short review

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Renal cell carcinoma

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Summary Kidney cancer accounts for 5% and 3% of all adult malignancies in men and women. Renal cell carcinoma (RCC) accounts for approximately 80% of all kidney cancer. This year's American Society of Clinical Oncology (ASCO) Annual Meeting was held from 2–6 June 2023, in Chicago, USA. Combination therapies for advanced RCC continue to be of interest at ASCO 2023, with the presentation of updated results from some ongoing studies. There were several studies presented at ASCO looking at treatments for non clear renal cell carcinoma. Immunotherapy- based therapy regimes are now the gold standard for rare histological subtypes of RCC.

Keywords IMDC risk groups · Combination therapies · Triplet therapy · Non-clear renal cell carcinoma · Metastasis

This year's annual meeting of the American Society of Clinical Oncology (ASCO) was held from June 2–6, 2023 in Chicago, IL, USA. The focus of this year's ASCO was combination therapies and the search for innovative treatment regimens with the main question: what is the ideal combination regime in front-line setting for advanced/metastatic renal cell carcinoma?

Front-line treatment of advanced/metastatic renal cell carcinoma

Sustained benefit for all IMDC risk groups?

Metastatic renal cell carcinoma (mRCC) is usually, depending on risk classification and on the performance status, treated with a combination of tumor-specific drugs, either two infusions of immunotherapy (IO) with nivolumab and ipilimumab or combination immunotherapy with avelumab, pembrolizumab or nivolumab plus a vascular endothelial growth factor receptor (VEGFR). However, tyrosine kinase inhibitor (TKI) monotherapy is the first-choice alternative therapy if IO is not tolerated or inapplicable.

At the 2023 ASCO annual meeting, the final prespecified overall survival (OS) analysis of the phase 3 CLEAR trial was presented. The extended 4-year follow-up of lenvatinib plus pembrolizumab showed sustained superiority over sunitinib for OS and progression-free survival (PFS) in previously untreated advanced kidney cancer patients [1, 2].

However, the difference between survival for the combination compared to sunitinib had decreased significantly. The average time to when the cancer started growing again was nearly 2 years with combination therapy, compared to just over 9 months for sunitinib. Reasons for this may be the effect of following treatments, stopping pembrolizumab at 2 years, or patients coming off combination treatment because of side effects or other reasons. Nearly three quarters of patients on the tyrosine kinase inhibitor IO combination arm had serious or, much more rarely, life-threatening side effects compared to 60% of patients on sunitinib.

There are demonstrated benefits to lenvatinib plus pembrolizumab in all risk groups, but the impact of this combination and other combinations—whether ipilimumab plus nivolumab or other IO/TKI combinations—on OS in this setting is much smaller in the favorable-risk vs the intermediate- and poor-risk subgroups. (Tables 1, 2 and 3).

In another presentation, Dr. Brian Rini discussed the 5-year analysis of KEYNOTE-426, a phase 3 study, assessing pembrolizumab plus axitinib vs sunitinib as

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Table 1 Memorial Sloan Kettering Cancer Center (MSKCC/Motzer) score

Karnofsky performance status < 80%
Time from diagnosis to systemic treatment < 1 year
Hemoglobin < lower limit of normal
Calcium > 10 mg/dL (> 2.5 mmol/L)
LDH > 1.5 × upper limit of normal normal: 140 U/L
LDH Lactate dehydrogenase

Table 2 International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic score

Karnofsky performance status
< 1 year from time of diagnosis to systemic therapy
Hemoglobin < lower limit of normal usually ~120 g/L or 12 g/dL
Corrected calcium > upper limit of normal usually ~8.5–10.2 mg/dL
Neutrophils > upper limit of normal usually ~2.0–7.0 × 10^9/L
Platelets > upper limit of normal usually ~150,000–400,000 cells/μL

first-line therapy for advanced clear cell renal cell carcinoma [4, 5].

KEYNOTE-426 represents the longest follow-up to date of the combination of an IO plus a VEGFR/TKI in the first-line setting. A substantial percentage of patients completed 35 cycles of pembrolizumab with good long-term outcomes.

At the prolonged analysis (median follow-up 67.2 months), first-line pembrolizumab plus axitinib showed statistically significant PFS in the intention-to-treat (ITT) population continued to favor pembrolizumab plus axitinib vs sunitinib (hazard ratio [HR] 0.69, 95% confidence interval [CI] 0.59–0.81). The 60-month PFS rates were 18.3% vs 7.3%, respectively.

The reported OS (HR 0.53, 95% CI 0.38–0.74), the reported PFs and the ORR in the entire population was (HR 0.69, 95% CI 0.57–0.84), and objective response rates (ORR; 59.3% vs 35.7%) over sunitinib for advanced clear cell carcinoma [4].

The doublet induced an ORR of 60.6% in the ITT population, which comprised a complete response (CR) rate of 11.6%, a partial response (PR) rate of 46.1%, and a stable disease (SD) rate of 22.7%; 11.6% of patients experienced disease progression.

Among patients with IMDC favorable-risk disease, there was no difference in OS (HR 1.10, 95% CI 0.79–1.54) or PFS (HR 0.76, 95% CI 0.57–1.02) for pembrolizumab plus axitinib vs sunitinib, with a slight benefit for pembrolizumab plus axitinib (68.8%) vs sunitinib (50.4%) with regard to ORR. Contrarily, among patients with IMDC intermediate/poor risk disease, there was a significant benefit in OS (HR 0.76, 95% CI 0.62–0.93) and PFS (HR 0.68, 95% CI 0.56–0.82) for IO/TKI combination vs TKI monotherapy [4].

It should be noted that this is the longest follow-up of a TKI/IO combination study showing that some patients in the front-line setting receiving the IO/TKI combination are going to have durable disease control rate.

Thus, there is a demonstrated benefit of TKI/IO combinations in all risk groups, but the impact of this combination or other combinations, ipilimumab plus nivolumab, on OS in this setting is much smaller in the favorable-risk versus intermediate- and poor-risk subgroups, which is why none of these studies can help us answer the critical question of which combination of treatments is best for an individual patient with advanced/metastatic RCC.

Second-line therapy and beyond …

Atezolizumab plus cabozantinib vs. cabozantinib monotherapy

The CONTACT-03 study was designed to look at the effectiveness of IO plus TKI after failure of previous IO treatment. One of the most pressing questions across the RCC treatment landscape is whether IO could still play a role in the treatment of patients following progression on a prior immune checkpoint inhibitor [6].

There were multiple lines of retrospective evidence and small prospective studies, including a phase 2 trial that hinted at a benefit of IO therapy given post-IO, using either anti-PD-1 therapy again or anti-PD-L1 therapy after progression on a prior similar therapy. This preliminary evidence suggested that it might be a viable strategy and the perfect setup for a randomized phase 3 clinical trial.

Data from the CONTACT-3 study show that PFS was not significantly different between the atezolizumab plus cabozantinib arm vs cabozantinib monotherapy arm (10.6 vs 10.8 months; stratified HR 1.03; $P = 0.784$). Therefore, the study did not meet its primary end-

Table 3 IMDC (International Metastatic Renal Cell Carcinoma [mRCC] Database Consortium) risk model for mRCC

Risk profile	Prognosis	Median OS [3]	OS after 2 years [3] (%)
0	Favorable	43.2 months	63–81
1–2	Intermediate	22.5 months	40–50
2–6	Poor	7.8 months	9–14

OS overall survival

point. The 12-month PFS rates were 44% and 48% in the 2 arms, respectively [6].

The side effects of the combination of atezolizumab plus cabozantinib were similar to those observed when the medicines were taken alone. Furthermore, there were more side effects in patients who took the combination therapy than in patients who took cabozantinib alone.

Although the results from this study are negative, they could potentially change clinical practice with respect to the type of second-line treatment. It will encourage researchers to look at other treatment combinations for patients who failed to respond to IO.

For now, the recommendations are to use a targeted therapy like cabozantinib alone in most cases when initial treatment with combination therapy stops working. Atezolizumab may not have been the ideal checkpoint inhibitor to partner with cabozantinib, given its lack of success in multiple randomized phase 3 trials in the metastatic and adjuvant settings of RCC and mRCC.

Promising treatments for rare renal cell cancer subtypes

There were several studies presented at ASCO looking at treatments for non-clear cell forms of renal cell cancer this year.

Non-clear cell renal cell cancer comprises about 20–25% of all renal cell cancer diagnoses and includes various subtypes like papillary, chromophobe, translocation and unclassified tumors. Non-clear cell renal cell carcinoma (ncRCC) usually has a poorer survival rate than clear cell renal cell cancer. The identification of an effective treatment for advanced non-clear cell renal cell cancer remains an unmet need.

Dr. Bradley McGregor presented the results of the phase 2 COSMIC-313 study of cabozantinib with nivolumab and ipilimumab in advanced renal cell carcinoma with variant histology (RCCvh) [7].

Triplet therapy of cabozantinib with nivolumab and ipilimumab improved PFS over IO /IO combination therapy alone in patients with clear renal cell carcinoma (cRCC) but the survival data remains immature. This combination of three anticancer medicines is being studied in patients with advanced non-clear cell renal cell cancer in a different phase 2 study.

In all, 40 patients were recruited for this study. Most patients had papillary (19), chromophobe (11) or translocation (5) renal cell cancer. One in 10 patients had received previous treatment with targeted therapy, excluding cabozantinib and immunotherapy. Based on this, the authors conclude that this triplet therapy appears to have clinically meaningful activity in a subset of patients with RCCvh. However, it should be noted that with significant dose reduction and a large proportion of patients having adverse effects, the benefit may be limited by toxicity and ability to receive the full dose of therapy. The dose reductions (TRAEs) were high.

Furthermore, 74% developed treatment-related grade 3 or higher toxicities. This included 37% ($n=14$) who developed ≥ grade 3 elevation in AST or ALT, while 29% ($n=11$) required high-dose steroids (prednisone ≥ 40 mg daily or equivalent).

This study shows that the triple combination of nivolumab, ipilimumab and cabozantinib showed some benefit in patients with ncRCC, especially when compared to other treatments like nivolumab plus cabozantinib, or lenvatinib plus pembrolizumab. However, the trial is ongoing, and a further 20 patients are being recruited and treated with a lower starting dose of cabozantinib (20 mg/day). Ongoing trials should seek to balance increased efficacy with manageable toxicity based on the safety profile and novel mechanism.

Are combination therapies the future?

There have been many advances in the treatment of mRCC in the past decade, and it continues to rapidly evolve, with various combinations improving outcomes in the first-line setting and especially beyond. Risk stratification of patients into favorable-, intermediate-, and poor-risk categories is now routinely performed. Combination therapies were of interest at ASCO 2023, with the presentation of updated results from some ongoing studies.

Take home message

- Combination therapies remain standard in the frontline setting.
- Advanced renal cell carcinoma with variant histology (RCCvh): immunotherapy-based combination therapy has become standard.

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