective after prior immunotherapy in patients with kidney cancer that had spread, regardless of previous VEGFR TKI treatment. In early results from the KEYNOTE-B61 study (Abstract 4518) showed that the combination of lenvatinib plus pembrolizumab is effective as a first-line treatment for advanced non-clear cell kidney cancer. The researchers presented more follow-up information from this study. Importance: This study shows that the combination of lenvatinib plus pembrolizumab is an effective first-line treatment for patients with different subtypes of non-clear cell kidney cancer. There is an unmet need for an accurate test to diagnose kidney cancer to guide patient management. Abstract 4554 shown the results from a phase 3 study of 89Zr-DFO-girentuximab for PET/CT imaging and this study confirms that 89Zr-DFO-girentuximab is well tolerated and



can accurately identify kidney cancer from a PET/CT scan.

The ASCO 2023 Annual Meeting yet again served as the premise for the unveiling of enticing clinical data from pivotal research. We can clearly witness the innovative mindset at the ASCO combined with the exploration of clinician and patient interaction to deliver promising therapeutic avenues, especially keeping patients front and center in drug development. With the focus on enhancing innovative therapies to meet the needs of patients, the industry requires effective strategies to improve trial diversity among underserved populations. Only then can we truly gauge how these treatments may provide real-world benefits to those most impacted by certain cancers. While combination therapies continue to receive attention at ASCO 2023 and tremendous progress has been made as well, but the question remains if their potential holds true with long-term durable outcomes and as well as for individualized patient strategy for patients with advanced/metastatic kidney cancer. We eagerly look forward to all study results that could once again shift practice in cancer care.

In this issue, Campbell et al presented a case study of a 44-year-old female with morbid obesity and hypertension found to have bilateral renal lesions with venous involvement who underwent right radical nephrectomy with IVC thrombectomy followed by left laparoscopic nephrectomy, ex vivo PN and autotransplantation. The role and timing for cytoreductive nephrectomy in mRCC have been a moving target over the past couple decades and continue to evolve. In the case study, Bhanji Y et al, shown that use of ICI prior to cPN was beneficial to downsize and downstage the primary tumor, thereby facilitating nephron preservation, while resolving the paraneoplastic manifestations of the cancer that would otherwise limit the patient's candidacy to undergo cytoreduction. This year's ASCO coverage is provided by Roy Elias, Yasser Ged, and Nirmish Singla.

Kidney Cancer Updates from the 2023 American Society of Clinical Oncology Annual Meeting in Chicago.

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doi.org/10.52733/ASCO23summary

ABSTRACT

This report highlights key research from the 2023 American Society of Clinical Oncology (ASCO) Annual Meeting, with a focus on clear cell renal cell carcinoma (ccRCC) and non-clear cell RCC (nccRCC) across clinical trials and translational studies. Essential updates in the metastatic ccRCC clinical space encompass results from the CONTACT-03 study, which evaluated an immunotherapy containing regimen for patients who progressed on an initial immunotherapy containing regimen, alongside updated results from the KEYNOTE-426 and CLEAR trials. In the metastatic nccRCC domain, we review clinical trials of combination immunotherapies and tyrosine kinase inhibitors (TKIs). Additionally, we highlight exciting early-phase studies exploring novel targets in RCC and engineered T-cell methodologies. Finally, we summarize notable efforts in translational research, emphasizing biomarker investigations to determine predictors of immunotherapy response, the application of molecular classifiers in RCC, and the relationship between the microbiome and RCC. There were many important RCC related abstracts presented at this year's ASCO conference, attesting to the continued momentum of research in the field. All conference materials, including abstracts and presentations, can be accessed online through the conference website.

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 RCC.

Metastatic ccRCC, Phase III studies

The oral abstract sessions for kidney cancer this year led to particularly insightful discussion. The frontline treatment landscape for metastatic ccRCC is currently dominated by immune-checkpoint inhibitor doublets (ICI) and combination vascular endothelial growth factor tyrosine kinase inhibitors (VEGF-TKI) with ICI[1]. We were presented with the updated analysis of two key trials of VEGF-TKI/ICI combination therapies, KEYNOTE-426 (Abstract #LBA4501) and CLEAR (Abstract #4502)[2,3]. The former assessed axitinib and pembrolizumab (axi/pem) versus sunitinib, while the latter compared lenvatinib and pembrolizumab (len/pem) versus sunitinib. Both trials were performed in treatment naïve metastatic ccRCC.

With over four years of follow-up data, the updated reports demonstrated consistent results with initial studies, showing significant improvements in objective response rates (ORR), progression-free survival (PFS), and overall survival (OS) relative to sunitinib. A key area of discussion was centered on the sustainability of responses and how these compared with the responses observed in the CHECKMATE-214 study, which evaluated the ipilimumab/nivolumab (ipi/nivo) combination in the same patient population4. Among patients who responded in aforementioned studies, the median duration of response was 43.7 months for the len/pem arm and 23.6 months in the axi/pem arm. However, less than 30% of responders in both studies maintained response at 48 months, and the response curves do not yet appear to have plateaued. In a subsequent discussion, Dr. David Braun from Yale University contended that ipi/nivo, with which over 50% of responses are durable over 60 months, should be the preferred choice for most metastatic RCC patients without oligometastatic disease. He suggested that exceptions to this would be patients with impending organ failure or those in need of a rapid response.

Another pivotal finding was the outcome of the CONTACT-03 study, presented by Dr. Choueiri (Abstract #LBA4500). This study assessed the efficacy of atezolizumab plus cabozantinib versus cabozantinib alone, following progression in a regimen containing immunotherapy in metastatic ccRCC. The researchers found no significant differences in ORR, PFS, or OS between the two groups. However, the atezolizumab plus cabozantinib combination led to a notable increase in grade III/IV adverse events. Full results of the study have been published in The Lancet[5].

This consequential study offers prospective evidence indicating that rechallenge with immunotherapy immediately post progression does not yield improved outcomes, but rather increases toxicity levels. Questions remain regarding the role of immunotherapy salvage in later lines, and the role of CTLA-4 targeted therapies in the salvage setting.

Novel therapeutic approaches in ccRCC

There were several early-stage trials and preclinical studies investigating novel therapies in ccRCC. Dr. Pili presented results from a combined Phase I/II study evaluating Etinostat (NCT03024437), an HDAC inhibitor with potential to modulate immunosuppressive tumor microenvironments. This was administered in combination with atezolizumab and bevacizumab in metastatic RCC (Abstract #4526). The dose escalation phase found Etinostat to be well tolerated, and in group A of the phase II study (evaluating the treatment in an immunotherapy naïve cohort, n = 15), the most common grade 3-4 adverse events were hypophosphatemia (25%), diarrhea (16.7%), thrombocytopenia (8.3%), and neutropenia (8.3%). In this cohort, the ORR was 60% (9 out of 14 patients evaluable patients), showcasing notable efficacy.

Dr. Beckerman reported results of a Phase II study that evaluated batiraxcept - an antibody targeting the AXL receptor, a protein implicated in RCC metastasis (NCT04300140). The antibody was studied as a standalone therapy, in combination with nivolumab and cabozantinib in the first-line setting, and paired with cabozantinib in previously treated patients (Abstract #4534). Batiraxcept was tolerable as a monotherapy, although the response rates were low with only 1 out of 10 patients demonstrating stable disease. However, in the prior therapy group, Batiraxcept with cabozantinib yielded a ORR of approximately 44% (11/25). Phase III trials examining this agent are planned.

Lastly, Dr. Roussy disclosed results of arm B5 from the Phase I/II KEYMAKER Trial (NCT04165798), which explored the use of belzutifan and lenvatinib post progression on immunotherapy and VEGF therapies in metastatic ccRCC. The combination proved well-tolerated with the most common adverse events being hypertension and anemia, which occurred at any grade in 43% of patients. The ORR in this cohort was 50% (12/24). This finding is promising, especially given the extensive prior exposure to immunotherapy and VEGF-TKI among this patient cohort.

Innovative work in the preclinical setting was also reported at the conference. Dr. Barisic presented a poster titled "T cell receptor-engineered T cells targeting a human endogenous retrovirus in kidney cancer" (Abstract #4542). The team developed a T-cell receptor-engineered T-cell that targets the human endogenous retrovirus, HERV-E, in an HLA-A11-restricted manner. In a murine model, these engineered HERV-E T-cells significantly slowed the progression of established human ccRCC tumor grafts, leading to a considerable increase in the survival of the animals compared to those that either received non-transduced T cells or no T cells (median survival 50 days vs. 20 and 20 days, respectively; $p < 0.001$).

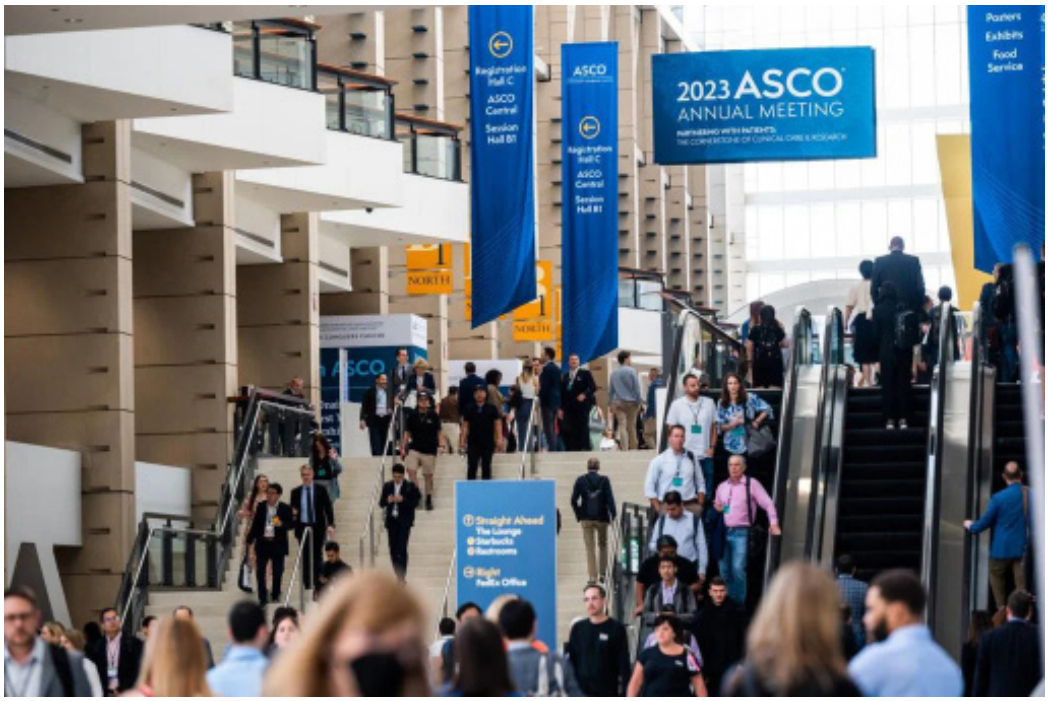
The exciting findings from this preclinical study are being carried forward into a Phase I clinical trial (NCT03354390), the preliminary results of which were presented by Dr. Nadal (Abstract #2549). Patients with HLA-A*11 positive, advanced, treatment-refractory ccRCC were included in this study. Out of the 14 patients enrolled, there were no dose-limiting toxicities or treatment-related deaths. However, 57% of patients developed Grade 3-4 neutropenic fever, and 7% developed Grade 3-4 capillary leak syndrome. Encouragingly, therapeutic responses were observed, with 7% (1/14) of patients demonstrating a partial response and 29% (4/14) maintaining stable disease for at least 8 weeks.

Metastatic non-ccRCC

Non-(n)ccRCC, comprising approximately 25% of new RCC diagnoses, represents a diverse collection of molecularly distinct tumors that necessitate focused study6. There were several prospective studies in the nccRCC space reported, including trials investigating combination Nivolumab/Cabozantinib (nivo/cabo) (Abstract #4537) and len/pem (Abstract #4518) in the first-line setting across nccRCC subtypes.

In the Phase II KEYNOTE-B561 study, len/pem were assessed as the first-line treatment for metastatic non-clear cell RCC (NCT04704219). This study involved a cohort of 158 patients with various histologies: papillary (n = 93), chromophobe (n = 29), unclassified (n = 21), translocation (n = 6), and others (n = 9). The toxicity profile aligned with expectations for this combination. The combined ORR was 49% (77/148) and the disease control rate was 82% (121/148). In all patients, median PFS and OS were 17.9 months (95% CI, 13.5-NR) and NR (95% CI, NR-NR)

Dr. Lee also presented results from a Phase II study evaluating nivo/cabo in nccRCC (NCT03635892), with a distinctive feature (relative to KEYNOTE-B561) being that the study permitted up to one previous line of therapy. Like KEYNOTE-B561, the toxicity



profile was as expected for an ICI/TKI combination. The ORR for this group was 54% (14/26) in the first-line setting and 36% (5/14)in the second-line setting. In all patients, median PFS and OS were 13 months (95% CI: 7, 16), and 28 months (95% CI: 23, 43), respectively.

Dr. McGregor shared findings from the CaNI study, a Phase II trial investigating a triplet combination of Cabozantinib, Ipilimumab, and Nivolumab (Cabo/Ipi/Nivo) in patients with metastatic nccRCC (Abstract #4520, NCT04413123). Prior systemic therapy was allowed in this cohort. In all patients, median PFS was 8.9 (95% CI, 4.2-12.7) months. Notably, most patients (n = 33, 84%) required dose reduction of cabozantinib, and only 45% received all four doses of ipi/nivo. This likely explains the lower-than-expected ORR (18%), though final results are still pending.

In all three studies, chromophobe RCC (chRCC) exhibited worse outcomes with immunotherapy/TKI therapies than other histological subtypes. A possible explanation for this disparity in outcomes was presented by Dr. Labaki, who performed immunoprofiling of chRCC through single-cell RNA sequencing and TCGA analysis, comparing it with other RCC subtypes. His analysis indicated that chRCC has a lower density of tumor infiltrating lymphocytes compared to other histological subtypes, and the infiltrating T-cells found in chRCC lack expression of immune checkpoints, suggesting a non-exhausted phenotype. Furthermore, these T-cells did not seem to display evidence of antitumor specificity, indicating that they might be "bystander" T-cells (Abstract #4558).

Another key presentation, also by Dr. Labaki, were the outcomes of immunotherapy as the first-line treatment in nccRCC with sarcomatoid or rhabdoid (S/R) features (Abstract #4519). In this retrospective analysis performed using International Metastatic RCC Database Consortium (IMDC) data, nccRCC patients with S/R features who received immunotherapy had a notably improved OS (median 19.3-NR in immunotherapy containing arms vs 3.9-13.0 in VEGF-TT arms, $p < 0.0001$). This provides compelling evidence supporting sarcomatoid features as a predictive biomarker for immunotherapy response in RCC, across histological subtypes.

Translational Research Highlights

Many abstracts at the conference explored kidney cancer biology. We have chosen to highlight advances in immunotherapy biomarkers, molecular classifications, and microbiome-based research.

Biomarkers to immunotherapy

Biomarkers which can predict ICI response are needed in RCC. Below, we highlight key abstracts investigating this important field. Dr. Motzer shared a subgroup analysis of the CHECKMATE 914 (Part A) trial, which examined the use of ipi/nivo as adjuvant therapy in patients with locally advanced ccRCC (Abstract #4506)[7]. Although the study failed to demonstrate a difference in disease-free survival (DFS) in the overall cohort, the subgroup analysis benefit for patients with grade 4 disease (n = 171) who were treated with ipi/nivo (n = 80, median DFS NR 95% CI: [35.9 – NE]) versus placebo (n = 91, DFS 41.4 months [23.8-NE]). Patients with sarcomatoid features (n = 40) appeared to derive even greater benefit, with a median DFS that was NR vs 21.0 months (5.2-NE) in the ipi/nivo (n = 19) vs placebo (n = 21) arms, respectively. Though limited by low numbers, these findings suggest a potential role for sarcomatoid de-differentiation as a biomarker in the adjuvant setting, particularly given the role of sarcomatoid features as a predictive biomarker to ipi/nivo in the metastatic setting[8]. Dr. Ahrmar examined tissue samples from the HCRN GU16-260 study[9], which investigated nivolumab monotherapy in metastatic RCC (Abstract #4549). The investigators performed multiparametric immunofluorescence on samples from 81 advanced RCC patients who received nivolumab as a first-line treatment. Their findings corroborated previous studies[10], revealing that higher levels of CD8+ PD1+ TIM-3 and LAG-3 negative tumor infiltrating lymphocytes were associated with a better response to immunotherapy. Dr. Braun presented additional biomarker analysis of the HCRN GU16-260 study[9]. Here, the investigators report on whole exome sequencing (WES) and single cell RNA sequencing (scRNAseq) on a subset of patients with primary refractory disease and compared to responders. They identified amplification of chromosome 11q13 in 6/18 primary refractory patients, compared to no 11q13 amplification in the responsive group. scRNAseq in primary refractory disease revealed an enrichment for a SLAMF7+ population of cytotoxic T cells. These findings reveal two new putative biomarkers (and mechanisms) for immunotherapy resistance in ccRCC which warrant further investigation.

Dr. Rene discussed cytokine profiling performed on 60 patients with advanced nccRCC enrolled in a Phase II study investigating atezolizumab and bevacizumab (Abstract #4535, NCT02724878). They identified a cluster of inflammatory cytokines - MIP-1b, IL-1, MCP-1, IL-6, and IL-13 - whose circulating levels correlated strongly at baseline. Patients with higher circulating levels of these cytokines tended to have a worse IMDC score and decreased PFS (p = 0.028). This study has been published in Cancer Immunology Research11. Dr. Sumanta Pal presented the results of CD8 cell PET imaging with 89-Zr-crefmirlimab in metastatic ccRCC patients who underwent checkpoint inhibition therapy (Abstract #4551). The study enrolled 17 patients (71% with ccRCC), who received an IO-containing regimen. Patients were required to have a baseline biopsy and a follow-up biopsy after the second scan (4-6 weeks post-therapy). CD8 SUV was highly correlated with the density of CD8 on tissue immunohistochemistry (IHC) (R = 0.77). Moreover, enhancement by CD8 PET was found to stratify IO responders, with a mean SUV at baseline of 14.68 in responders and 8.28 in non-responders (p = 0.006).

Molecular classification of RCC

RCC is increasingly recognized as a disease with significant molecular heterogeneity. Accordingly, molecular-based classifiers, such as the IMmotion151 clusters, have been proposed to further subdivide and understand this disease[12]. We reported that genetic ancestry is associated with IMmotion151 subgroup classifications in a cohort of 253 patients with clear cell RCC (Abstract #4536). In particular, African ancestry is associated with an increased frequency of the "proliferative" cluster, which is characterized by VHL wild type disease, and low expression of a HIF2α gene signature. It is noteworthy that no specific cluster was exclusive to an ancestry group, and when considering IMmotion151 molecular clusters, genetic ancestry did not account for additional variation in gene expression. These findings emphasize the importance of stratifying patients based on tumor biology. Dr. Reddy from Vindhya Data Science discussed this strategy further in her poster "Biomarker-driven prospective clinical trial in renal cell carcinoma: Developing machine learning models to allocate patients to treatment arms using RNA sequencing" (Abstract #4525). Through machine learning methods, the researchers were able to identify a model that can predict IMmotion151 cluster types in a manner that can be applied to individual samples in a prospective way. This ability to apply the model to single samples addresses a significant limitation of the original classifier. This strategy of stratifying patients based on IMmotion151 cluster type is now being applied in the OPTIC trial (NCT05361720), which aims to determine if patients should be allocated to TKI/IO or IO/IO treatment arms based on their cluster type. The results of this study will be watched closely as an example of how to integrate advancements in molecular classifications and machine learning with clinical practice.

Microbiome and RCC

The microbiome's role in immunotherapy efficacy for Renal Cell Carcinoma (RCC) is a subject of ongoing investigation, as illustrated by several abstracts presented at this conference. Dr. Costa Silva presented a correlative analysis of the NIVOREN phase II trial (NCT03013335), which examined the impact of nivolumab in patients with ccRCC who had shown progression on VEGF-TKI therapy (Abstract #4548). The researchers focused on serum soluble mucosal addressin cell adhesion molecule-1 (ssMAdCAM-1), a molecule expressed in the gastrointestinal (GI) tract that helps retain immunosuppressive enterotropic T-cells. The researchers hypothesized that high levels of ssMAdCAM-1, associated with ileal MADCAM-1 transcripts, could be linked to immunotherapy effectiveness. They found that low ssMAdCAM-1 levels were associated with antibiotic use and a low clinical benefit rate (37% versus 63%, p=0.0004). Additionally, low ssMAdCAM-1 predicted OS in a cohort of lung and bladder patients undergoing ICI therapy.

Dr. Dizman presented a correlative analysis of a phase I study examining CBM588 (NCT03829111)[13], a live bacterial product that produces butyric acid, in combination with nivo/ipi versus nivo/ipi alone in treatment-naïve advanced ccRCC patients (Abstract #4556). Increased baseline levels of isobutyrate were observed in patients receiving CBM588, and further increases during treatment were associated with objective response. Moreover, the level of circulating acetic acid was correlated with CCL2 and CCL4, potentially providing a biological rationale for the combination therapy.

Dr. Bari conducted an analysis comparing stool and plasma metabolomics in responders versus non-responders among 79 treatment-naïve

RCC patients receiving immunotherapy-containing regimens (Abstract #4564). Microbial metabolites of Tryptophan were associated with ICB resistance and found at significantly higher levels in non-responders.

Lastly, Dr. Mezza examined the intratumoral microbiome in 96 patients with metastatic RCC undergoing immunotherapy treatment (Abstract #4561). Increased bacterial diversity within tumors was linked with improved immunotherapy response, suggesting a potential role for the intratumoral microbiome in determining patient outcomes.

CONCLUDING REMARKS

This year's ASCO Conference was notable for several important studies ranging from practice changing phase III studies to important translational work. Herein we highlighted key abstracts, organized by study type (phase III, early clinical studies, and exploratory) and histological subtype (ccRCC and nccRCC). There are many more RCC related abstracts available through the ASCO conference materials, and we encourage our readers to explore these important studies.

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These recommended abstracts from ASCO 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/ASCO23abs

ABSTRACT LBA 4500: **Efficacy and safety of atezolizumab plus cabozantinib vs cabozantinib alone after progression with prior immune checkpoint inhibitor (ICI) treatment in metastatic renal cell carcinoma (RCC): Primary PFS analysis from the phase 3, randomized, open-label CONTACT-03 study).** *Choueiri TK et al.*

METHODS: CONTACT-03 enrolled pts with histologically confirmed, inoperable, locally advanced or metastatic cc or non-cc RCC, regardless of PD-L1 status, that progressed on or after ICI treatment. Randomization was 1:1 to atezo (1200 mg IV q3w) plus cabo (60 mg oral qd) or cabo alone. Stratification factors were IMDC risk factors (0 vs 1-2 vs ≥3); most recent line of prior ICI therapy (adjuvant vs 1L vs 2L); and histology (dominant cc without sarcomatoid vs dominant non-cc [papillary or unclassified] without sarcomatoid vs cc or non-cc with any sarcomatoid component). The multiple primary efficacy endpoints were centrally reviewed RECIST 1.1 PFS and OS. Key secondary endpoints were investigator (INV)-assessed PFS, centrally reviewed RECIST 1.1 ORR and DOR and safety.

RESULTS: Of 522 pts randomized to atezo + cabo (n=263) or cabo (n=259), 55% and 51% had most recent ICI in the 1L setting and 10% and 11% had sarcomatoid RCC, respectively. At the data cutoff (Jan 3, 2023), median follow-up was 15.2 mo. No PFS or OS benefit was observed with atezo + cabo vs cabo. ORR was 41% in both arms; DOR was 12.7 (95% CI: 10.5, 17.4) mo with atezo + cabo and 14.8 (95% CI: 11.3, 20.0) mo with cabo. All-cause Grade 3/4 adverse events (AEs) occurred in 68% (177/262) and 62% (158/256) of safety-evaluable pts receiving atezo + cabo or cabo, respectively; all-cause Grade 5 AEs occurred in 6% and 4%. AEs leading to treatment withdrawal occurred in 16% of pts on atezo + cabo and 4% on cabo. treatment-emergent adverse events (TEAEs), 2 TEAEs were treatment related.

	Atezo + cabo (n=263)	Cabo (n=259)
Centrally reviewed PFS events, n (%)	171 (65)	166 (64)
Median (95% CI), mo	10.6 (9.8, 12.3)	10.8 (10.0, 12.5)
Stratified HR (95% CI)	1.03 (0.83, 1.28)	
P value	0.7844	
OS events, n (%)[a]	89 (34)	87 (34)
Median (95% CI), mo	25.7 (21.5, NE)	NE (21.1, NE)
Stratified HR (95% CI)	0.94 (0.70, 1.27)	
P value	0.6902	

NE, not evaluable. [a] Interim analysis.

CONCLUSIONS: The addition of atezo to cabo did not improve clinical outcomes and led to increased toxicity in patients with RCC that progressed on or after prior ICI treatment. CONTACT-03 is the first randomized, phase III oncology trial to test the benefit of PD-(L)1 inhibitor continuation by direct addition to a standard control arm; the results prompt caution with this approach in other cancers. *Clinical trial information: NCT04338269.*

ABSTRACT4501- **Pembrolizumab plus axitinib versus sunitinib as first-line therapy for advanced clear cell renal cell carcinoma: 5-year analysis of KEYNOTE-426).** *Brian et al et al.*

METHODS: Adults with confirmed locally advanced or metastatic ccRCC with or without sarcomatoid features, no previous systemic therapy for metastatic ccRCC, KPS ≥70%, and ≥1 lesion measurable per RECIST v1.1 were randomly assigned 1:1 to receive pembro 200 mg IV Q3W for 35 doses (~2 y) + axi 5 mg PO BID or sun 50 mg PO QD on a 4-wk-on/2-wk-off schedule. Dual primary end points were OS and PFS per RECIST v1.1 by blinded independent central review (BICR). Secondary end points included ORR and DOR per RECIST v1.1 by BICR, and safety. A post hoc analysis adjusting for the effect of subsequent therapy on OS using a 2-stage adjustment model was conducted.

RESULTS: Of 861 enrolled patients (pts), 432 were assigned to pembro + axi and 429 to sun. Median study follow-up was 67.2 mo (range, 60.0-75.0). Efficacy for the ITT population and IMDC risk subgroups are shown in table. For pembro + axi vs sun, the 60-mo OS rates were 41.9% vs 37.1%, and the 60-mo PFS rates were 18.3% vs 7.3%. Median DOR (range) was 23.6 mo (1.4+ to 68.6+)

for pembro + axi and 15.3 mo (2.3-68.3) for sun. In pts who discontinued treatment, 237/381 pts (62.2%) in the pembro + axi arm and 300/406 pts (73.9%) in the sun arm received subsequent anticancer treatment. The HR for OS when adjusted for subsequent therapy was 0.67 (95% CI, 0.52-0.84). Clinical data on pts who completed 2 y of pembro will be presented. No new safety signals were observed.

CONCLUSIONS: After 5 y of follow-up, pembro + axi had sustained OS, PFS, and ORR benefits over sun in advanced ccRCC. These results are the longest follow-up to date of an anti–PD-1/L1 inhibitor + VEGFR TKI in this pt population and continue to support the use of pembro + axi as a 1L standard of care for advanced ccRCC. *Clinical trial information: NCT02853331.*

ABSTRACT 4502 **Final prespecified overall survival (OS) analysis of CLEAR: 4-year follow-up of lenvatinib plus pembrolizumab (L+P) vs sunitinib (S) in patients (pts) with advanced renal cell carcinoma (aRCC).**

Motzer RJ et al.

METHODS: Treatment-naïve pts (n=1069) who had aRCC with a clear-cell component were randomized (1:1:1) to receive: L 20 mg PO QD + P 200 mg IV Q3W; or L 18 mg + everolimus 5 mg PO QD; or S 50 mg PO QD (4 wks on/2 wks off). Stratification factors were GEOGRAPHIC REGION AND MSKCC PROGNOSTIC risk group. This final prespecified OS analysis was triggered by ~304 death events in 2 arms. OS, PFS, ORR, duration of response (DOR), and PFS on next-line therapy (PFS2) were assessed for L+P and S. PFS, ORR and DOR were assessed per independent review using RECIST v1.1. Nominal P-values are shown.

	L+P (n = 355)	S (n = 357)
OS HR vs S (95% CI); nominal *P*-value	0.79 (0.63–0.99); 0.0424	
Median OS, mos (95% CI)	53.7 (48.7–not estimable [NE])	54.3 (40.9–NE)
OS rate at 24 / 36 / 48 mos, %	80.4 / 66.4 / 55.9	69.6 / 60.2 / 52.5
PFS HR vs S (95% CI); nominal *P*-value	0.47 (0.38–0.57); <0.0001	
Median PFS, months (95% CI)	23.9 (20.8–27.7)	9.2 (6.0–11.0)
PFS rate at 24 / 36 / 48 mos, %	49.0 / 37.3 / 24.5	23.4 / 17.6 / 13.1
ORR relative risk vs S (95% CI); nominal *P*-value	1.94 (1.67–2.26); <0.0001	
ORR, % (95% CI); CR, %	71.3 (66.6–76.0); 18.3	36.7 (31.7–41.7); 4.8
Median DOR, mos (95% CI)	26.7 (22.8–34.6)	14.7 (9.4–18.2)

RESULTS: At a median follow-up (IQR) of 49.8 mos (41.4–53.1) for L+P and 49.4 mos (41.6–52.8) for S, 149 and 159 deaths had occurred, respectively. OS benefit with L+P vs S was maintained (HR, 95% CI; 0.79, 0.63–0.99). OS favored L+P vs S across MSKCC risk groups (HR, 95% CI; favorable [fav]: 0.89, 0.53–1.50; intermediate [int]: 0.81, 0.62–1.06; poor: 0.59, 0.31–1.12). PFS benefit of L+P vs S was maintained (HR, 95% CI; 0.47, 0.38–0.57). PFS favored L+P vs S across MSKCC risk groups (HR, 95% CI; fav: 0.46, 0.32–0.67; int: 0.51, 0.40–0.65; poor: 0.18, 0.08–0.42). ORR was greater with L+P (71.3%; complete response [CR], 18.3%) vs S (36.7%; CR, 4.8%) (relative risk, 95% CI; 1.94, 1.67–2.26). Less pts in the L+P arm (181/355, 51.0%) received subsequent anticancer therapies compared with the S arm (246/357, 68.9%); 56 (15.8%) and 195 (54.6%) received PD-1/PD-L1 checkpoint inhibitors, respectively. Analysis of OS adjusted for subsequent therapies will be presented. PFS2 was longer with L+P vs S (43.3 vs 25.9 mos; HR, 95% CI; 0.63, 0.51–0.77). Grade ≥3 treatment-related adverse events occurred in 74.1% and 60.3% pts in the L+P and S arms, respectively.

CONCLUSIONS: L+P continues to demonstrate clinically meaningful benefit vs S in OS, PFS, ORR, and CR in the 1L treatment of pts with aRCC at 4-yr follow-up, thus supporting the robustness of the primary analysis data from CLEAR. Clinical trial information: NCT02811861.

ABSTRACT 4506 - **Adjuvant nivolumab plus ipilimumab vs placebo for patients with localized renal cell carcinoma at high risk of relapse after nephrectomy: Subgroup analyses from the phase 3 CheckMate 914 (part A) trial.** *Motzer RJ et al.*

METHODS: Key study inclusion criteria were radical/partial nephrectomy with negative margins > 4 and ≤ 12 weeks before randomization; predominant clear cell histology; pathological TNM stage T2a (grade [G] 3/4) N0M0, T2b-T4 (any G) N0M0, or any pT (any G) N1M0;

		NIVO+IPI	PBO	DFS HR (95% CI)
Fuhrman grade	1-2	n = 136	n = 147	0.95 (0.58-1.57)
	2	n = 126	n = 136	0.97 (0.58-1.62)
	3	n = 189	n = 173	1.08 (0.73-1.60)
	4	n = 80	n = 91	0.72 (0.44-1.18)
NIVO+IPI exposure	≤ 6 cycles	n = 102	–	0.74 (0.48-1.13)
	> 6 cycles	n = 302	–	

CI, confidence interval; HR, hazard ratio.

and no evidence of residual disease/metastases. Pts in part A were randomized 1:1 to NIVO 240 mg Q2W (× 12) + IPI 1 mg/kg Q6W (× 4) or equivalent PBO for 24 weeks or until recurrence/unacceptable toxicity. Primary endpoint is DFS per blinded independent central review. Exploratory analyses assessed DFS by key subsets including Fuhrman grade, sarcomatoid features (yes/no), PD-L1 expression, and NIVO+IPI exposure (≤ 6 cycles [1–2 IPI doses] vs > 6 cycles [3–4 IPI doses]). Safety was assessed by exposure.

RESULTS: 816 pts were randomized to adjuvant NIVO+IPI (N = 405) or PBO (N = 411). At 37.0 months median follow-up (min, 15.4 months), subset analyses suggested a DFS benefit for NIVO+IPI vs PBO in pts with Fuhrman grade 4 or sarcomatoid features. DFS by PD-L1 expression will be reported in the presentation. Pts who received > 6 NIVO+IPI cycles trended toward improved DFS vs pts receiving ≤ 6 NIVO+IPI cycles. Of the 102 pts who received ≤ 6 NIVO+IPI cycles, 3% had sarcomatoid features, and 20% had Fuhrman grade 4; treatment discontinuation in these pts was due to study drug toxicity (75%), unrelated adverse events (AEs; 6%), pt request (5%), recurrence (4%), consent withdrawal/non-compliance (4%), or other (6%), and most pts receiving ≤ 6 NIVO+IPI cycles were discontinued without initial dose delay (NIVO, 84%; IPI, 89%). In the group of patients who received ≤ 6 NIVO+IPI cycles, grade 1–2 all-cause AEs were reported in 35% of pts (grade ≥ 3, 63%) and 31% of pts discontinued treatment due to grade 1–2 all-cause AEs (grade ≥ 3, 44%).

CONCLUSIONS: Exploratory analyses suggest that tumor grade and sarcomatoid features influence outcomes with adjuvant NIVO+IPI. Limited NIVO+IPI exposure (≤ 6 cycles) and discontinuation for low-grade AEs may have contributed to the lack of DFS benefit observed in CheckMate 914 part A. Clinical trial information: NCT03138512.

ABSTRACT 4518: **First-line lenvatinib + pembrolizumab treatment across non-clear cell renal cell carcinomas: Results of the phase 2 KEYNOTE-B61 study.**
Lee C-H et al.

METHODS: Adults with previously untreated advanced non-clear cell RCC and measurable disease per RECIST v1.1 received lenva 20 mg PO QD + pembro 400 mg IV Q6W for up to 18 cycles (~2 y). The primary end point was ORR per RECIST v1.1 by blinded independent central review (BICR). Secondary end points included DOR, DCR, and PFS per RECIST v1.1 by BICR; OS; and safety. Histology was assessed by investigator (assessment by central review is planned).

	Total N=158	Papillary n=93	Chromophobe n=29	Unclassified n=21	Translocatio n=6
ORR, % (95% CI)	49 (41-57)	54 (43-64)	28 (13-47)	52 (30-74)	67 (22-96)
DCR, % (95% CI)	82 (75-88)	85 (76-92)	69 (49-85)	90 (70-99)	83 (36-100)
CR, n (%)	9 (6)	8 (9)	0 (0)	0 (0)	0 (0)
PR, n (%)	69 (44)	42 (45)	8 (28)	11 (52)	4 (67)
SD, n (%)	52 (33)	29 (31)	12 (41)	8 (38)	1 (17)
PD, n (%)	17 (11)	9 (10)	4 (14)	2 (10)	1 (17)

RESULTS: Of 158 treated pts, 93 (59%), 29 (18%), and 21 (13%) had papillary, chromophobe, and unclassified histology, respectively. Additionally, 6 pts (4%) had translocation and 9 (6%) had other histology. 70 pts (44%) had IMDC favorable risk and 88 (56%) had intermediate/poor risk. Median follow-up was 14.9 mo (range 8.7-19.7). ORR was 49% (95% CI, 41-57; 9 CRs [6%]; 69 PRs [44%]). DCR was 82% (95% CI, 75-88). Median DOR was not reached (NR; range, 1.5+ to 15.3+ mo). By Kaplan-Meier estimate, 75% of responders had a response for ≥12 mo. ORR and DCR by histology are shown in the table. For the IMDC favorable risk group, ORR was 51% (95% CI, 39-64) and DCR was 87% (95% CI, 77-94). For the IMDC intermediate/poor risk group, ORR was 48% (95% CI, 37-59) and DCR was 78% (95% CI, 68-86). In all pts, median PFS and OS were 17.9 mo (95% CI, 13.5-NR) and NR (95% CI, NR-NR), respectively; 12-mo rates were 63% and 82%. Treatment-related AEs (TRAEs) occurred in 149 pts (94%) and were consistent with results from other studies. The most common (≥30%) TRAEs were hypertension (n=90; 57%), diarrhea (n=69; 44%), and hypothyroidism (n=58; 37%). Grade 3-4 TRAEs occurred in 81 pts (51%). Overall, 17 pts (11%) discontinued pembro, 14 (9%) discontinued lenva, and 5 (3%) discontinued both drugs because of TRAEs. No deaths occurred because of TRAEs..

CONCLUSIONS In pts with advanced non-clear cell RCC enrolled in KEYNOTE-B61, lenva + pembro showed antitumor activity with no new safety signals. These data support the use of lenva + pembro as first-line treatment for pts with non-clear cell RCC, regardless of histology.
Clinical trial information: NCT04704219.

ABSTRACT 4519 **Efficacy of first-line (1L) immunotherapy (IO)-based regimens in patients with sarcomatoid and/or rhabdoid (S/R) metastatic non-clear cell renal cell carcinoma (nccRCC): Results from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC).** *Labaki C et al.*

METHODS: Patients with advanced nccRCC treated with 1L IO regimens (IO/IO or IO/VEGF-TT) or 1L VEGF-TT monotherapy (sunitinib or pazopanib) were included. Cases were categorized as S/R or non-S/R. The primary outcomes were overall survival (OS) and time to treatment failure (TTF) in patients with S/R nccRCC receiving 1L IO or VEGF-TT. Overall response rate (ORR) was a secondary outcome. OS and TTF were compared between groups (IO vs. VEGF-TT) using Cox regression models adjusted for age, IMDC risk groups, and nccRCC subtype. ORR was compared between groups (IO vs. VEGF-TT) using a logistic regression adjusted for the same confounders.

BACKGROUND: Overall, 103 patients with S/R nccRCC were included, of whom 33 (32%) received 1L IO regimens. Median follow-up was 31 months. After adjustment for confounding factors, patients with S/R nccRCC treated with IO regimens presented with significantly improved survival outcomes as compared to those receiving VEGF-TT (median OS [mOS]: NR vs. 7.1 and mTTF: 9.4 vs. 2.9 mos for IO regimens and VEGF-TT, respectively). Similarly, a higher ORR was seen in patients with S/R nccRCC receiving IO regimens versus VEGF-TT (34.1 vs. 10.9%, respectively). Among 430 patients with non-S/R nccRCC (IO regimens: n=44), no significant differences in survival outcomes between regimen classes were seen (mOS: 24.4 vs. 14.8 and mTTF: 4.2 vs. 5.0 mos for IO regimens and VEGF-TT, respectively).

CONCLUSIONS: To our knowledge, this represents the largest effort to characterize the outcomes of patients with S/R nccRCC treated with IO regimens. Patients with S/R nccRCC appear to derive a substantial and selective benefit from IO regimens (vs. VEGF-TT). These data support the use of IO-based regimens in patients with S/R nccRCC.

OS, TTF and ORR in patients with S/R and non-S/R nccRCC treated with 1L IO regimens vs. VEGF-TT.

	Median OS – IO regimens, mos (95%CI)	Median OS – VEGF-TT, mos (95%CI)	Adjusted HR (95%CI)	Median TTF – IO regimens, mos (95%CI)	Median TTF – VEGF-TT, mos (95%CI)	Adjusted HR (95%CI)	ORR – IO regimens, %	ORR – VEGF-TT, %	p-value*
S/R nccRCC (N=103)	NR (19.3-NR)	7.1 (3.9-13)	0.25 (0.13-0.49)	9.4 (2.8-NR)	2.9 (2.2-4.3)	0.34 (0.21-0.59)	34.4	10.9	0.006
Non-S/R nccRCC (N=430)	24.4 (16.6-NR)	14.8 (12.7-18.1)	0.74 (0.46-1.21)	4.2 (2.8-12.9)	5.0 (4.4-5.7)	1.20 (0.85-1.71)	22.5	17.5	0.94

*Logistic regression.

ABSTRACT 4520: **Phase II study of cabozantinib (Cabo) with nivolumab (Nivo) and ipilimumab (Ipi) in advanced renal cell carcinoma with variant histologies (RCCvh).** *Martin H Voss et al.*

METHODS: Eligible patients (pts) had metastatic RCCvh with ECOG performance status of 0-1 and may have received one line of prior therapy excluding immunotherapy or Cabo. Pts underwent a baseline biopsy and received treatment with Nivo 3 mg/kg and Ipi 1 mg/kg intravenously Q3 weeks (W) for 4 cycles followed by Nivo 480 mg IV Q4W. Cabo was given continuously at dose of 40 mg daily; reductions to 20 mg daily and 20 mg every other day were allowed.

	Total (N=38)	Histology					Prior Systemic Therapy		Sarcomatoid differentiation	
	N (%)	Papillary (N=19)	Chromophobe (N=11)	Translocation (N=5)	Unclassified (N=1)	Other (N=2)	No (N=34)	Yes (N=4)	No (N=29)	Yes (N=9)
PR	8 (21%)	6	1	0	1	0	8	0	5	3
SD	19 (50%)	9	4	4	0	2	17	2	17	2
PD	9 (24%)	4	5	0	0	0	7	2	6	3
NE	2 (5%)	0	1	1	0	0	2	0	1	1

PR=partial response, SD=stable disease, PD=progressive disease, NE=not evaluable.

The primary endpoint was objective response rate (ORR) by RECIST 1.1. Safety was a secondary endpoint.

RESULTS: 40 pts have been enrolled. At the time of data cut-off (Dec 9, 2022), 38 pts received at least 1 study drug. 11% (n=4) pts received prior systemic therapy. 45% (n=17) received all 4 doses of Nivo and Ipi; 18% (n=7) received 3 and 37% (n=14) received ≤ 2 doses. 61% (n=23) (15 of whom received 4 cycles Nivo/Ipi) received Nivo maintenance (median number of cycles, 5 (range, 1-21)). 71% (n=27) and 13% (n=5) required Cabo dose reduction to 20 mg and 20 mg every other day, respectively. Median follow-up was 8.4 (range, 2.1-23) months. Objective response was achieved in 8 pts (ORR 21%, two-sided 80% CI, 13%-32%). Median duration of response was not reached with 5 pts maintaining response > 6 months. Median progression-free survival was 8.9 (95% CI, 4.2-12.7) months. 74% (n=28) developed treatment-related grade 3 or higher toxicities; 37% (n=14) developed ≥ grade 3 elevation in AST or ALT. 29% (n=11) required high dose steroids (prednisone ≥ 40 mg daily or

equivalent). 13% (n=5) discontinued all study drugs due to toxicity. No grade 5 toxicity has been reported.
CONCLUSIONS: The study suggests activity for this combination in patients with RCCvh particularly among those without chromophobe histology. An additional cohort of 20 pts is enrolling with Cabo starting dose of 20 mg daily. Clinical trial information: NCT04413123

ABSTRACT 4541 **Core biopsy (bx) accuracy and safety of biopsy and preoperative immunotherapy in predicting histological subtype and nuclear grade in ECOG-ACRIN EA8143 perioperative nivolumab (nivo) versus observation in patients (pts) with renal cell carcinoma (RCC) undergoing nephrectomy.**
Haas NB et al.
METHODS: Concordance of both core bx and primary tumor by site and central pathology review of histology and grade (1-2 vs 3-4) are reported, along with the Cohen's Kappa value, which measures the agreement and concordance (kappa=0 is no concordance and 1 is highest). AEs relating to core bxs and preoperative nivo, as well as time from enrollment to surgery for each arm, comparing pre- and post-amendment (dropping bx requirement in surgery alone arm) are also reported.
RESULTS: 387/404 pts in the nivo arm and 171/415 pts in the surgery alone arm had core bxs. 632 patients had both central pathology and site review available. 41 of all randomized patients (819) were considered as non-RCC and 26/41 were identified via bx. The median times from enrollment to surgery for nivo and control arms pre-amendment were 32d vs 19 d, and post-amendment were 21 d vs 14 d, respectively. The median (25th-75th percentile) number of days from last preoperative nivo to surgery was 14 d (9-20). AEs related to core bx, generally from bleeding, were reported in 13/558 (2.3%) pts. 2/13 bxs resulted in life-threatening complications. 21/353 (6%) of pts receiving nivo pre-surgery had ≥ grade 3-5 AE attributed to nivo. 181/353 (51%) pts had any grade AE attributed to nivo. Concordance between bxs and primary tumor pathologies for determining histological subtype was Kappa = 0.62. Agreement between central pathology and originating site review of primary tumor for determining nuclear grade was Kappa = 0.56, and concordance of histology was Kappa = 0.78.
CONCLUSIONS: The PROSPER trial use of core bxs in advance of neoadjuvant therapy was generally safe, largely consistent with primary tumor histology and grade, and did not delay resection of the primary tumor. AEs of preoperative nivo were consistent with nivo AEs in metastatic disease. This approach is valid for future neoadjuvant trials. Clinical trial information: NCT03055013.

ABSTRACT 4551 **CD8 cell PET imaging with 89-Zr-crefmirlimab berdoxam (crefmirlimab) in patients with metastatic renal cell carcinoma (mRCC) receiving checkpoint inhibitors (CPIs): Association with response and tissue CD8 expression.** *Pal SK et al.*
METHODS: Eligible pts had pathologically verified RCC, metastatic disease and an intent to initiate standard of care CPI therapy. Patients received crefmirlimab PET/CT within 1 wk of CPI infusion and 4-6 weeks after initiating therapy. Baseline biopsy was mandated, along with repeat biopsy 0-2 weeks following the second PET/CT scan. PET signal was characterized as SUVmax, SUVpeak and SUVmean of the biopsied lesions, up to 5 index lesions and representative CD8 avid lymph nodes. Mean SUVmax in responders and non-responders were compared using students t-test (1-sided). CD8 expression in tissue was characterized as the number of positive cells per mm2; PET avidity and CD8 expression were compared using the Spearman correlation coefficient.
RESULTS: 17 pts (9 M: 8 F) were enrolled; most pts had clear cell histology (12; 71%) followed by unclassified (3; 17%) and papillary (2; 12%). The most commonly rendered CPI-based regimens were nivolumab alone (6 pts; 35%) and cabozantinib/nivolumab (3 pts; 17%). Follow-up data was available in 15 of the patients. By RECIST v1.1, 3 of 15 patients were classified as responders (best overall response [BOR] of complete response or partial response) and 12 patients were classified as non-responders (BOR of stable disease or progressive disease). Average SUVmax, SUVpeak and SUVmean per patientamong all quantified index lesions and representative lymph nodes were 10.02, 6.95 and 6.11 for baseline and 8.82, 6.23 and 5.39 during treatment, respectively. Average SUVmax at baseline was 14.68 in responders to CPI and 8.28 in non-responders (P=0.006). On treatment SUVmax was 10.93 in responders to CPI and 8.22 in non-responders (P=0.19). A strong correlation between CD8 expression in baseline tissue and normalized SUVmean was observed (r=0.77; 95%CI 0.53-0.91).
CONCLUSIONS: To our knowledge, this is the first series in RCC to demonstrate that functional imaging of immune cells (here, CD8s) may segregate response to CPIs, with responders having a higher baseline SUV and a larger

decrement in SUV with therapy. Our results are bolstered by a significant correlation between tissue and imaging CD8 expression. Larger studies are underway to validate this noninvasive strategy. Clinical trial information: NCT03802123.

ABSTRACT 4554 **89Zr-DFO-girentuximab for PET/CT imaging of clear cell renal cell carcinoma: Results from phase 3 ZIRCON study.** *Shuch BM et al.*

METHODS: In this open label, multicenter trial, patients with an IDRM (≤7cm; cT1) who were scheduled for partial nephrectomy within 90 days from planned 89Zr-DFO-girentuximab administration were eligible. Enrolled patients received a single dose IV (37 MBq±10%; 10mg girentuximab) on Day 0 and underwent PET/CT imaging on Day 5 (±2d). Blinded central histology review determined ccRCC status. The co-primary objectives were to evaluate both the sensitivity and specificity of 89Zr-DFO-girentuximab 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 ≤4cm (cT1a). Other secondary objectives included positive and negative predictive values, and evaluation of 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 89Zr-DFO-girentuximab (mean age, 62±12y; 71% Male). Of 288 patients with central histopathology of surgical samples, 193 (67%) had ccRCC, and 179 (62%) had cT1a. Of 284 evaluable patients, the average across all 3 readers for sensitivity and specificity was 86% [80%, 90%] and 87% [79%, 92%] resp. for coprimary, and 85% [77%, 91%] and 90% [79%, 95%] resp. for key secondary endpoints. For all evaluable patients, positive and negative predictive values were ≥ 91.7% and ≥ 73.7%, resp. PET+ ccRCC had higher mean CAIX expression compared with PET- ccRCC patients ($p << 0.05$). Sensitivity and specificity were consistent with masses ≤2cm (n=46) of which, 26 were ccRCC+, 13 ccRCC–, and 3 unevaluable at central histopathology. Of 263 adverse events (AEs) in 124 patients, 2 AEs of mild intensity were treatment related.

CONCLUSIONS: ZIRCON study confirms 89Zr-DFO-girentuximab PET/CT is a well-tolerated and accurate modality for noninvasive identification of ccRCC in IDRM. This tool could be included in the diagnosis/management of patients with IDRM, limiting unnecessary treatment of benign lesions. Clinical trial information: NCT03849118.

ABSTRACT 4560 **Patient priorities and expectations of systemic therapy in metastatic renal cell carcinoma..** *Battle D, et al.*

METHODS: The survey was developed by the Kidney Cancer Research Alliance (KCCure) and was broadcast between 07/2022 and 09/2022 to patients via website, mailing lists and social media platforms. Those who agreed to participate were surveyed for demographics (age, gender, race, income, country) and clinical characteristics (date of the diagnosis, disease stage, treatment history). Descriptive statistics summarized the survey data.

RESULTS: 399 out of 1,062 patients surveyed had metastatic disease. 80% of patients were receiving or had received systemic therapy, 20% of patients had not yet received systemic therapy. 52% were female and 48% were male, with a median age of 57 years (range 28-86). Patients identified as white (89%) and living in the United States (86%). 69% of patients reported that they did not know their IMDC or risk status, 10% were favorable risk, 11% were intermediate risk and 10% were poor risk. When asked to select the most important outcome for treatment selection on a rank-choice scale from 1 to 8, the chance to eliminate all evidence of disease (complete response) scored highest (6.6), followed by durability of response (5.1), improved quality of life (5.0), rapid reduction of tumors (4.9), ability to go off therapy (4.2), low risk of toxicity (4.0) and reduction of tumor symptoms (4.0). Patients ranked low cost as the least important factor in selecting treatment (2.3). 70% of patients defined "long-term" response to therapy as five years or longer, and over a quarter of patients (26%) defined long-term response as 10 years or longer. When asked to define treatment success, patients rank radiological reduction in tumor size (83%) as the most important factor, followed by stable disease (67%), improved quality of life (48%) and the ability to return back to work (22%). The lowest ranked choice was "I just trust my doctor" (17%).

CONCLUSIONS: Most patients are not familiar with their risk classification and may not realize the significance of this factor in treatment selection. Patients rank complete response as the most important outcome/desire when considering treatment options. Cost is the least important factor for patients in selecting treatment. Patient perceptions of long-term response to therapy may differ from provider perceptions. More research is needed to improve patient/provider communication in the therapy selection process.

https://doi.org/10.52733/KCJ21n2-jc

Gemcitabine plus platinum-based chemotherapy in combination with bevacizumab for kidney metastatic collecting duct and medullary carcinomas: Results of a prospective phase II trial (BEVABEL-GETUG/AFU24). *Constance Thibault et al. Eur J Cancer . 2023 Jun;186:83-90. doi: 10.1016/j.ejca.2023.03.018.*

BACKGROUND: Renal medullary carcinoma (RMC) and collecting duct carcinoma (CDC) are rare entities with a poor outcome. First-line metastatic treatment is based on gemcitabine + platinum chemotherapy (GC) regimen but retrospective data suggest enhanced anti-tumour activity with the addition of bevacizumab. Therefore, we performed a prospective assessment of the safety and efficacy of GC + bevacizumab in metastatic RMC/CDC.

METHODS: We conducted a phase 2 open-label trial in 18 centres in France in patients with metastatic RMC/CDC and no prior systemic treatment. Patients received bevacizumab plus GC up to 6 cycles followed, for non-progressive disease, by maintenance therapy with bevacizumab until progression or unacceptable toxicity. The co-primary end-points were objective response rates (ORRs) and progression-free survival (PFS) at 6 months (ORR-6; PFS-6). PFS, overall survival (OS) and safety were secondary end-points. At interim analysis, the trial was closed due to toxicity and lack of efficacy.

RESULTS: From 2015 to 2019, 34 of the 41 planned patients have been enroled. After a median follow-up of 25 months, ORR-6 and PFS-6 were 29.4% and 47.1%, respectively. Median OS was 11.1 months (95% confidence interval [CI]: 7.6-24.2). Seven patients (20.6%) discontinued bevacizumab because of toxicities (hypertension, proteinuria, colonic perforation). Grade 3-4 toxicities were reported in 82% patients, the most common being haematologic toxicities and hypertension. Two patients experienced grade 5 toxicity (subdural haematoma related to bevacizumab and encephalopathy of unknown origin).

CONCLUSION: Our study showed no benefit for bevacizumab added to chemotherapy in metastatic RMC and CDC with higher than expected toxicity. Consequently, GC regimen remains a therapeutic option for RMC/CDC patients

Long-term Outcome With Prolonged Use of Interferon-alpha Administered Intermittently for Metastatic Renal Cell Carcinoma: A Phase II Study *Kankuri-Tammilehto et al. Anticancer Res. 2023 Jun;43(6):2645-2657.*

BACKGROUND: Interferon-alpha (IFN-alpha) has shown survival benefits in metastatic renal cell carcinoma (mRCC), but the knowledge about long-term outcome is sparse. Additional knowledge is beneficial because IFN-alpha usage in combination therapy such as immune checkpoint inhibitor for mRCC is an area of interest. This is the longest follow-up concerning IFN-alpha treatment.

METHODS: A total of 117 metastatic renal cell cancer (mRCC) patients without prior chemotherapy were enrolled between 1994-2002 and followed-up until January 2022. The median follow-up was 18 months. After progression to IFN-alpha, the patients were not treated with tyrosine kinase, mTOR inhibitors or bevacizumab as these were not standard therapies at that time or the patients' performance status was too poor. Mean treatment duration was 11 months.

FINDINGS: Median overall survival was 19.0 months, 5-year survival rate 16.2%, and 10-year survival rate 9.0%. There were statistically significant differences in survival in response to treatment (log-rank test, p<0.001): median overall survival was 52.0 months for objective responses, 25.0 months for stable disease and 5.0 months for progressive disease. Proportion of 5-year survivors was 29% in low, 20% in intermediate, and 7% in high-risk groups, respectively (p=0.001).

CONCLUSION: With prolonged INF-alpha treatment stable and responding patients can obtain late objective responses, long-lasting complete responses, and long-term outcome with acceptable toxicity. IFN-alpha is an alternative therapy when multiple treatment lines are used for mRCC and an interesting option to study for combined therapies such as immune checkpoint inhibitor-based therapies.

The role of immune checkpoint inhibitors (ICI) as adjuvant treatment in renal cell carcinoma (RCC): A systematic review and meta-analysis. *Marques Monteiro FM et al. Clin Genitourin Cancer. 2023 Jun;21(3):324-333.*

ABSTRACT: Pembrolizumab, a PD-1 ICI is approved for the adjuvant treatment of postnephrectomy patients with clear cell RCC in some countries worldwide. However, recent negative data from randomized clinical trials (RCT) with another ICIs makes the benefit of this treatment uncertain. A systematic review and study-level meta-analysis was performed to evaluate the benefit of disease-free survival (DFS) with adjuvant ICI treatment for patients with localized and/or metastatic resected RCC. Using the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement, a systematic search was performed in PUBMED/MEDLINE, Scopus and EMBASE up to September 15, 2022. The statistical analysis was performed by ProMeta 3 software in intention-to-treat (ITT) population and in predetermined subgroups. Four RCT totalizing 3407 patients were included in this analysis. Systemic immunotherapy was pembrolizumab, atezolizumab, nivolumab, and ipilimumab plus nivolumab in 496, 390, 404, and 405 patients, respectively. In the ITT population there was a nonstatistically significant DFS benefit with adjuvant ICI (HR: 0.85, 95% CI: 0.69-1.04). Regarding the subgroups, there was a DFS benefit for PD-L1 positive (HR: 0.72; 95% CI: 0.55-0.94), intermediate-high risk patients (HR: 0.77; 95% CI: 0.63-0.94), and patients with sarcomatoid component (HR: 0.66; 95% CI: 0.43-0.99). This meta-analysis did not demonstrate a statistically significant DFS benefit in overall population, however considering the heterogeneity between the RCTs the use of adjuvant ICI should be individualized.

Phase II trial of neoadjuvant sitravatinib plus nivolumab in patients undergoing nephrectomy for locally advanced clear cell renal cell carcinoma *Karam JA. Nat Commun. 2023 May 10;14(1):2684.*

ABSTRACT: Sitravatinib is an immunomodulatory tyrosine kinase inhibitor that can augment responses when combined with programmed death-1 inhibitors such as nivolumab. We report a single-arm, interventional, phase 2 study of neoadjuvant sitravatinib in combination with nivolumab in patients with locally advanced clear cell renal cell carcinoma (ccRCC) prior to curative nephrectomy (NCT03680521). The primary endpoint was objective response rate (ORR) prior to surgery with a null hypothesis ORR = 5% and the alternative hypothesis set at ORR = 30%. Secondary endpoints were safety; pharmacokinetics (PK) of sitravatinib; immune effects, including changes in programmed cell death-ligand 1 expression; time-to-surgery; and disease-free survival (DFS). Twenty patients were evaluable for safety and 17 for efficacy. The ORR was 11.8%, and 24-month DFS probability was 88·0% (95% CI 61.0 to 97.0). There were no grade 4/5 treatment-related adverse events. Sitravatinib PK did not change following the addition of nivolumab. Correlative blood and tissue analyses showed changes in the tumour microenvironment resulting in an immunologically active tumour by the time of surgery (median time-to-surgery: 50 days). The primary endpoint of this study was not met as short-term neoadjuvant sitravatinib and nivolumab did not

substantially increase ORR.

Phase II Study Investigating the Safety and Efficacy of Savolitinib and Durvalumab in Metastatic Papillary Renal Cancer (CALYPSO) *Cristina Suárez et al. 2023 J Clin Oncol. 2023 May 10;41(14):2493-2502.*

PURPOSE: Metastatic papillary renal cancer (PRC) has poor outcomes, and new treatments are required. There is a strong rationale for investigating mesenchymal epithelial transition receptor (MET) and programmed cell death ligand-1 (PD-L1) inhibition in this disease. In this study, the combination of savolitinib (MET inhibitor) and durvalumab (PD-L1 inhibitor) is investigated.
METHODS: This single-arm phase II trial explored durvalumab (1,500 mg once every four weeks) and savolitinib (600 mg once daily; ClinicalTrials.gov identifier: NCT02819596). Treatment-naïve or previously treated patients with metastatic PRC were included. A confirmed response rate (cRR) of > 50% was the primary end point. Progression-free survival, tolerability, and overall survival were secondary end points. Biomarkers were explored from archived tissue (MET-driven status).
RESULTS: Forty-one patients treated with advanced PRC were enrolled into this study and received at least one dose of study treatment. The majority of patients had Heng intermediate risk score (n = 26 [63%]). The cRR was 29% (n = 12; 95% CI, 16 to 46), and the trial therefore missed the primary end point. The cRR increased to 53% (95% CI, 28 to 77) in MET-driven patients (n/N = 9/27) and was 33% (95% CI, 17 to 54) in PD-L1-positive tumors (n/N = 9/27). The median progression-free survival was 4.9 months (95% CI, 2.5 to 10.0) in the treated population and 12.0 months (95% CI, 2.9 to 19.4) in MET-driven patients. The median overall survival was 14.1 months (95% CI, 7.3 to 30.7) in the treated population and 27.4 months (95% CI, 9.3 to not reached [NR]) in MET-driven patients. Grade 3 and above treatment related adverse events occurred in 17 (41%) patients. There was 1 grade 5 treatment-related adverse event (cerebral infarction).
CONCLUSION: The combination of savolitinib and durvalumab was tolerable and associated with high cRRs in the exploratory MET-driven subset.

First-line therapy for adults with advanced renal cell carcinoma: a systematic review and network meta-analysis. *Angela Aldin, Cochrane Database Syst Rev. 2023 May 4;5(5):CD013798.*

OBJECTIVES: To evaluate and compare the benefits and harms of first-line therapies for adults with advanced RCC, and to produce a clinically relevant ranking of therapies. Secondary objectives were to maintain the currency of the evidence by conducting continuous update searches, using a living systematic review approach, and to incorporate data from clinical study reports (CSRs).
Search methods: We searched CENTRAL, MEDLINE, Embase, conference proceedings and relevant trial registries up until 9 February 2022. We searched several data platforms to identify CSRs.
SELECTION CRITERIA: We included randomised controlled trials (RCTs) evaluating at least one targeted therapy or immunotherapy for first-line treatment of adults with advanced RCC. We excluded trials evaluating only interleukin-2 versus interferon-alpha as well as trials with an adjuvant treatment setting. We also excluded trials with adults who received prior systemic anticancer therapy if more than 10% of participants were previously treated, or if data for untreated participants were not separately extractable.
Data collection and analysis: All necessary review steps (i.e. screening and study selection, data extraction, risk of bias and certainty assessments) were conducted independently by at least two review authors. Our outcomes were overall survival (OS), QoL, serious adverse events (SAEs), progression-free survival (PFS), adverse events (AEs), the number of participants who discontinued study treatment due to an AE, and the time to initiation of first subsequent therapy. Where possible, analyses were conducted for the different risk groups (favourable, intermediate, poor) according to the International Metastatic Renal-Cell Carcinoma Database Consortium Score (IMDC) or the Memorial Sloan Kettering Cancer Center (MSKCC) criteria. Our main comparator was sunitinib (SUN). A hazard ratio (HR) or risk ratio (RR) lower than 1.0 is in favour of the experimental arm.
RESULTS: We included 36 RCTs and 15,177 participants (11,061 males and 4116 females). Risk of bias was predominantly judged as being 'high' or 'some concerns' across most trials and outcomes. This was mainly due to a lack of information about the randomisation process, the blinding of outcome assessors, and methods for outcome measurements and analyses. Additionally, study protocols and statistical analysis plans were rarely available. Here we present the results for our primary outcomes OS, QoL, and SAEs, and for all risk groups combined for contemporary treatments: pembrolizumab + axitinib (PEM+AXI), avelumab + axitinib (AVE+AXI), nivolumab + cabozantinib (NIV+CAB), lenvatinib + pembrolizumab (LEN+PEM), nivolumab + ipilimumab (NIV+IPI), CAB, and pazopanib (PAZ). Results per risk group and results for our secondary outcomes are reported in the summary of findings tables and in the full text of this review. The evidence on other treatments and comparisons can also be found in the full text. Overall survival (OS) Across risk groups, PEM+AXI (HR 0.73, 95% confidence interval (CI) 0.50 to 1.07, moderate certainty) and NIV+IPI (HR 0.69, 95% CI 0.69 to 1.00, moderate certainty) probably improve OS, compared to SUN, respectively. LEN+PEM may improve OS (HR 0.66, 95% CI 0.42 to 1.03, low certainty), compared to SUN. There is probably little or no difference in OS between PAZ and SUN (HR 0.91, 95% CI 0.64 to 1.32, moderate certainty), and we are uncertain whether CAB improves OS when compared to SUN (HR 0.84, 95% CI 0.43 to 1.64, very low certainty). The median survival is 28 months when treated with SUN. Survival may improve to 43 months with LEN+PEM, and probably improves to: 41 months with NIV+IPI, 39 months with PEM+AXI, and 31 months with PAZ. We are uncertain whether survival improves to 34 months with CAB. Comparison data were not available for AVE+AXI and NIV+CAB. Quality of life (QoL) One RCT measured QoL using FACIT-F (score range 0 to 52; higher scores mean better QoL) and reported that the mean post-score was 9.00 points higher (9.86 lower to 27.86 higher, very low certainty) with PAZ than with SUN. Comparison data were not available for PEM+AXI, AVE+AXI, NIV+CAB, LEN+PEM, NIV+IPI, and CAB. Serious adverse events (SAEs) Across risk groups, PEM+AXI probably increases slightly the risk for SAEs (RR 1.29, 95% CI 0.90 to 1.85, moderate certainty) compared to SUN. LEN+PEM (RR 1.52, 95% CI 1.06 to 2.19, moderate certainty) and NIV+IPI (RR 1.40, 95% CI 1.00 TO 1.97, moderate certainty) probably increase the risk for SAEs, compared to SUN, respectively. There is probably little or no difference in the risk for SAEs between PAZ and SUN (RR 0.99, 95% CI 0.75 to 1.31, moderate certainty). We are uncertain whether CAB reduces or increases the risk for SAEs (RR 0.92, 95% CI 0.60 to 1.43, very low certainty) when compared to SUN. People have a mean risk of 40% for experiencing SAES when treated with SUN. The risk increases probably to: 61% with LEN+PEM, 57% with NIV+IPI, and 52% with PEM+AXI. It probably remains at 40% with PAZ. We are uncertain whether the risk reduces to 37% with CAB. Comparison data were not available for AVE+AXI and NIV+CAB.

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