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

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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.

Introduction

The 2023 American Society of Clinical Oncology (ASCO) Annual Meeting, held from June 2 to 6 at the McCormick Center in Chicago, Illinois, drew a diverse and large group of participants including medical providers, industry leaders, researchers, patient advocates, and cancer foundations. Over 12,000 scientific studies were presented, covering a broad spectrum of cancer types and stages of care. This report focuses on the critical findings and discussions related to renal cell carcinoma (RCC). The full conference proceedings can be accessed through the ASCO website.

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.

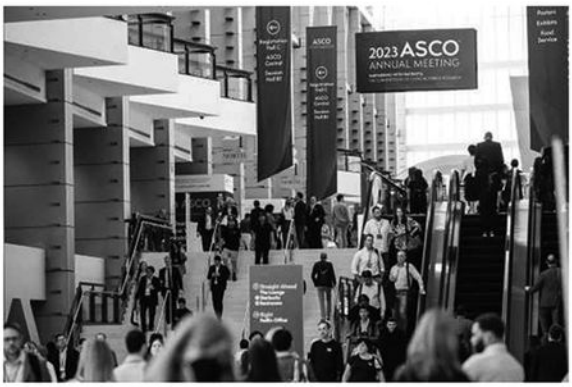
Innovative work in the preclinical setting was also reported at the conference. Dr. Barisic presented a poster titled “T cell receptor-engineered T cells targeting a human endogenous retrovirus in kidney cancer” (Abstract #4542). The team developed a T-cell receptor-engineered T-cell that targets the 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+ PDi+ 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 10 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 aceticacid 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. Here-in 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.

REFERENCES:

1. Kashima S &Braun DA The Changing Landscape of Immunotherapy for Advanced Renal Cancer. Urologic Clinics 50, 335–349 (2023). [PubMed: 36948676]
2. Rini BI et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. New England Journal of Medicine 380, 1116–1127 (2019). [PubMed: 30779529]
3. Motzer R. et al. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. New England Journal of Medicine 384, 1289–1300 (2021). [PubMed: 33616314]

4. Albiges L. et al. Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial. ESMO Open 5, e001079 (2020). [PubMed: 33246931]
5. Pal SK et al. Atezolizumab plus cabozantinib versus cabozantinib monotherapy for patients with renal cell carcinoma after progression with previous immune checkpoint inhibitor treatment (CONTACT-03): a multicentre, randomised, open-label, phase 3 trial. The Lancet o, (2023).
6. Zoumpourlis P, Genovese G, Tannir NM & Msaouel P, Systemic Therapies for the Management of Non–Clear Cell Renal Cell Carcinoma: What Works, What Doesn't, and What the Future Holds. Clin Genitourin Cancer 19, 103–116 (2021). [PubMed: 33358151]
7. Motzer RJ et al. Adjuvant nivolumab plus ipilimumab versus placebo for localised renal cell carcinoma after nephrectomy (CheckMate 914): a double-blind, randomised, phase 3 trial. The Lancet 401, 821–832 (2023).
8. Tannir NM et al. Efficacy and safety of nivolumab plus ipilimumab versus sunitinib in first-line treatment of patients with advanced sarcomatoid renal cell carcinoma. Clinical Cancer Research 27, 78–86 (2021). [PubMed: 32873572]
9. Atkins MB et al. Phase II Study of Nivolumab and Salvage Nivolumab/Ipilimumab in Treatment-naive Patients with Advanced Clear Cell Renal Cell Carcinoma (HCRN GU16-260-Cohort A). Journal of Clinical Oncology 373, (2022).
10. Pignon JC et al. Irrecist for the evaluation of candidate biomarkers of response to nivolumab in metastatic clear cell renal cell carcinoma: Analysis of a phase II prospective clinical trial. Clinical Cancer Research 25, 2174–2184 (2019). [PubMed: 30670497]
11. Saliby RM et al. Circulating and intratumoral immune determinants of response to atezolizumab plus bevacizumab in patients with variant histology or sarcomatoid renal cell carcinoma. Cancer Immunol Res (2023) doi:10.1158/2326-6066.CIR-22-0996.
12. Motzer RJ et al. Molecular Subsets in Renal Cancer Determine Outcome to Checkpoint and Angiogenesis Blockade. Cancer Cell 38, 803–817.e4 (2020). [PubMed: 33157048]
13. Dizman N. et al. Nivolumab plus ipilimumab with or without live bacterial supplementation in metastatic renal cell carcinoma: a randomized phase 1 trial. Nature Medicine 2022 28:428, 704–712 (2022).