

## Management of Metastatic Renal Clear Cell Cancer: ASCO Guideline Rapid Recommendation Update

Recommendation	Type	Evidence Quality	Strength
3.6. Treatment with IpiNivoCabo is not recommended for patients with metastatic ccRCC. Patients interested in triplet therapy should enroll in a clinical trial.	EB	H	S

**Abbreviations.** ccRCC, renal clear cell cancer; IpiNivoCabo, ipilimumab, nivolumab, cabozantinib

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How is metastatic clear cell renal cell carcinoma defined and how is it diagnosed?	<b>1.1.</b> 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).	EB	H	S
	<b>1.2.</b> 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.	CB	L	W
What is the role of cytoreductive nephrectomy in metastatic clear cell renal cell carcinoma?	<b>2.1.</b> Select patients (see <i>Practical Information</i> ) with metastatic clear cell renal cell carcinoma may be offered cytoreductive nephrectomy.	EB	H	S
	<i>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.</i>			
What are the preferred options for first line systemic treatment of metastatic clear cell renal cell carcinoma?	<b>3.1.</b> Select patients with metastatic clear cell renal cell carcinoma (see <i>Practical Information</i> ) may be offered an initial active surveillance strategy.	EB	M	S
	<i>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.</i>			
	<b>3.2.</b> 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. <sup>1</sup> 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.	EB	H	S

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	<b>3.3.</b> Patients with favorable risk disease who require systemic therapy may be offered an immune checkpoint inhibitor in combination with a VEGFR TKI.	EB	H	S
	<b>3.4.</b> 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.	EB	M	S
	<b>3.5.</b> 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 <i>Practical Information</i> ). Attempts to develop criteria to predict those patients most likely to derive benefit from HD-IL2 have been unsuccessful.	EB	M	W
	<i>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-IL-2 should be administered in experienced high-volume centers, and that enrollment in clinical trials was preferred.</i>			
What is the optimal second or later line systemic treatment for metastatic clear cell renal cell carcinoma?	<b>4.1.</b> Nivolumab or cabozantinib should be offered to patients who progressed on a VEGFR TKI alone.	EB	H	S
	<b>4.2.</b> Patients progressing on combination immunotherapy (e.g. nivolumab, ipilimumab) should be offered a VEGFR TKI.	CB	M	S
	<b>4.3.</b> 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.	EB	H	S
	<b>4.4.</b> 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.	EB	M	W
What is the optimal application of metastasis directed therapy for metastatic clear cell renal cell carcinoma?	<b>5.1.</b> 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.	EB	M	S
	<b>5.2.</b> For patients undergoing complete metastasectomy subsequent TKIs are not routinely recommended.	EB	M	S
What considerations	<b>6.1.1.</b> Patients with symptomatic bone metastases from metastatic clear cell renal cell carcinoma should receive bone-directed radiation.	CB	M	S

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should be applied to treatment of special subsets of metastatic clear cell renal cell carcinoma? (e.g., bone metastases, brain metastases, sarcomatoid carcinomas).	<b>6.1.2.</b> 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.	CB	M	S
	<b>6.1.3.</b> 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.	CB	L	M
	<b>6.2.1.</b> Patients with brain metastases from metastatic clear cell renal cell carcinoma should receive brain-directed local therapy with radiation therapy and/or surgery.	CB	H	S
	<b>6.2.2.</b> No recommendation regarding optimal systemic therapy for patients with metastatic clear cell renal cell carcinoma and brain metastases can be made.	CB	N/A	S
	<b>6.3.</b> 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).	EB	H	S

**Abbreviations.** CAIX, carbonic anhydrase IX; CB, consensus based; EB, evidence based; H, high; HD-IL2, high dose interleukin-2; IMDC, International Metastatic RCC Database Consortium; L, low; M, moderate; N/A, not applicable; PAX8, paired box gene 8; RANKL, receptor activator of nuclear factor kappa-B ligand; RECIST, Response Evaluation Criteria in Solid Tumours; S, strong; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor; W, weak

**Reference.** <sup>1</sup> Heng DY, Xie W, Regan MM, et al: External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium