Title: Updated EAU 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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Updated EAU 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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Keywords:
renal cell carcinoma; metastatic; immune checkpoint inhibitors; ipilimumab; nivolumab; sunitinib; pazopanib; cabozantinib; guidelines

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Abstract:

Recent randomized 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 (EAU) 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 International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria.

Introduction

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

Data influencing new guidelines

The CheckMate 214 study was the first of these trials to report a superiority of nivolumab and ipilimumab over sunitinib. The primary endpoint focused on the intermediate- and poor-risk population according to International Metastatic Renal Cell Carcinoma Database Consortium (IMDC), where the combination demonstrated an overall survival (OS) benefit (HR 0.63 95% 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 (RR) (39%), complete response (CR) rates (8%) and duration of response compared to sunitinib. Progression-free survival (PFS) did not achieve the pre-defined 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 as well as real-world data are required. A recent update with 30 months of data showed ongoing 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.

The Keynote-426 trial (NCT02853331) has recently reported results for the combination of pembrolizumab plus axitinib vs. sunitinib in 861 treatment-naïve cc mRCC patients [3]. OS and PFS (assessed by central independent review) in the intention-to-treat (ITT) population were the co-primary endpoints. RR and sub-group analyses of the PD-L1-positive patient population were secondary endpoints. The first interim analysis was triggered after at least 7 months of follow-up and 305 events. The trial was ended at the first interim analysis (median follow-up = 12.8 months) as both primary endpoints were achieved. The median PFS in the pembrolizumab plus axitinib arm was 15.1 months versus 11.1 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 when
compared to the sunitinib arm (OS HR 0.53; 95% CI 0.38–0.74; p<0.0001). Response rates 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 3) occurred in 63% of patients receiving pembrolizumab and axitinib vs. 58% of patients receiving sunitinib. Treatment-related deaths occurred in approximately 1% in both arms.

The JAVELIN 101 trial, a 886-patient phase 3 RCT of avelumab plus axitinib vs. sunitinib was simultaneously published [2]. It met one of its co-primary endpoints (PFS in the PD-L1 positive population at first interim analysis; median follow-up 11.5 months). PFS and OS in the ITT population were HR 0.69 (95% CI 0.56-0.84) and 0.78 (95% CI 0.55-1.08), respectively. Treatment-related adverse events (≥ grade 3) occurred in 55% in both arms. The trial is ongoing 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 bevacizu [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 proportion of patients across risk groups in the trials were inconsistent, as the ipilimumab plus nivolumab trial focused on the 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. Response rates 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 pembrolizumab plus axitinib (8% 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 for 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 (figure 1; 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). 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 first line 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-TKI) alone in front-line metastatic RCC 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 (figure 1).

Monotherapy immune checkpoint inhibitors in the front line setting
There are no randomised trials to support the use of single-agent pembrolizumab nor nivolumab in the front-line setting. This is a major shortcoming and delayed the approval of the combination of ipilimumab and nivolumab by the European Medicine Agency. Randomised phase II data for atezolizumab vs. sunitinib showed a HR of 1.19 (95%CI 0.82-1.71) which did not justify further development as single agents in first-line [8]. Single-arm phase II data for pembrolizumab showed high response rates 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, 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 ongoing randomised phase III trials with sunitinib as comparator and may place new VEGFR TKI immune-oncology (IO) combinations in the discussion [10].

**Subsequent therapy after progression on front-line IO therapy.**

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 this 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 VEGF TKI above another after IO-based combination therapy (figure 2). After pembrolizumab plus axitinib combination, changing the VEGF TKI at progression is recommended which may be cabozantinib or any other TKI not previously used (table 3). Data on sequencing immune checkpoint inhibitors after failure of immune checkpoint inhibitors is lacking and is presently not recommended.

References

Response to reviewers

Comments to Author:

Reviewer #1: To the Authors

Title: as the Authors provided new recommendations even for systemic treatments following the first line, the title should be limited to immune check point inhibition, including "clear cell", i.e. "Updated EAU Guidelines on Renal Cell Carcinoma: immune checkpoint inhibition in metastatic clear-cell renal cell carcinoma".

**RESPONSE:** We thank the reviewer for the suggestion but the main focus of our manuscript is the change in first-line treatment. In order to address the issues of second-line treatments following the new immune checkpoint inhibitor based first-line treatment we discuss briefly further line treatments but this update is primarily meant to discuss the recent publication of the pembrolizumab and axitinib and avelumab and axitinib trials in view of guideline changes. We want to point out that 'clear-cell' was already added to “metastatic renal cell carcinoma” and we believe that our chosen title captures the update appropriately.

Data influencing new guidelines:
- Page 2, line 6 "paradigm shift in the treatment of the disease and a change in the EAU guidelines in 2017 [5]": it is not 2017, but 2019, referring to reference nr 5

**RESPONSE:** We thank the reviewer, this is indeed 2019.

- Page 3, line 5 "positive population revealed an OS of 0.45 (95%CI: 0.29-0.71)": of HR 0.45 maybe; please check

**RESPONSE:** Indeed, this should be HR. We added …”revealed an OS HR of 0.45”. Thank you

- Page 4, lines 7-10 "It met one of its co-primary endpoints (PFS in the PD-L1 positive population at first interim analysis; median follow-up 11.5 months. PFS and OS in the ITT population was HR 0.69 (95% CI 0.56-0.84) and 0.78 (95% CI 0.55-1.08), respectively": is parenthesis necessary after "11.5 months"? Is "was" correct after "PFS and OS" or is "were" better? = "It met one of its co-primary endpoints (PFS in the PD-L1 positive population at first interim analysis; median follow-up 11.5 months). PFS and OS in the ITT population were HR 0.69 (95% CI 0.56-0.84) and 0.78 (95% CI 0.55-1.08), respectively". Please check

**RESPONSE:** Thank you. Indeed a parenthesis is necessary after 11.5 months and it should be ‘were’ instead of ‘was’. We changed accordingly.

- Page 4, lines 13-17 "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). Since OS results are awaited, this combination cannot currently be recommended."; please consider to correct as follows, or as you prefer "This combination has also achieved a PFS advantage over sunitinib in the PD-L1 positive population at interim analysis (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 ITT
population. Since OS results are awaited, even this combination cannot currently be recommended."

**RESPONSE:** We thank the reviewer for this suggestion which we have adapted.

-Page 5, lines 11-12 "This combination can therefore be recommended as a new standard of care in all IMDC risk groups."

**RESPONSE:** Good suggestion which we adapted. Thank you.

-Page 5, lines 17-21 "The role of vascular endothelial growth factor receptor-tyrosine kinase inhibitors (VEGFR-TKI) alone in front-line metastatic RCC 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 (figure 1)."

**RESPONSE:** To answer your question, TKI have indeed been superseded in every risk group. Sunitinib has been the comparator in Keynote 426 and was inferior. It is correct that sunitinib and pazopanib have level 1b evidence in figure 1 because this recommendation is grouped under the box “Alternative in patients who cannot receive or tolerate immune checkpoint inhibitors”. In these instances, TKI are still the preferred choice and the level of evidence of the pivotal sunitinib trial and COMPARZ was 1b (1b= based on one well-performed RCT).

We believe that our paragraph on immune checkpoint inhibitor monotherapy is clear and concise and reflects accurately that there is no observation. We do not feel this needs further specification.

Subsequent therapy after progression on front-line IO therapy:

-Page 6, line 1 "not possible to recommend one VEGFR TKI above another after IO-IO combination (figure": IO-IO or IO? Please check

**RESPONSE:** This is indeed not specifically after IO-IO combination, as this can also be IO-TKI combination or – moving away from first-line – even IO monotherapy (after for example nivolumab in second line). We therefore changed the sentence to “...not possible to recommend one VEGFR TKI above another after IO-based therapy”.

**References:**

-Please check if References have been listed according to Eur Urol Guidelines (i.e. Ref nr 1,9,11) -Please add vol/pages to Ref nr 2,3,4,5,6 -Please add abstract number or pages to Ref nr 9,13 -Please add journal to Ref nr 10.
RESPONSE: We checked and adapted accordingly. Thank you

Reviewer #2: Albiges et al have performed a comprehensive review of existing data from KEYNOTE-426 and JAVELIN-101. The resulting recommendations that they have produced are clear and concise; there is no dispute that I have with the rationale for their recommendations, nor with the ultimate recommendations for the group. The rationale for not including axitinib with avelumab may be viewed as contentious but I feel that this was a rational decision based on the lack of survival benefit seen in the study at most recent update.

RESPONSE: We thank the reviewer for the review. Indeed, we did not include avelumab and axitinib in the recommendations due to a lack of OS data.

Reviewer #3: This update of the EAU guideline on treatment of metastatic renal cancer contextualizes the multiple recently published randomized phase 3 trials in the systemic-treatment naive setting evaluating immune checkpoint-blockade based combination approaches. This synthesis of the data is clear, concise, and offers practical information extremely helpful to the practicing clinician. Given the US FDA approval of pembrolizumab/axitinib just yesterday, it is probably timely to include such information.

RESPONSE: We thank the reviewer for the positive review of our update.
Take home message
Pembrolizumab plus axitinib are recommended as a new standard of care in all IMDC risk groups. For treatment-naive IMDC intermediate- and poor-risk patients, ipilimumab plus nivolumab remains standard treatment. Sunitinib, pazopanib, and cabozantinib (in IMDC intermediate- and poor-risk disease) are alternative treatment options in patients who cannot receive or tolerate immune checkpoint inhibition in a first-line setting.
Figures 1 – 2

Figure 1. Guidelines Recommendations for first-line therapy

- **Standard of care**
  - Alternative in patients who can not receive or tolerate immune checkpoint inhibitors

- IMDC favourable risk
  - Pembrolizumab / Axitinib [1b]
  - Sunitinib* [1b]
  - Pazopanib* [1b]

- IMDC intermediate and poor risk
  - Pembrolizumab / Axitinib [1b]
  - Ipilimumab / Nivolumab [1b]
  - Cabozantinib [2a]
  - Sunitinib* [1b]
  - Pazopanib* [1b]

Figure 1: Guidelines Recommendations for first-line therapy
* no OS benefit proven
[ ] = 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

Figure 2. Guidelines Recommendations for later-line therapy

- **Standard of Care**
  - Alternative

- Prior IO
  - Any VEGF targeted therapy that has not been used previously in combination with IO [4]

- Prior TKI
  - Nivolumab [1b]
  - Cabozantinib [1b]
  - Axitinib* [2b]

Figure 2: Guidelines Recommendations for later-line therapy
* no OS benefit proven
[ ] = Oxford Level of Evidence [14]
[1b] = based on one randomised controlled phase 3 trial
[2b] = subgroup analysis of a randomised controlled phase 3 trial
[4] = expert opinion
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Experimental arm</th>
<th>Primary endpoint</th>
<th>Risk groups</th>
<th>PFS Median (95% CI) Hazard Ratio (HR)</th>
<th>OS Median (95% CI) Hazard Ratio (HR)</th>
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</thead>
<tbody>
<tr>
<td>KEYNOTE-426</td>
<td>861</td>
<td>Pembrolizumab 200 mg IV Q3W plus axitinib 5 mg PO BID vs sunitinib 50 mg PO QD 4/2 weeks</td>
<td>PFS and OS in the ITT by BICR</td>
<td>IMDC FAV 31% IMD 56% POOR 13% MSKCC FAV 23% IMD 66% POOR 12%</td>
<td>PFS: PEMBRO + AXI 15.1 (12.6-17.7) HR, 0.69 (95% CI: 0.57, 0.84) P = &lt;0.0001</td>
<td>OS: PEMBRO + AXI NR HR, 0.53 (95% CI: 0.38, 0.74) P = &lt; 0.0001</td>
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<td>NCT02853331 [3]</td>
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<tr>
<td>JAVELIN 101</td>
<td>886</td>
<td>Avelumab 10 mg/kg IV Q2W plus axitinib, 5 mg PO BID vs sunitinib 50 mg PO QD 4/2 weeks</td>
<td>PFS in the PD-L1+ population and OS in the ITT by BICR</td>
<td>IMDC FAV 22% IMD 62% POOR 16% MSKCC FAV 23% IMD 66% POOR 12%</td>
<td>PFS: AVE + AXI 13.8 (11.1-NE) HR, 0.61 (95% CI: 0.475, 0.790) P &lt; .0001</td>
<td>OS: AVE + AXI NR HR, 0.78 (95% CI: 0.554, 1.084) P = 0.0679</td>
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<td>NCT02684006 [2]</td>
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<td>Immotion 151</td>
<td>915</td>
<td>Atezolizumab 1200 mg fixed dose IV plus bevacizumab 15 mg/kg IV on days 1 and 22 of each 42-day cycle vs sunitinib 50 mg PO QD 4/2 weeks</td>
<td>PFS in the PD-L1+ population and OS in the ITT by IR</td>
<td>IMDC Not determined MSKCC FAV 20% IMD 70% POOR 10%</td>
<td>PFS: ATEZO + BEV 11.2 (8.9-15.0) HR, 0.74 (95% CI: 0.57, 0.96) P = 0.02</td>
<td>OS: ATEZO + BEV NR HR, 0.81 (95% CI: 0.63, 1.03) P = 0.09</td>
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<td>NCT02420821 [4]</td>
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<td>Checkmate 214</td>
<td>1096</td>
<td>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 weeks</td>
<td>PFS and OS in the IMDC intermediate and poor population by BICR</td>
<td>IMDC FAV 23% IMD 61% POOR 17% MSKCC Not determined</td>
<td>PFS: NIVO + IPI 11.8 (8.7-15.5) HR, 0.82 (99.1% CI: 0.64, 1.05) P = 0.03</td>
<td>OS: NIVO + IPI NR HR, 0.63 (99.8% CI: 0.44, 0.89) P = &lt; 0.0001</td>
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<td>NCT02231749 [6,7]</td>
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</table>
Table 1: Immune checkpoint inhibition combination trials that reported results for the front-line treatment of clear-cell mRCC*

Information under the table:
*PFS and OS results in **bold** indicate that the primary endpoint has been met.

*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; IR = investigator review; ITT = intention-to-treat population; IV = intravenous; OS = overall survival; PD-L1+ = programmed death-ligand-1 positive population; PFS = progression free survival; PO = per os (oral); POOR = poor; MSKCC = Memorial Sloan Kettering Cancer Center; N = number of patients; NE = not estimable; NR = not reached; QD = daily; Q2W/Q3W = every second/third week.

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

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offer pembrolizumab plus axitinib to treatment-naive patients with any IMDC risk metastatic clear-cell RCC.</td>
<td>Strong</td>
</tr>
<tr>
<td>Offer ipilimumab plus nivolumab to treatment-naive patients with IMDC intermediate – and poor-risk metastatic clear-cell RCC.</td>
<td>Strong</td>
</tr>
<tr>
<td>Offer sunitinib and pazopanib to treatment-naive patients with IMDC favourable-, intermediate- and poor-risk metastatic clear-cell RCC</td>
<td>Strong</td>
</tr>
</tbody>
</table>
who cannot receive or tolerate immune checkpoint inhibition.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offer cabozantinib to treatment-naive patients with IMDC intermediate- and poor-risk metastatic clear-cell RCC who cannot receive or tolerate immune checkpoint inhibition.</td>
<td>Strong*</td>
</tr>
</tbody>
</table>

*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.

Table 3: New recommendations for treatment after immune checkpoint combination therapy in front-line

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>Weak</td>
</tr>
</tbody>
</table>

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C. Each author has participated sufficiently in the work to take public responsibility for all of the content.

D. Each author qualifies for authorship by listing his or her name on the appropriate line of the categories of contributions listed below.

The authors listed below have made substantial contributions to the intellectual content of the paper in the various sections described below.

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