

## Brief Correspondence

# Updated European Association of Urology Guidelines on Renal Cell Carcinoma: Immune Checkpoint Inhibition Is the New Backbone in First-line Treatment of Metastatic Clear-cell Renal Cell Carcinoma

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### Abstract

Recent randomised trials have demonstrated a survival benefit for a front-line ipilimumab and nivolumab combination therapy, and pembrolizumab and axitinib combination therapy in metastatic clear-cell renal cell carcinoma. The European Association of Urology Guidelines Panel has updated its recommendations based on these studies.

**Patient summary:** Pembrolizumab plus axitinib is a new standard of care for patients diagnosed with kidney cancer spread outside the kidney and who did not receive any prior treatment for their cancer (treatment naïve). This applies to all risk groups as determined by the International Metastatic Renal Cell Carcinoma Database Consortium criteria.

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Immune checkpoint inhibitors, including programmed death 1 (PD-1) inhibitors, programmed death ligand 1 (PD-L1) inhibitors, and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitors, have activity in metastatic clear-cell renal cell carcinoma (cc mRCC). Four studies investigating these combinations in the front-line cc mRCC setting have recently been published (Table 1) [1–4]. These have had a major impact on the European Association of Urology (EAU) guidelines that are updated in this article.

The CheckMate 214 study was the first of these trials to report superiority of nivolumab and ipilimumab over sunitinib. The primary endpoint focused on the intermediate- and poor-risk population according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC), where the combination demonstrated an overall survival (OS) benefit (hazard ratio [HR] 0.63; 95% confidence interval [CI] 0.44–0.89) and led to regulatory approval [1]. This led to a paradigm shift in the treatment of the disease and a change in the EAU guidelines in 2019 [5]. Results from CheckMate 214 further established that the combination of ipilimumab and nivolumab was

associated with higher response rates (RRs; 42%), complete response (CR) rates (9%), and duration of response compared with sunitinib. Progression-free survival (PFS) did not achieve the predefined endpoint. The exploratory analysis of data in the PD-L1-positive population revealed an OS HR of 0.45 (95% CI 0.29–0.71). Frequency of grade 3–4 adverse events and quality of life (QoL) data favoured the immune combination. The frequency of steroid use has generated controversy, and further analysis and real-world data are required. A recent update with 30 mo of data showed on-going benefits for the immune combination with investigator-assessed CR rates of 11% and an OS HR in the IMDC intermediate- and poor-risk group of 0.66 (95% CI 0.54–0.80) [6]. The IMDC good-risk group continues to perform better with sunitinib, although this appears less pronounced than in earlier analysis (HR for OS 1.22; 95% CI 0.73–2.04). For these reasons, the guideline panel continues to recommend ipilimumab and nivolumab in the intermediate- and poor-risk population (Supplementary material).

The Keynote-426 trial (NCT02853331) has recently reported results for the combination of pembrolizumab

**Table 1 – Immune checkpoint inhibition combination trials that reported results for the front-line treatment of clear-cell mRCC<sup>a</sup>**

Study	N	Experimental arm	Primary endpoint	Risk groups	PFS Median (95% CI) Hazard ratio	OS Median (95% CI) Hazard ratio
KEYNOTE-426 NCT02853331 [3]	861	Pembrolizumab 200 mg IV Q3W plus axitinib 5 mg PO BID Vs Sunitinib 50 mg PO QD 4/2 wk	PFS and OS in the ITT by BICR	<b>IMDC</b> FAV: 31% IMD: 56% Poor: 13% <b>MSKCC</b> Not determined	<b>(ITT)</b> <b>PEMBRO + AXI: 15.1 (12.6–17.7)</b> <b>SUN: 11.1 (8.7–12.5)</b> <b>HR 0.69 (95% CI: 0.57, 0.84)</b> <b>p ≤ 0.0001</b> <b>(PD-L1+)</b> <b>AVE + AXI: 13.8 (11.1–NE)</b> <b>SUN: 7.2 (5.7–9.7)</b> <b>HR 0.61 (95% CI: 0.475, 0.790)</b> <b>p &lt; 0.0001</b>	<b>(ITT)</b> <b>PEMBRO + AXI: NR</b> <b>SUN: NR</b> <b>HR 0.53 (95% CI: 0.38, 0.74)</b> <b>p ≤ 0.0001</b>
JAVELIN 101 NCT02684006 [2]	886	Avelumab 10 mg/kg IV Q2W plus axitinib, 5 mg PO BID Vs Sunitinib 50 mg PO QD 4/2 wk	PFS in the PD-L1+ population and OS in the ITT by BICR	<b>IMDC</b> FAV: 22% IMD: 62% Poor: 16% <b>MSKCC</b> FAV: 23% IMD 66% Poor: 12%	<b>(PD-L1+)</b> <b>ATEZO + BEV: 11.2 (8.9–15.0)</b> <b>SUN: 7.7 (6.8–9.7)</b> <b>HR 0.74 (95% CI: 0.57, 0.96)</b> <b>p = 0.02</b>	<b>(ITT)</b> AVE + AXI: NR SUN: NR HR 0.78 (95% CI: 0.554, 1.084) p = 0.0679
Immotion 151 NCT02420821 [4]	915	Atezolizumab 1200 mg fixed dose IV plus bevacizumab 15 mg/kg IV on days 1 and 22 of each 42-d cycle Vs Sunitinib 50 mg PO QD 4/2 wk	PFS in the PD-L1+ population and OS in the ITT by IR	<b>IMDC</b> Not determined <b>MSKCC</b> FAV: 20% IMD: 70% Poor: 10%	<b>(PD-L1+)</b> <b>ATEZO + BEV: 11.2 (8.9–15.0)</b> <b>SUN: 7.7 (6.8–9.7)</b> <b>HR 0.74 (95% CI: 0.57, 0.96)</b> <b>p = 0.02</b>	<b>(ITT)</b> ATEZO + BEV: NR SUN: NR HR 0.81 (95% CI: 0.63, 1.03) p = 0.09
Checkmate 214 NCT02231749 [6,7]	1096	Nivolumab 3 mg/kg plus ipilimumab 1 mg/ kg IV Q3W for 4 doses then nivolumab 3 mg/ kg IV Q2W Vs Sunitinib 50 mg PO QD 4/2 wk	PFS, OS and ORR in IMDC intermediate and poor population by BICR	<b>IMDC</b> FAV: 23% IMD: 61% Poor: 17% <b>MSKCC</b> Not determined	<b>(IMDC intermediate/poor)</b> NIVO + IPI: 11.8 (8.7–15.5) SUN: 8.4 (7.0–10.8) HR 0.82 (99.1% CI: 0.64, 1.05) p = 0.03	<b>(IMDC intermediate/ poor)</b> NIVO + IPI: NR <b>(28.2–NE)</b> SUN: <b>26.0 (22.1–NE)</b> <b>HR 0.63 (99.8% CI: 0.44, 0.89)</b> <b>p ≤ 0.0001</b>

ATEZO = atezolizumab; AVE = avelumab; AXI = axitinib; BEV = bevacizumab; BICR = blinded independent central review; BID = bis in dies (twice daily); CI = confidence interval; FAV = favourable; HR = hazard ratio; IMD = intermediate; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IPI = ipilimumab; IR = investigator review; ITT = intention-to-treat population; IV = intravenous; mRCC = metastatic renal cell carcinoma; MSKCC = Memorial Sloan Kettering Cancer Center; N = number of patients; NE = not estimable; NIVO = nivolumab; NR = not reached; OS = overall survival; PD-L1+ = programmed death-ligand-1-positive population; PEMBRO = pembrolizumab; PFS = progression free survival; PO = per os (oral); QD = daily; Q2W/Q3W = every 2nd/3rd week; SUN = sunitinib; ORR = objective response rate.

<sup>a</sup> PFS and OS results in **bold** indicate that the primary endpoint has been met.

plus axitinib versus sunitinib in 861 treatment-naïve cc mRCC patients [3]. OS and PFS (assessed by a central independent review) in the intention-to-treat (ITT) population were the coprimary endpoints. RR and subgroup analyses of the PD-L1-positive patient population were secondary endpoints. The first interim analysis was triggered after at least 7 mo of follow-up and 305 events. The trial was ended at the first interim analysis (median follow-up = 12.8 mo) as both primary endpoints were achieved. The median PFS was 15.1 mo in the pembrolizumab plus axitinib arm versus 11.1 mo in the sunitinib arm (HR 0.69; 95% CI 0.57–0.84;  $p < 0.001$ ). Median OS has not been reached in either arm, but the risk of death was 47% lower in the pembrolizumab plus axitinib arm than in the sunitinib arm (OS HR 0.53; 95% CI 0.38–0.74;  $p < 0.0001$ ). RRs were also higher in the experimental arm (59.3% vs 35.7%), with efficacy being demonstrated irrespective of IMDC group and PD-L1 status. Treatment-related adverse events (grade  $\geq 3$ ) occurred in 63% of patients receiving pembrolizumab and axitinib versus 58% of patients receiving sunitinib. Treatment-related deaths occurred in approximately 1% in both arms.

The JAVELIN 101 trial, an 886-patient phase 3 randomised controlled trial of avelumab plus axitinib versus sunitinib, was simultaneously published [2]. It met one of its coprimary endpoints (PFS in the PD-L1-positive population at the first interim analysis; median follow-up 11.5 mo). HRs for PFS and OS in the ITT population were 0.69 (95% CI 0.56–0.84) and 0.78 (95% CI 0.55–1.08), respectively. Treatment-related adverse events (grade  $\geq 3$ ) occurred in 55% in both arms. The trial is on-going and OS results are awaited. It is premature to recommend this combination in the absence of a survival signal. The same applies regarding recommendations for the well-tolerated combination of atezolizumab and bevacizumab [4]. This combination has also achieved a PFS advantage over sunitinib in the PD-L1-positive population at interim analysis and ITT (HR 0.74; 95% CI 0.57–0.96), but does not yet have a significant OS advantage (HR 0.81; 95% CI 0.63–1.03) in the ITT population.

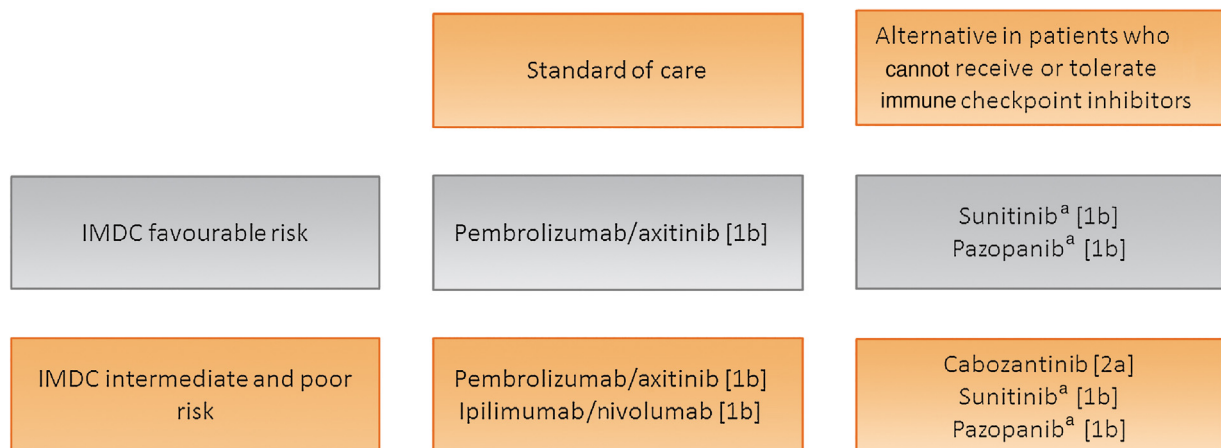
Since OS results are awaited, even this combination cannot currently be recommended.

Cross-trial comparison is not recommended and should be done with caution (Table 1). However, there were some inconsistencies across trials, which should be discussed. The proportions of patients across risk groups in the trials were inconsistent, as the ipilimumab plus nivolumab trial focused on intermediate- and poor-risk populations. The geography of recruitment may have an effect on subsequent therapy, and the pembrolizumab plus axitinib trial had a large proportion of patients from outside the USA and Western Europe. RRs and PFS appeared higher for the avelumab plus axitinib and pembrolizumab plus axitinib studies than in the ipilimumab plus nivolumab trial. It is possible that CR rates for ipilimumab plus nivolumab may be higher than those for pembrolizumab plus axitinib (9% vs 6% at interim analysis), but follow-up remains short and numbers are too small to draw any conclusions at this stage. More mature data from the two most recent studies will address some, but not all, of these issues.

This leaves, to date, two immune checkpoint inhibitor-based combinations with proven OS benefit as new standards of care for first-line cc mRCC patients (Fig. 1 and Table 2). Pembrolizumab plus axitinib was active irrespective of IMDC risk group and PD-L1 status. The combination achieved all three endpoints of RR, PFS, and OS (47% reduced risk of death). The adverse event profile was in line with the control arm, while QoL data are awaited. This combination can therefore be recommended as a new standard of care in the first-line setting in all IMDC risk groups.

For treatment-naïve IMDC intermediate- and poor-risk patients, ipilimumab plus nivolumab remains the other standard, with positive RR and OS endpoints (37% reduced risk of death). High CR rates, positive QoL data, and OS enrichment in the PD-L1-positive population (HR 0.45; 95% CI 0.29–0.71) are attractive features of this combination [7].

The role of vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR TKIs) alone in front-line

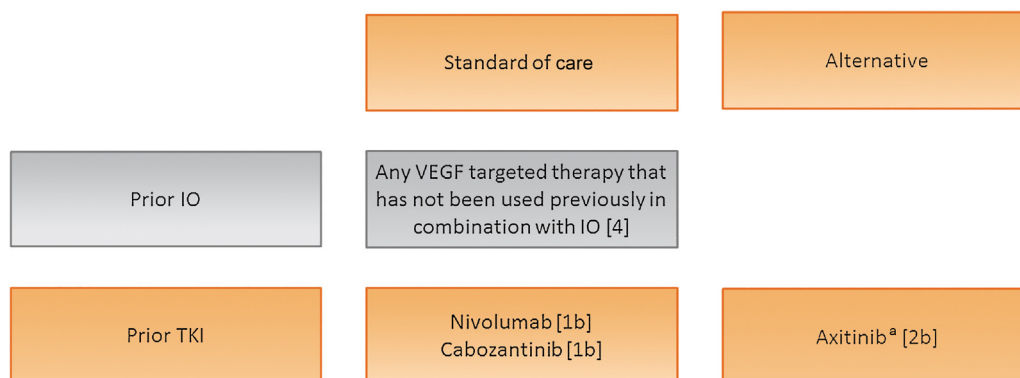


**Fig. 1 – Guideline recommendations for first-line therapy.** IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; OS = overall survival; [] = Oxford level of evidence [14]; [1b] = based on one randomised controlled phase 3 trial; [2a] = based on one randomised controlled phase 2 trial; [2b] = subgroup analysis of a randomised controlled phase 3 trial; [4] = expert opinion. <sup>a</sup>No OS benefit proven.

**Table 2 – New recommendations for front-line treatment of metastatic clear-cell RCC**

Recommendation	Strength rating
Offer pembrolizumab plus axitinib to treatment-naïve patients with any IMDC risk metastatic clear-cell RCC.	Strong
Offer ipilimumab plus nivolumab to treatment-naïve patients with IMDC intermediate- and poor-risk metastatic clear-cell RCC.	Strong
Offer sunitinib and pazopanib to treatment-naïve patients with IMDC favourable-, intermediate-, and poor-risk metastatic clear-cell RCC who cannot receive or tolerate immune checkpoint inhibition.	Strong
Offer cabozantinib to treatment-naïve patients with IMDC intermediate- and poor-risk metastatic clear-cell RCC who cannot receive or tolerate immune checkpoint inhibition.	Strong <sup>a</sup>

IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; RCC = renal cell carcinoma.  
<sup>a</sup> While this is based on a randomised phase II trial, cabozantinib (weak) looks at least as good as sunitinib in this population. This justified the same recommendation under exceptional circumstances.



**Fig. 2 – Guideline recommendations for later-line therapy.** IO = immune oncology; TKI = tyrosine kinase inhibitor; OS = overall survival; VEGF = vascular endothelial growth factor: [ ] = Oxford level of evidence [14]; [1b] = based on one randomised controlled phase 3 trial; [2b] = subgroup analysis of a randomised controlled phase 3 trial; and [4] = expert opinion. <sup>a</sup> No OS benefit proven.

mRCC has been superseded. Sunitinib, pazopanib, and cabozantinib (IMDC intermediate- and poor-risk disease) remain alternative treatment options for patients who cannot receive or tolerate immune checkpoint inhibition in this setting (Fig. 1).

There are no randomised trials to support the use of single-agent pembrolizumab or nivolumab in the front-line setting. This is a major shortcoming, which delayed the approval of the combination of ipilimumab and nivolumab by the European Medicine Agency. Randomised phase II data for atezolizumab versus sunitinib showed an HR of 1.19 (95% CI 0.82–1.71), which did not justify further development as single agents in the first-line setting [8]. Single-arm phase II data for pembrolizumab showed high RRs of 38% (up to 50% in PD-L1+ patients) but PFS of 8.7 (95% CI 6.7–12.2) [9]. Based on these results and in the absence of a randomised phase III study, a single-agent checkpoint inhibitor is presently not recommended as an alternative in the first-line setting.

CLEAR NCT02811861 (pembrolizumab plus lenvatinib vs lenvatinib plus everolimus vs sunitinib) and CHECKMATE 9ER NCT03141177 (nivolumab plus cabozantinib vs sunitinib) are on-going randomised phase III trials with sunitinib as a comparator and may place new VEGFR TKI immunoncology (IO) combinations in the discussion [10].

The impact of front-line immune-checkpoint inhibition on subsequent therapies is unclear. Randomised data on patients with disease refractory to either nivolumab plus ipilimumab or pembrolizumab plus axitinib in a first-line

setting are lacking, and available cohorts are limited [11]. Prospective data on cabozantinib and axitinib are available for patients progressing on immune therapy, but these studies do not focus on the front-line setting and merely involve subset analysis, and are too small for definitive conclusions [12,13]. Retrospective data on VEGFR TKI therapy after progression on front-line immune combinations exist but have significant limitations. When considering these data in totality, it is reasonable to conclude that there is some activity, but it remains to be defined. It is therefore not possible to recommend one VEGFR TKI above another after IO-based therapy (Fig. 2). After pembrolizumab plus axitinib combination, changing the VEGFR TKI at progression is recommended, which may be cabozantinib or any other TKI not previously used (Table 3). Data on sequencing of immune checkpoint inhibitors after failure of immune checkpoint inhibitors are lacking, and thus these inhibitors are presently not recommended.

**Table 3 – New recommendations for treatment after immune checkpoint combination therapy in the front-line setting**

Recommendation	Strength rating
Offer any vascular endothelial growth factor-targeted therapy that has not been used previously to patients who progress after combination therapy with immune checkpoint inhibition.	Weak

**Author contributions:** Axel Bex had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Bex, Albiges, Powles, Ljungberg.

**Acquisition of data:** Bex, Albiges, Powles.

**Analysis and interpretation of data:** Bex, Powles, Ljungberg, Albiges, Bensalah, Giles, Hora, Kuczyk, Lam, Marconi, Merseburger, Staehler, Volpe.

**Drafting of the manuscript:** Bex.

**Critical revision of the manuscript for important intellectual content:** Albiges, Bensalah, Giles, Hora, Kuczyk, Lam, Marconi, Merseburger, Staehler, Volpe, Hofmann, Dabestani, Tahbaz, Fernández-Pello, Abu-Ghanem, Kuusk.

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## Appendix A. Supplementary data

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