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European Association of Urology

Position Paper – Kidney Cancer

Updated European Association of Urology Guidelines Recommendations for the Treatment of First-line Metastatic Clear Cell Renal Cancer

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Abstract

The randomised phase III clinical trial Checkmate-214 showed a survival superiority for the combination of ipilimumab and nivolumab when compared with the previous standard of care in first-line metastatic/advanced clear cell renal cell carcinoma (RCC) (Escudier B, Tannir NM, McDermott DF, et al. CheckMate 214: efficacy and safety of nivolumab plus ipilimumab vs sunitinib for treatment-naïve advanced or metastatic renal cell carcinoma, including IMDC risk and PD-L1 expression subgroups. LBA5, ESMO 2017, 2017). These results change the frontline standard of care for this disease and have implications for the selection of subsequent therapies. For this reason the European Association of Urology RCC guidelines have been updated.

Patient summary: The European Association of Urology guidelines will be updated based on the results of the phase III Checkmate-214 clinical trial. The trial showed superior survival for a combination of ipilimumab and nivolumab (IN), compared with the previous standard of care, in intermediate- and poor-risk patients with metastatic clear cell renal cell carcinoma. When IN is not safe or feasible, alternative agents such as sunitinib, pazopanib, and cabozantinib should be considered. Furthermore, at present, the data from the trial are immature in favourable-risk patients. Therefore, sunitinib or pazopanib remains the favoured agent for this subgroup of patients.

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1. Background

Until recently, the treatment of metastatic/advanced clear cell renal cell carcinoma (ccRCC) focused on vascular endothelial growth factor (VEGF)–targeted therapy and mammalian target of rapamycin (mTOR) inhibition. The COMPARZ trial established both pazopanib and sunitinib as the standard of care for patients with treatment-naïve RCC, irrespective of prognostic risk group [1]. Other agents such as bevacizumab in combination with interferon (for good- and intermediate-risk disease), tivozanib (all risk groups), and temsirolimus (for poor-risk disease) have European Medicines Agency regulatory approval in this setting. However, the data for these agents are less robust and they are not widely used, which is also reflected in the recent European Association of Urology (EAU) RCC guidelines [2].

All, but one, of the previous studies on first-line treatment of metastatic RCC (mRCC) failed to demonstrate an overall survival (OS) advantage over previous standards of care such as interferon [3]. Therefore, regulatory approval had been based on progression-free survival (PFS) benefit. Irrespective of this, OS in patients with mRCC has effectively doubled over the last decade, largely due to the availability and sequencing of these agents [2].

2. Immune checkpoint inhibitors

Immune checkpoint inhibition has revolutionised the treatment of many cancers. Programmed death receptor (PD-1) and ligand (PD-L1) inhibition have both been investigated in mRCC. Randomised data support the use of nivolumab (a PD-1 inhibitor) in VEGF-refractory disease [4]. A survival advantage was seen in this study, although no PFS advantage occurred, which is not unexpected with this class of drug. For the combination of Ipilimumab abs nivolumab, safety data in a spectrum of tumours, including RCC, are available [5]. However, there have been inconsistencies around dosing of both drugs, which may affect efficacy [5].

3. Recommendations for frontline therapy

Checkmate-214 is a global randomised phase III trial testing the combination of two immune checkpoint inhibitors ipilimumab and nivolumab (IN; 3 mg/kg nivolumab IV + 1 mg/kg ipilimumab IV Q3W [every 3 wk] for four doses, then 3 mg/kg nivolumab IV Q2W [every 2 wk] versus sunitinib [50 mg sunitinib orally once daily for 4 wk: 6-wk cycles]) [6]. The patient population consisted of those with treatment-naïve advanced or metastatic ccRCC, measurable disease (RECIST v1.1), Karnofsky Performance Score ≥70%, adequate organ function, and tumour tissue available for PD-L1 testing. Patients ineligible for immune checkpoint inhibitors or VEGF-targeted therapies were excluded. The trial had triple coprimary end points of response rate (RR), PFS, and OS in intermediate- and poor-risk patients, as defined by the International Metastatic Renal Cell Carcinoma Database Consortium. Intention to treat (ITT) was a secondary end point in the unselected population.

A total of 1096 patients were randomised in the ITT population; 23%, 61%, and 17% of patients had favourable-, intermediate-, and poor-risk disease, respectively [6]. Twenty-four per cent of the ITT population and 28% of the intermediate/poor-risk population with quantifiable PD-L1 expression were biomarker positive (>1% of tumour cell staining with 288 antibody). The study successfully achieved the primary end points of RR and OS (Table 1). It failed to achieve the third end point of PFS, which may have been due to the allocation of alpha in the statistical analysis plan. Landmark analysis showed a tail to the survival curve favouring IN. Other data showed that more of the patients receiving IN had durable remissions. All together, these results show that IN is the new standard of care in the intermediate- and poor-prognosis subgroups of patients with mRCC.

Secondary end points included investigating outcomes in the ITT population. Testing this population was only permitted once the primary end points had been achieved. The data analysis used a hierarchical model, which allowed for reporting of RR and OS (but not PFS) in the ITT population for statistical significance. Results showed that IN was associated with a significant advantage for both RR and OS. Again a higher proportion of the IN patients achieved durable remissions, justifying their use in unselected patients (including favourable-risk disease).

Median duration of therapy was almost identical in the two arms at 7.9 and 7.8 mo for IN and sunitinib, respectively. Treatment discontinuation due to adverse events (AEs) was 24% and 12% for IN and sunitinib, respectively. Grade 3–5

Table 1 – Summary of Checkmate-214 data [6]

	IMDC intermediate and poor risk			ITT population (secondary end point)		
	IPI + NIVO	Sunitinib	HR	IPI + NIVO	Sunitinib	HR
n	425	422		550	546	
RR	42	27		39	32	
95% CI	(37–47)	(22–31)		35–43	28–36	
PFS	11.6	8.4	0.82	12.4	12.3	0.98
99.1 CI	(8.5–15.5)	(7.0–10.8)	(0.64–1.05)	(9.9–16.5)	(9.8–15.2)	(0.79–1.23)
OS	NR	26.0	0.63	NE	32.9	0.68
99.8 CI	(28.2–NR)	(22–NR)	(0.44–0.82)	(NE–NE)	(NE–NE)	(0.49–0.95)

CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ITT = intention to treat; *n* = number of patients; NE = neutral effect; NIVO = nivolumab; NR = not reported; OS = overall survival; PFS = progression-free survival; RR = relative risk.

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AEs were more common with sunitinib than for IN (63% vs 46%). The most frequent three to five AEs observed with IN were fatigue (37%), pruritus (28%), and diarrhoea (27%), compared with diarrhoea (52%), fatigue (49%), and palmar plantar erythema (43%) for sunitinib. A health-related quality of life assessment, based on the National Comprehensive Cancer Network Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI-19), was performed, which favoured IN.

Exploratory end points included outcomes in favourable-risk patients and by tumour PD-L1 expression level. Results in the favourable-risk population showed RRs of 29% (95% confidence interval [CI]: 21–38%) versus 52% (95% CI: 43–61%) and median PFS of 15.3 mo (95% CI: 9.7–20.3) versus 25 mo (95% CI: 20.9–neutral effect) for IN and sunitinib, respectively (PFS hazard ratio [HR] 2.18 [95% CI: 1.29–3.68]). Owing to the exploratory nature of these analyses, small sample size, lack of OS data, and premature results in this subpopulation, definitive conclusions cannot be drawn.

The OS advantage for IN in the ITT population justifies its use in unselected patients, although these exploratory results in the favourable-risk group highlight the need for caution. The impressive results for sunitinib in the favourable-risk subgroup justify its continued strong recommendation in the EAU guidelines. In view of the noninferiority of pazopanib compared with sunitinib, this is also included in the guidelines for this subgroup of patients. Mature OS data are awaited.

Tumours that overexpressed the PD-L1 biomarker at baseline were associated with a better RR and PFS with IN than with sunitinib (PFS HR 0.48, 95% CI: 0.28–0.82). This was not the case in the PD-L1–negative cohort, where PFS was almost identical (HR 1.0, 95% CI: 0.74–1.36). Therefore, the PD-L1 biomarker appears to be predictive for PFS. Owing to the exploratory nature of this work, no significant conclusions could be drawn. As no group receiving IN appeared to have a worse outcome compared with sunitinib, and PROs favoured IN, selection based on the PD-L1 biomarker is currently not recommended. Further work will be required.

IN was associated with 15% grade 3–5 toxicity and 1.5% treatment-related deaths. It should, therefore, be administered in centres with experience of immune combination therapy and appropriate supportive care within the context of a multidisciplinary team. Currently, IN should not be offered outside of the first-line setting. Patients who stop IN due to toxicity should not be challenged with the same drugs in the future without expert guidance and support from a multidisciplinary team. Patients who do not receive the full four doses of ipilimumab due to toxicity should continue on the single agent nivolumab, where safe and feasible. Treatment past progression with IN can be justified, but requires close scrutiny and the support of an expert multidisciplinary team. IN should not be combined with other agents outside of a clinical trial. The PD-L1 biomarker (>1% expression using the 288 antibody) should not routinely be used to select patients for therapy, as these data are promising but still exploratory. Patients who are not able to receive first-line IN should follow the EAU guidelines recommendations [2].

The EAU guidelines, which will be updated based on these data, recommend IN as the standard of care in intermediate- and poor-risk patients with mRCC (Fig. 1 and Table 2). Alternative agents such as sunitinib, pazopanib, and cabozantinib should be considered when IN is not safe or feasible. In favourable-risk patients, IN is recommended, due to the positive ITT results in the Checkmate-214 study. However, at present, the data with sunitinib in this subgroup of patients are more promising. Sunitinib or pazopanib, therefore, remain the preferred agents in favourable-risk patients.

Recent phase II data comparing cabozantinib and sunitinib in intermediate- and poor-risk disease favoured cabozantinib for RR and PFS, but not OS [7]. This underpins the activity of cabozantinib, but the lack of a randomised phase III study means that it cannot be supported above alternative VEGF tyrosine kinase inhibitors such as sunitinib or pazopanib. Tivozanib has recently been approved based on conflicting data, but the evidence is inferior over existing choices [8,9].

4. Subsequent therapies

Sequencing of targeted therapies is established in mRCC and maximises outcomes [10]. IN is a new standard of care for frontline therapy. Its impact on subsequent therapies is unclear, although OS with IN in the CheckMate-214 trial is longer than one would predict from PFS, suggesting significant activity of subsequent agents. The Guidelines Panel provides the recommendation, as listed in Table 3, which is weak due to a lack of high-level data.

Subsequent therapy for patients with IN-refractory disease in first line has not been prospectively tested. However, progression of disease while receiving IN should result in subsequent sequencing of targeted therapy (Fig. 1). VEGF-targeted therapies have the most robust efficacy record of activity in mRCC [2]. These agents should be initially prioritised. The Guidelines Panel was unable to specify which VEGF-targeted therapy to use. Axitinib has positive data in VEGF and cytokine-refractory disease for PFS [11]. Cabozantinib has positive trials in multiple settings in mRCC, including OS [12]. Sunitinib and pazopanib were the standard first-line VEGF-targeted therapies in unselected patients justifying their use [1]. Tivozanib, sorafenib, and bevacizumab/interferon are less favoured and not widely used [2].

The panel does not favour the use of mTOR inhibitors unless VEGF-targeted therapy is contraindicated, as they have been outperformed by other VEGF-targeted therapies in mRCC [2]. The combination of bevacizumab and interferon alpha would involve rechallenge with immune therapy, which requires further data prior to a positive recommendation [13].

Drug choice in the third-line setting, after IN and subsequent VEGF-targeted therapy, is unknown. The panel recommends a subsequent agent that is approved in VEGF-refractory disease, with the exception of a rechallenge with

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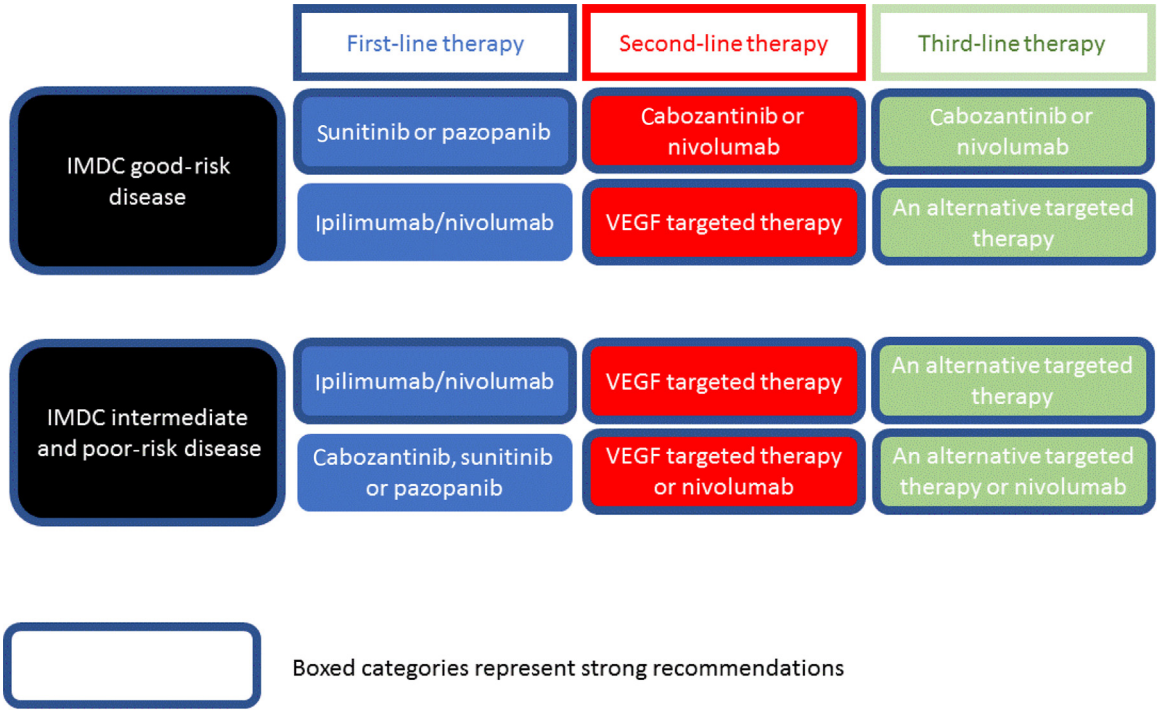

Fig. 1 – Updated European Association of Urology guideline recommendations for the treatment of first-line metastatic clear-cell renal cancer. IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; VEGF = vascular endothelial growth factor.

Table 2 – Recommendations for first-line therapy of advanced/metastatic RCC

Recommendation	Strength rating
Offer ipilimumab plus nivolumab to treatment-naïve patients with IMDC intermediate- and poor-risk metastatic ccRCC	Strong
Offer sunitinib or pazopanib to treatment-naïve patients with IMDC favourable-risk metastatic ccRCC	Strong
Offer ipilimumab plus nivolumab to treatment-naïve patients with IMDC favourable-risk metastatic ccRCC	Weak
Offer cabozantinib to treatment-naïve patients with IMDC intermediate- and poor-risk metastatic ccRCC	Weak
Do not offer tivozanib to patients with treatment-naïve metastatic ccRCC	Weak

ccRCC = clear cell renal cell carcinoma; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; RCC = renal cell carcinoma.

Table 3 – Recommendation for second-line therapy

Recommendation	Strength rating
Offer a VEGFR-TKI as second-line therapy to IN-refractory patients	Weak

IN = ipilimumab and nivolumab; VEGFR-TKI = vascular endothelial growth factor receptor tyrosine kinase inhibitor.

nivolumab. Cabozantinib is the only agent in VEGF-refractory disease with a survival advantage in a randomised phase III trial and should be used preferentially [12]. Axitinib has positive PFS data in VEGF-refractory disease. Both sorafenib and everolimus have been outperformed by other agents in VEGF-refractory disease and are therefore less attractive [2]. Lenvatinib and everolimus has regulatory approval based on randomised phase II data and is an alternative despite the fact that only phase II data are available [14].

There is no evidence for sequencing of immune therapies, which remains within the realm of clinical trials. Patients should only receive individual immune checkpoint inhibition once, in the opinion of the panel. Rechallenge with nivolumab or IN is not recommended at this stage. While data with the combination of VEGF-targeted therapy and immune checkpoint inhibition are promising, further randomised data will be needed before any recommendations can be provided.

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Study concept and design: Powles, Albiges, Ljungberg, Bex.
Acquisition of data: Powles, Albiges, Bex.
Analysis and interpretation of data: Powles, Albiges, Ljungberg, Bex.
Drafting of the manuscript: Powles, Bex.

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References

[1] Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med 2013;369:722–31.
[2] Powles T, Staehler M, Ljungberg B, et al. Updated EAU guidelines for clear cell renal cancer patients who fail VEGF targeted therapy. Eur Urol 2016;69:4–6.
[3] Coppin C, Kollmannsberger C, Le L, Porzsolt F, Wilt TJ. Targeted therapy for advanced renal cell cancer (RCC): a Cochrane systematic review of published randomised trials. BJU Int 2011;108:1556–63.
[4] Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015;373:1803–13.
[5] Hammers HJ, Plimack ER, Infante JR, et al. Safety and efficacy of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma: the CheckMate 016 study. J Clin Oncol 2017. http://dx.doi.org/10.1200/JCO.2016.72.1985.
[6] Escudier B, Tannir NM, McDermott DF, et al. CheckMate 214: Efficacy 316 and safety of nivolumab plus ipilimumab vs sunitinib for treatment-naïve 317 advanced or metastatic renal cell carcinoma, including 318 IMDC risk and PD-L1 expression subgroups. Ann of Oncol 2017;28(Suppl. 5):v605–49, LBA5, ESMO 319 2017.
[7] Choueiri TK, Halabi S, Sanford BL, et al. Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: the alliance A031203 CABOSUN trial. J Clin Oncol 2017;35:591–7.
[8] Kim ES. Tivozanib: first global approval. Drugs 2017;77:1917–23.
[9] Motzer RJ, Nosov D, Eisen T, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial. J Clin Oncol 2013;31:3791–9.
[10] Albiges L, Choueiri T, Escudier B, et al. A systematic review of sequencing and combinations of systemic therapy in metastatic renal cancer. Eur Urol 2015;67:100–10.
[11] Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet 2011;378:1931–9.
[12] Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015;373:1814–23.
[13] Escudier B, Pluzanska A, Koralewski P, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet 2007;370:2103–11.
[14] Motzer RJ, Hutson TE, Glen H, et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. Lancet Oncol 2015;16:1473–82.

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