Management of Metastatic Renal Clear Cell Cancer

ASCO Guideline Rapid Recommendation Update

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1 Background & Methodology

Introduction

- In 2022, ASCO published a guideline on the management of metastatic renal clear cell cancer (ccRCC).[1]
- At that time, no recommendations for or against triplet therapy in this setting were made as that option was not available at that time.
- Since then, results of the phase 3 COSMIC 313 trial by Choueiri TK et al,[2] that compared ipilimumab, nivolumab, cabozantinib, (IpiNivoCabo) against matched placebo with ipilimumab and nivolumab have been published, providing the signal to update the 2022 guideline.

Development Methodology

- The COSMIC 313 trial[2] is the only trial that informs this rapid recommendation update (literature search updated August 18, 2023).
- The Expert Panel reconvened to assess evidence and to review and approve the amended guideline.
- The ASCO Guideline methodology manual can be found at: www.asco.org/guideline-methodology

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2 Rapid Recommendation Update

Rapid Recommendation Update

Recommendation 3.6

- Treatment with IpiNivoCabo is not recommended for patients with metastatic ccRCC. Patients interested in triplet therapy should enroll in a clinical trial.

Evidence-based harms outweigh the benefits (harms of IpiNivoCabo outweigh the benefits)	
Evidence Quality	**Strength of Recommendation**
High	Strong

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3 Summary of Previous Recommendations

Summary of Previous Recommendations

- Recommendations that are unchanged are provided in the following slides

Summary of Previous Recommendations

Clinical Question 1

- How is metastatic clear cell renal cell carcinoma defined and how is it diagnosed?

Recommendation 1.1

- The diagnosis of metastatic clear cell renal cell carcinoma should ideally involve comparison of tissue acquired outside the site of primary disease to the primary histology. Histologic evaluation should include common markers of clear cell renal cell carcinoma including paired box gene 8 (PAX8) and Carbonic anhydrase IX (CAIX).

Evidence based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
High	Strong

Summary of Previous Recommendations

Recommendation 1.2

- Radiographic diagnosis of metastatic clear cell renal cell carcinoma may be applied in selected circumstances, such as settings in which a prior diagnosis of renal cell carcinoma has been established, when metastatic tissue is not readily accessible by biopsy, or when RECIST 1.1 measurable disease is evident, especially within a year of the initial diagnosis.

Consensus based
benefits outweigh harms

Evidence Quality	Strength of Recommendation
Low	Weak

Summary of Previous Recommendations

Clinical Question 2

- What is the role of cytoreductive nephrectomy in metastatic clear cell renal cell carcinoma?

Recommendation 2.1

- Select patients (see *Practical Information*) with metastatic clear cell renal cell carcinoma may be offered cytoreductive nephrectomy.
- *Practical Information: Select patients include those with optimally 1 IMDC risk factor who can have a significant majority of their tumor burden removed at the time of surgery.*

Evidence based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
High	Strong

Summary of Previous Recommendations

Clinical Question 3

- What are the preferred options for first line systemic treatment of metastatic clear cell renal cell carcinoma?

Recommendation 3.1

- Select patients with metastatic clear cell renal cell carcinoma (see Practical Information) may be offered an initial active surveillance strategy.
- *Practical Information: Select patients include those with IMDC favorable and intermediate risk, patients with limited or no symptoms related to disease, a favorable histologic profile, a long interval between nephrectomy and the development of metastasis or with limited burden of metastatic disease.*

Evidence based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Summary of Previous Recommendations

Recommendation 3.2

- All patients with metastatic clear cell renal cell carcinoma who require systemic therapy in the first line setting should undergo risk stratification into IMDC favorable (0), intermediate (1-2), and poor (3+) risk groups.[3] Patients with intermediate or poor risk disease should be offered combination treatment with two immune checkpoint inhibitors (i.e., ipilimumab and nivolumab) or an immune checkpoint inhibitor in combination with a VEGFR TKI.

Evidence based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
High	Strong

Summary of Previous Recommendations

Recommendation 3.3

- Patients with favorable risk disease who require systemic therapy may be offered an immune checkpoint inhibitor in combination with a VEGFR TKI.

Evidence based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
High	Strong

Recommendation 3.4

- Select patients with metastatic clear cell renal cell carcinoma receiving systemic therapy in the first-line setting including those with favorable risk disease or with certain co-existing medical problems may be offered monotherapy with either a VEGFR TKI or an immune checkpoint inhibitor.

Evidence based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Summary of Previous Recommendations

Recommendation 3.5

- The use of high dose Interleukin-2 (HD-IL2) may be considered in the first-line systemic therapy setting for patients with metastatic clear cell renal cell carcinoma (see *Practical Information*). Attempts to develop criteria to predict those patients most likely to derive benefit from HD-IL2 have been unsuccessful.

Evidence based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
Moderate	Weak

- *Practical Information: The significant toxicity of this regimen must be weighed in relation to the newer immunotherapy regimens which have largely replaced this treatment. The expert panel was not able to identify a patient population who should receive this treatment preferentially based on available data. The expert panel did agree that HD-IL2 should be administered in experienced high-volume centers, and that enrollment in clinical trials was preferred.*

Summary of Previous Recommendations

Clinical Question 4

- What is the optimal second or later line systemic treatment for metastatic clear cell renal cell carcinoma?

Recommendation 4.1

- Nivolumab or cabozantinib should be offered to patients who progressed on a VEGFR TKI alone.

Evidence based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
High	Strong

Summary of Previous Recommendations

Recommendation 4.2

- Patients progressing on combination immunotherapy (e.g. nivolumab, ipilimumab) should be offered a VEGFR TKI.

Consensus based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Recommendation 4.3

- Patients who progress after initial therapy combining VEGFR TKI with an immune checkpoint inhibitor may be offered an alternate VEGFR TKI as a single agent.

Evidence based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
High	Strong

Summary of Previous Recommendations

Recommendation 4.4

- For patients on immunotherapy who experience limited disease progression (e.g., one site of progression), local therapy (radiation, thermal ablation, excision) may be offered, and immunotherapy may be continued.

Evidence based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
Moderate	Weak

Summary of Previous Recommendations

Clinical Question 5

- What is the optimal application of metastasis directed therapy for metastatic clear cell renal cell carcinoma?

Recommendation 4.1

- For patients with low volume metastatic renal cell carcinoma, definitive metastasis-directed therapies may be offered and include surgical resection (metastasectomy), ablative measures, or radiotherapy.

Evidence based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Summary of Previous Recommendations

Recommendation 5.2

- For patients undergoing complete metastasectomy subsequent TKIs are not routinely recommended.

Evidence based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Summary of Previous Recommendations

Clinical Question 6

- What considerations should be applied to treatment of special subsets of metastatic clear cell renal cell carcinoma? (e.g., bone metastases, brain metastases, sarcomatoid carcinomas)

Recommendation 6.1.1

- Patients with symptomatic bone metastases from metastatic clear cell renal cell carcinoma should receive bone-directed radiation.

Consensus based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Summary of Previous Recommendations

Recommendation 6.1.2

- Patients with bone metastases from metastatic clear cell renal cell carcinoma should be offered a bone resorption inhibitor (either bisphosphonate or RANKL inhibitor) when clinical concern for fracture or skeletal related events is present.

Consensus based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Recommendation 6.1.3

- No recommendation regarding optimal systemic treatment for metastatic clear cell renal cell carcinoma patients with bone metastasis can be made; however, it is our expert opinion that cabozantinib-containing regimens may be preferred.

Consensus based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
Low	Moderate

Summary of Previous Recommendations

Recommendation 6.2.1

- Patients with brain metastases from metastatic clear cell renal cell carcinoma should receive brain-directed local therapy with radiation therapy and/or surgery.

Consensus based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
High	Strong

Recommendation 6.2.2

- No recommendation regarding optimal systemic therapy for patients with metastatic clear cell renal cell carcinoma and brain metastases can be made.

Consensus based benefits to harms ratio unknown	
Evidence Quality	**Strength of Recommendation**
N/A	Strong

Summary of Previous Recommendations

Recommendation 6.3

- Patients with metastatic clear cell renal cell carcinoma with sarcomatoid features should receive immune checkpoint inhibitor-based combination first-line treatment (ipilimumab plus nivolumab, or alternatively, an immune checkpoint inhibitor plus a TKI).

Evidence based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
High	Strong

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4 Additional Information

Additional Resources

- More information, including clinical tools and resources, is available at www.asco.org/genitourinary-cancer-guidelines

- Patient information is available at www.cancer.net

Guideline Panel Members

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Abbreviations

- ASCO, American Society of Clinical Oncology
- CAIX, carbonic anhydrase IX
- ccRCC, clear cell renal cell carcinoma
- HD-IL2, high dose interleukin-2
- IMDC, International Metastatic RCC Database Consortium
- IpiNivoCabo, ipilimumab, nivolumab, cabozantinib
- PAX8, paired box gene 8
- RANKL, receptor activator of nuclear factor kappa-B ligand
- RCC, renal cell carcinoma
- RECIST, Response Evaluation Criteria in Solid Tumours
- TKI, tyrosine kinase inhibitor
- VEGFR, vascular endothelial growth factor receptor

References

1. Rathmell WK, Rumble RB, Van Veldhuizen PJ, et al: Management of Metastatic Clear Cell Renal Cell Carcinoma: ASCO Guideline. J Clin Oncol 40:2957-2995, 2022
2. Choueiri TK, Powles T, Albiges L, et al: Cabozantinib plus Nivolumab and Ipilimumab in Renal-Cell Carcinoma. N Engl J Med 388:1767-1778, 2023
3. Heng DY, Xie W, Regan MM, et al: External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium

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