

SPECIAL ARTICLE

ESMO Clinical Practice Guideline update on the use of immunotherapy in early stage and advanced renal cell carcinoma

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INTRODUCTION

This article focuses on the recent immunotherapy updates to the treatment of renal cell carcinoma (RCC) as given in the RCC: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.¹

View the ESMO eUpdate here: [<https://www.esmo.org/guidelines/genitourinary-cancers/renal-cell-carcinoma/eupdate-renal-cell-carcinoma-treatment-recommendations-4>].

MANAGEMENT OF LOCAL/LOCOREGIONAL DISEASE

Adjuvant therapy in clear cell renal cell carcinoma

The KEYNOTE-564 phase III trial evaluated pembrolizumab (17 cycles of 200 mg 3-weekly therapy) versus placebo as adjuvant therapy for 994 patients with clear cell RCC (ccRCC) with intermediate (pT2, grade 4 or sarcomatoid, N0 M0; or pT3, any grade, N0 M0) or high risk (pT4, any grade, N0 M0; or any pT any grade, N+ M0); or M1 and no evidence of disease (NED; after primary tumour plus soft tissue metastases completely resected ≤1 year from nephrectomy).² The median follow-up, defined as time from randomisation to data cut-off, was 24.1 months. The primary endpoint of disease-free survival (DFS) per investigator assessment was met [hazard ratio (HR) 0.68, 95% confidence interval (CI) 0.53-0.87, $P = 0.001$]. The estimated 24-month DFS rate was 77% versus 68% for pembrolizumab and placebo, respectively. Benefit occurred across broad

subgroups of patients including those with M1/NED disease after metastasectomy. Investigator-assessed DFS was considered preferable to DFS by central review due to its clinical applicability. Overall survival (OS) showed a non-statistically significant trend towards a benefit in the pembrolizumab arm (HR 0.54, 95% CI 0.30-0.96, $P = 0.0164$). Follow-up was short and few OS events occurred [2-year OS rate of 97% (pembrolizumab) versus 94% (placebo)]. Grade 3-5 all-cause adverse events occurred in 32% versus 18% of patients for pembrolizumab and placebo, respectively. Adjuvant pembrolizumab should be considered optional for patients with intermediate- and high-risk (defined as per study) operable ccRCC after careful patient counselling regarding immature OS and potential long-term adverse events [I, C]. Treatment should start within 12 weeks of surgery and continue for up to 1 year. The significant DFS efficacy signal, the early but promising OS signal and the acceptable tolerability profile all contributed to this decision. This level [I, C] recommendation distinguishes adjuvant pembrolizumab from the adjuvant vascular endothelial growth factor receptor (VEGFR)-targeted trials, which gave inconsistent DFS signals and showed no trend towards OS benefit.³

The authors of this article acknowledge that the correlation between DFS and OS is uncertain for operable ccRCC and unproven for adjuvant immunotherapy in renal cancer.⁴ Therefore, a number of issues need to be addressed to underpin this recommendation for the future. Firstly, a significant and clinically meaningful OS signal will be needed. Secondly, disclosure of the impact of the different patient populations, including the M1/NED population, in the KEYNOTE-564 study on OS is required. Thirdly, it is

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apparent that a high proportion of patients, cured by surgery alone, are receiving unnecessary and potentially harmful treatment. This requires urgent attention with clinical and molecular biomarkers for outcome and predisposition to toxicity, as well as quality-of-life data. Finally, the results of other adjuvant trials with immune checkpoint inhibitors (ICIs) will be relevant, especially if more mature OS data are available from other studies. Meta-analysis studies should occur, although the authors acknowledge that different ICIs may have different efficacy in advanced ccRCC, and should be considered distinct from one another.

The authors would ideally like ongoing, supportive efficacy data while waiting for the final and statistically robust OS analysis, which is unlikely to occur in the short term.

Recommendations

- Adjuvant pembrolizumab should be considered optional for patients with intermediate- or high-risk operable ccRCC (as defined by the study) after careful patient counselling regarding immature OS and potential long-term adverse events [I, C]. Further data are required in the future including positive OS data. Treatment should start within 12 weeks of surgery and continue for up to 1 year.
- Regarding the M1 NED population, systemic therapy with programmed cell death protein 1 (PD-1)-based combination therapy is the standard of care for patients who relapse within 1 year of nephrectomy [I, A].
- Metastasectomy as an alternative to this systemic therapy in patients with synchronous or early oligometastatic disease is not usually recommended [I, D] and requires a multidisciplinary team decision.
- Adjuvant pembrolizumab can be offered to these patients after complete resection of their oligometastatic disease [II, B].
- Incomplete resection should not be offered to patients with oligometastatic disease [III, D].

MANAGEMENT OF METASTATIC DISEASE

The ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) table has been updated (Table 7). The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee. ESMO-MCBS v1.1⁵ was used to calculate scores for new therapies/indications approved by the European Medicines Agency (EMA) since 1 January 2016 or the Food and Drug Administration (FDA) since 1 January 2020 (<https://www.esmo.org/guidelines/esmo-mcbs>).

Systemic treatment of advanced/metastatic ccRCC

First-line treatment of ccRCC. First-line PD-1 inhibitor therapy with either VEGFR-targeted therapy or cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibition has improved overall outcome for patients with advanced ccRCC.⁶⁻⁹ Recent data from the CLEAR trial show a significant OS advantage for lenvatinib—pembrolizumab (20 mg daily and 200 mg every 3 weeks, respectively, until progression)

compared with sunitinib alone (HR 0.66, 95% CI 0.49-0.88, $P = 0.005$) [median OS not reached (NR)].⁶ Response rates (RRs) and progression-free survival (PFS) also favoured lenvatinib—pembrolizumab [RR 71% versus 36%; PFS HR 0.39, (95% CI 0.32-0.49), median PFS 23.9 months (20.8, 27.7) versus 9.2 months (95% CI 6.0-11.0 months), $P < 0.001$].⁶ Dose reductions for treatment-related toxicity were common in the combination arm (68.8% versus 50.3% for sunitinib).⁶ These results led to the FDA approval of lenvatinib—pembrolizumab (not EMA approved). Lenvatinib—pembrolizumab joins other VEGFR—PD-1 inhibitor-targeted combinations (axitinib—pembrolizumab or cabozantinib—nivolumab) to be recommended for first-line treatment of advanced ccRCC irrespective of International Metastatic RCC Database Consortium (IMDC) risk groups [I, A]. There is no preferred VEGFR tyrosine kinase inhibitor (TKI)—PD-1 inhibitor-targeted combination, and indirect comparisons across trials are not recommended [I, D].^{1,6,7} Ipilimumab—nivolumab also continues to be recommended for first-line treatment of IMDC intermediate- and poor-risk disease [I, A].⁹ Sunitinib [I, A], pazopanib [I, A] and tivozanib [II, B] are alternatives to PD-1 inhibitor-based first-line combinations when immunotherapy is contraindicated or not available.⁸⁻¹² Cabozantinib [II, A] is an alternative in IMDC intermediate- and poor-risk disease for those patients who cannot receive first-line PD-1 inhibitor-based therapy,¹³ while surveillance may be appropriate for selected patients with IMDC favourable-risk disease with low tumour burden [III, C].¹⁴ The OS signals in the IMDC favourable-risk patients treated with VEGFR—PD-1 combinations are immature and not yet superior to sunitinib. Better response and PFS data, however, support the use of the combination in this exploratory and underpowered subset. Further follow-up data are awaited.

The combination of lenvatinib—everolimus (18 mg daily and 5 mg daily, respectively, until progression) was also included as a third arm in the CLEAR trial and was compared with sunitinib alone.⁶ This combination achieved a significant PFS advantage compared with sunitinib [HR 0.65, 95% CI 0.53-0.80, $P < 0.001$, median PFS 14.7 months (95% CI 11.1-16.7 months) versus 9.2 months (95% CI 6.0-11.0 months)], but did not demonstrate an OS benefit (HR 1.15, 95% CI 0.88-1.50). Dose reductions for treatment-related toxicity with lenvatinib—everolimus were common (73.2% versus 50.3% for sunitinib), reflecting the adverse event profile. Thus, lenvatinib—everolimus should not be regarded as a standard first-line treatment of metastatic disease [I, D]. The PFS advantage over sunitinib underpins the activity for the combination, however, which can be recommended as a subsequent therapy after first-line treatment, along with other agents [III, B].

Second-line treatment of ccRCC. Robust prospective second-line data exclusively after first-line PD-1 inhibitor-based combination therapy are lacking. Prospective datasets exist for axitinib, pazopanib and sunitinib, but they include mixed patient populations and small numbers.¹⁵⁻¹⁷

Table 7. ESMO-MCBS table for new therapies/indications in RCC^a	
Therapy	Cabozantinib
Disease setting	Advanced RCC after prior VEGF-targeted therapy
Trial	A study of cabozantinib versus everolimus in subjects with metastatic RCC that has progressed after prior VEGFR TKI therapy (METEOR) ^{18,28-31} Phase III NCT01865747
Control	Everolimus Median OS: 17.1 months
Absolute survival gain	OS gain: 4.3 months
HR (95% CI)	OS HR: 0.70 (0.58-0.85)
QoL/toxicity	QoL was an exploratory endpoint; not eligible for ESMO-MCBS grading
ESMO-MCBS score ^b	3 (Form 2a)
Therapy	Cabozantinib plus nivolumab
Disease setting	First-line treatment of advanced RCC in combination with nivolumab
Trial	A study of nivolumab combined with cabozantinib versus sunitinib in participants with previously untreated advanced or metastatic RCC (CheckMate 9ER) ⁷ Phase III NCT03141177
Control	Sunitinib Median PFS: 8.3 months OS at 1 year 75.6%
Absolute survival gain	PFS gain: 8.3 months OS gain: 10.1%
HR (95% CI)	PFS HR: 0.51 (0.41-0.64) OS HR: 0.60 (0.40-0.89) ^c
QoL/toxicity	QoL was an exploratory endpoint; not eligible for ESMO-MCBS grading
ESMO-MCBS score ^b	4 ^{d,e} (Form 2b)
Therapy	Lenvatinib plus everolimus
Disease setting	Advanced or metastatic RCC following one prior VEGF-targeted therapy
Trial	A study of lenvatinib alone, and in combination with everolimus, in subjects with unresectable advanced or metastatic RCC following one prior VEGF-targeted treatment ³² Phase II NCT01136733
Control	Everolimus Median PFS: 5.5 months Median OS: 15.4 months
Absolute survival gain	PFS gain: 9.1 months OS gain: 10.1+ months
HR (95% CI)	PFS HR: 0.40 (0.24-0.68) OS HR: 0.51 (0.30-0.88)
QoL/toxicity	
ESMO-MCBS score ^b	4 (Form 2a)
Therapy	Lenvatinib plus pembrolizumab
Disease setting	First-line treatment of advanced RCC
Trial	Trial to compare the efficacy and safety of lenvatinib in combination with everolimus or pembrolizumab versus sunitinib alone in first-line treatment of subjects with advanced renal cell carcinoma (CLEAR) ⁵ Phase III NCT02811861
Control	Sunitinib Median PFS: 9.2 months OS at 2 years 70.4%
Absolute survival gain	PFS gain: 14.7 months OS gain: 8.8%
HR (95% CI)	PFS HR: 0.39 (0.32-0.49) OS HR: 0.66 (0.49-0.88); $P = 0.005 < 0.016$ for early stopping
QoL/toxicity	
ESMO-MCBS score ^b	4 ^{e,f} (Form 2b)
Therapy	Nivolumab
Disease setting	Treatment of advanced RCC after failure of one or two regimens of antiangiogenic therapy
Trial	Study of nivolumab versus everolimus in subjects with advanced or metastatic clear cell RCC who have received prior antiangiogenic therapy (CheckMate 025) ³³⁻³⁶ Phase III NCT01668784
Control	Everolimus Median OS: 19.6 months
Absolute survival gain	OS gain: 5.4 months
HR (95% CI)	OS HR: 0.73 (0.57-0.93)
QoL/toxicity	Reduced grade 3-4 AEs 19% versus 37% QoL was reported in an exploratory analysis; not eligible for ESMO-MCBS grading
ESMO-MCBS score ^b	5 (Form 2a)

Table 7. Continued	
Therapy	Nivolumab plus ipilimumab
Disease setting	First-line treatment of intermediate-/poor-risk advanced RCC
Trial	A study of nivolumab combined with ipilimumab versus sunitinib monotherapy in subjects with previously untreated, advanced or metastatic RCC (CheckMate 214) ^{9,37-40} Phase III NCT02231749
Control	Sunitinib Median OS: 26.6 months
Absolute survival gain	OS gain: 21.5 months
HR (95% CI)	OS HR: 0.65 (0.54-0.78)
QoL/toxicity	QoL was reported in an exploratory analysis; not eligible for ESMO-MCBS grading
ESMO-MCBS score ^b	4 ^d (Form 2a)
Therapy	Pembrolizumab plus axitinib
Disease setting	First-line treatment of advanced clear cell RCC
Trial	A study to evaluate efficacy and safety of pembrolizumab in combination with axitinib versus sunitinib monotherapy as a first-line treatment of locally advanced or metastatic RCC (KEYNOTE-426) ^{8,41} Phase III NCT02853331
Control	Sunitinib Median PFS: 11.1 months Median OS: 35.7 months
Absolute survival gain	PFS gain: 4.3 months Estimated OS gain: 16.8 months ^e
HR (95% CI)	PFS HR: 0.71 (0.60-0.84) OS HR: 0.68 (0.55-0.85)
QoL/toxicity	
ESMO-MCBS score ^b	4 ^d (Form 2a)
Therapy	Tivozanib
Disease setting	Treatment as first targeted therapy in recurrent or metastatic RCC with a clear cell component
Trial	A study to compare tivozanib with sorafenib in subjects with advanced RCC (TIVO-1) ¹¹ Phase III NCT01030783
Control	Sorafenib Median PFS: 9.1 months Median OS: 28.8 months
Absolute survival gain	PFS gain: 2.8 months OS gain: 0.5 months
HR (95% CI)	PFS HR: 0.80 (0.64-0.99) OS HR: 1.245 (0.954-1.624) NS
QoL/toxicity	No QoL benefit
ESMO-MCBS score ^b	1 (Form 2b)

AE, adverse event; CI, confidence interval; EMA, European Medicines Agency; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; FDA, Food and Drug Administration; HR, hazard ratio; HRQoL, health-related quality of life; NR, not reached; NS, not significant; OS, overall survival; PE, point estimate; PFS, progression-free survival; QoL, quality of life; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

^a EMA approvals since January 2016 and FDA approvals since 1 January 2020.

^b ESMO-MCBS v1.1⁵ The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (<https://www.esmo.org/guidelines/esmo-mcbs/scale-evaluation-forms-v1.0-v1.1/scale-evaluation-forms-v1.1>).

^c 98.89% CI.

^d >30% of control arm patients never received subsequent immunotherapy, suboptimal post-progression treatment may exaggerate OS benefit.⁴²

^e Form 2a cannot be applied since median OS was NR in the control arm; consequently, the score was derived from Form 2b criteria with an upgrade for early stopping based on the OS advantage detected.

^f FDA approved; not EMA approved.

^g Calculated estimate of gain based on the PE HR 0.68.

There are also retrospective, exploratory, subset analyses from studies with other endpoints (cabozantinib, tivozanib, lenvatinib—everolimus).¹⁸⁻²⁰ Responses were seen (~20%) in all of these studies and outcome was in line with the expectations for sequencing therapy. All of these agents have been given the same level of cautious recommendation, due to the imperfections of the datasets [III, B]. It is likely that all approved VEGFR-targeted therapy has some activity and should be considered the standard of care. The role of further ICIs after PD-1 inhibitor-based first-line combination therapy remains experimental and is not considered standard of care.

Third-line treatment of ccRCC. Prospective data on further lines of therapy after first-line PD-1 inhibitor combination therapy and second-line VEGFR-based therapy are lacking. It is likely that sequencing different targeted therapies approved in advanced RCC is beneficial, as was the case in the pre-ICI era [IV, B]. Rechallenge with ICIs is unproven, and should not be regarded as a standard option.

The treatment algorithms for systemic first-line and second-line treatment of ccRCC have been updated (Figures 1 and 2 in the original published guideline, respectively).¹ These are now combined into one algorithm for this update (Figure 1).

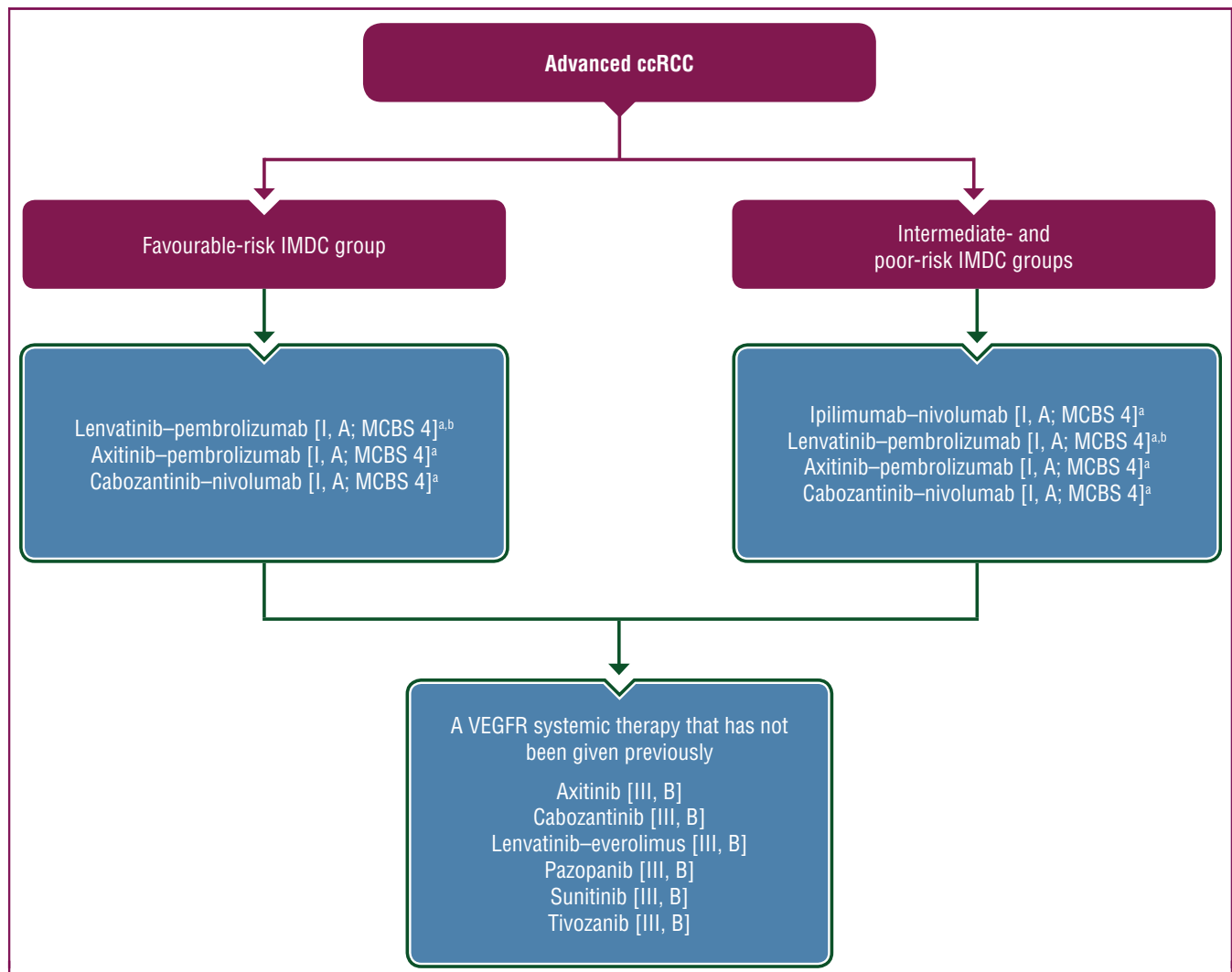


Figure 1. Systemic first- and second-line treatment of ccRCC.

Purple: general categories or stratification; blue: systemic anticancer therapy.

ccRCC, clear cell renal cell cancer; EMA, European Medicines Agency; ESMO-MCBS, European Society for Medical Oncology–Magnitude of Clinical Benefit Scale; FDA, Food and Drug Administration; IMDC, International Metastatic RCC Database Consortium; MCBS, ESMO–Magnitude of Clinical Scale; VEGFR, vascular endothelial growth factor receptor.

^a ESMO-MCBS v1.1 score for new therapy/indication approved by the EMA or FDA. The score has been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (<https://www.esmo.org/guidelines/esmo-mcbs/scale-evaluation-forms-v1.0-v1.1/scale-evaluation-forms-v1.1>).

^b FDA approved; not currently EMA approved.

Medical treatment of advanced/metastatic papillary RCC

Until recently, guidelines for the treatment of advanced papillary renal cancer patients have been largely based on subset analysis from small, randomised trials that compared everolimus and sunitinib, and included all non-ccRCC patients.^{21,22} The papillary subsets of patients in these trials were modest (ESPN $n = 27$ and ASPEN $n = 70$). ASPEN showed improved RR and PFS for sunitinib compared with everolimus [RR of 24% versus 5%; median PFS 8.1 months (80% CI 5.8–11.1 months) versus 5.5 months (80% CI 4.4–5.6 months), HR 1.6, (80% CI 1.1–2.3)], but not OS.²¹ Therefore, sunitinib became the preferred agent. Small, single-arm datasets for axitinib ($n = 44$) and pazopanib ($n = 18$) also reported modest responses in papillary renal cancer, but have not been widely adopted.^{23,24} Early evidence

suggested that mesenchymal-epithelial transition (*MET*) exon alterations occur in papillary RCC (type 1) and may be used to select patients for a precision medicine-based therapy.²⁵

First-line treatment recommendations for papillary RCC have changed based on three recent datasets. The Southwest Oncology Group (SWOG) PAMMET trial, a randomised, phase II study, explored cabozantinib ($n = 44$) versus sunitinib ($n = 46$) versus savolitinib ($n = 29$) versus crizotinib ($n = 28$) in advanced papillary renal cancer.²⁶ The last two arms of this study were discontinued due to futility. PFS was the primary endpoint. Results showed a PFS advantage for cabozantinib over sunitinib [9.0 months (95% CI 6–12 months) versus 5.6 months (95% CI 3–7 months), HR 0.60, (95% CI 0.37–0.97), $P = 0.02$]. Cabozantinib was also associated with higher RRs (23% versus 4% for sunitinib). OS (an

underpowered secondary endpoint) was not significantly different between the arms. Median OS for cabozantinib and sunitinib was 20 months (95% CI 19.3 months-NR) versus 16 months (95% CI 13-22 months), respectively. Adverse event profiles were in line with previous reports for these agents.

Pembrolizumab was explored in a single-arm trial which included a spectrum of non-ccRCC patients (Keynote 427).²⁷ Data on 118 papillary cancer patients were reported. RR was 29%, PFS was 5.5 months (95% CI 3.9-6.1 months) and OS was 31.5 months (95% CI 25.5 months-NR). Adverse event profiles were in line with pembrolizumab single-agent studies.

The SAVOIR trial explored savolitinib (a MET inhibitor) as first-line treatment of MET-driven tumours [defined as chromosome 7 gain, *MET* amplification, MET kinase domain variations or hepatocyte growth factor (HGF) amplification by DNA alteration analysis (~30% of screened patients were *MET* positive)].²⁵ Savolitinib ($n = 27$) was compared with sunitinib ($n = 33$). The trial was stopped early, largely due to accrual issues. The efficacy data appeared to favour savolitinib [median PFS 7.0 months (95% CI 2.8 months-NR) versus 5.6 months (95% CI 4.1-6.9 months), PFS HR 0.71 (95% CI 0.37-1.36), OS HR 0.51 (94% CI 0.21-1.17), RR 27% versus 7%, for savolitinib and sunitinib, respectively]. The median OS for savolitinib was NR. Savolitinib was well tolerated compared with sunitinib, with 42% grade 3 or more adverse events (versus 81% with sunitinib).

Robust data with a statistically significant OS signal remain elusive in this disease, mainly due to the challenges of conducting large, randomised trials in rare cancers. The guideline authors therefore focused on the randomised data available or those from larger phase II trials to support their recommendations. Clinical trials are required in this disease.

Robust data are also lacking for second-line therapy for papillary renal cancer. Any targeted therapy or immunotherapy recommended in the first-line setting that has not previously been given is cautiously recommended [IV, B].

The evidence of an OS advantage for second-line therapy and the principal of sequencing therapy have not been proven in randomised trials. Best supportive care alone may be considered in selected individuals [IV, C].

A new treatment algorithm for systemic first-line and second-line treatment of papillary renal cancer has been added (Figure 5); this figure replaces part of Figure 4 in the original published guideline.

Recommendations

First-line treatment of advanced ccRCC

- Lenvatinib–pembrolizumab [I, A; ESMO-MCBS v1.1 score: 4] is now FDA approved but not EMA approved and joins other VEGFR–PD-1 inhibitor-targeted combinations (axitinib–pembrolizumab [I, A; ESMO-MCBS v1.1 score: 4] or cabozantinib–nivolumab [I, A; ESMO-MCBS v1.1 score: 4]) to be recommended for first-line treatment of advanced ccRCC, irrespective of the IMDC risk groups. There is no preferred VEGFR TKI–PD-1 inhibitor combination and indirect comparisons across trials are not recommended [I, D].

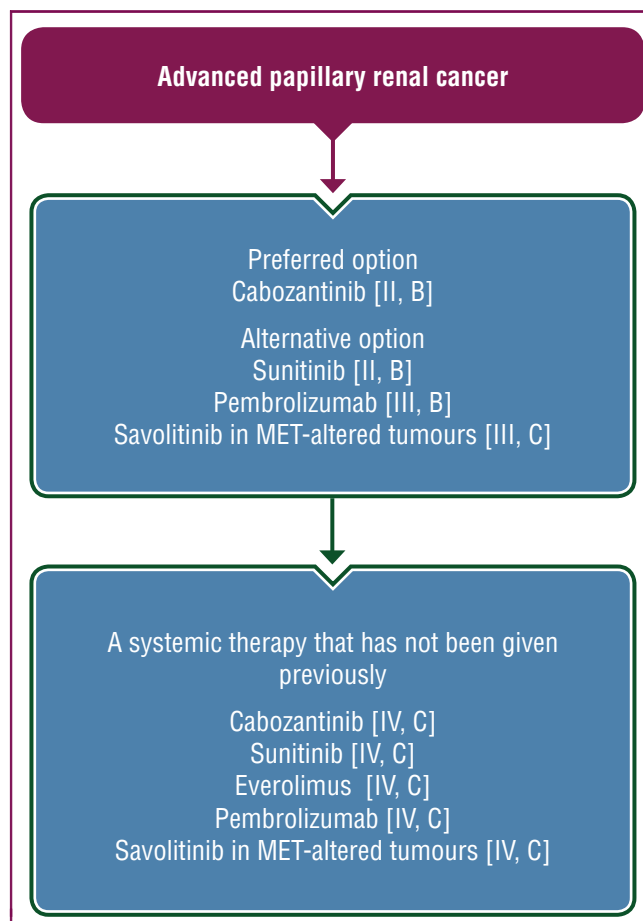


Figure 5. Systemic first- and second-line treatment of papillary renal cancer. Purple: general categories or stratification; blue: systemic anticancer therapy. MET, mesenchymal-epithelial transition.

- Ipilimumab–nivolumab continues to be recommended as first-line treatment of IMDC intermediate- and poor-risk disease [I, A; ESMO-MCBS v1.1 score: 4].
- ICI-based therapy is particularly active in sarcomatoid renal tumours and should be strongly recommended above single-agent VEGFR TKI [II, A].
- Sunitinib [I, A], pazopanib [I, A] and tivozanib [II, B; ESMO-MCBS v1.1 score: 1] are alternatives to PD-1 inhibitor-based first-line combinations when immunotherapy is contraindicated or not available. Cabozantinib [II, A] is also an alternative in IMDC intermediate- and poor-risk disease for those patients who cannot receive first-line PD-1 inhibitor-based therapy.
- Sunitinib or pazopanib are potential alternatives to PD-1 inhibitor-based combination therapy in IMDC favourable-risk disease due to a lack of clear superiority for PD-1-based combinations over sunitinib in this subgroup of patients, and the non-inferior effectiveness of sunitinib and pazopanib demonstrated by the COMPARZ trial [I, B].
- Surveillance is an alternative approach in a small subset of patients. This requires careful consideration [III, C].
- Only ICI-based combinations with a survival advantage are recommended in the first-line setting. Axitinib–

avelumab and bevacizumab—atezolizumab are not yet associated with an OS advantage and are therefore not recommended [I, D].

- Cessation of ICIs should be considered after 2 years of therapy [IV, C].
- Lenvatinib—everolimus should not be regarded as a standard first-line treatment of metastatic disease [I, D] but can be recommended as a subsequent therapy after first-line treatment, along with other agents [III, B].

After disease progression on PD-1 inhibitor-based combination therapy for ccRCC

- Sequencing VEGFR TKI therapy after PD-1 inhibitor-based first-line therapy is associated with modest RRs and should be considered the standard of care [III, B]. These data are derived from suboptimal studies. The chosen agent should be a VEGFR-targeted agent that they have not previously received [III, B].
- Randomised data to support continued ICIs after progression on first-line ICI-based therapy is lacking and this therapy is not recommended [IV, D].

Medical treatment of advanced/metastatic papillary RCC

- Cabozantinib is the preferred first-line agent for advanced papillary RCC without additional molecular testing [II, B].
- Alternative options include sunitinib [II, B], pembrolizumab [III, B] without additional molecular testing and savolitinib (where available) in MET-driven tumours [III, C].
- Second-line therapy should focus on those first-line agents that have not been used previously [IV, C]. Best supportive care can be considered in selected patients due to the lack of data for systemic therapy [IV, C].

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