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Platinum Opinion

The 2021 Updated European Association of Urology Guidelines on Renal Cell Carcinoma: Immune Checkpoint Inhibitor–based Combination Therapies for Treatment-naive Metastatic Clear-cell Renal Cell Carcinoma Are Standard of Care

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Abstract

The recent randomized controlled phase III CLEAR trial results are the last to complement immune checkpoint inhibitor (ICI)-based doublet combination therapies for treatment-naïve metastatic clear-cell renal cell carcinoma. The CLEAR trial demonstrated an improved progression-free survival (PFS), overall survival (OS), and an objective response rate (ORR) benefit for the combination of lenvatinib plus pembrolizumab over sunitinib. The CheckMate-9ER trial update demonstrated an ongoing PFS, OS, and quality-of-life benefit for cabozantinib plus nivolumab over sunitinib as did the update of Keynote-426 for axitinib plus pembrolizumab in the intention-to-treat population, with a PFS benefit seen across all International Metastatic Database Consortium (IMDC) subgroups. In the IMDC intermediate- and poor-risk groups, the CheckMate-214 trial of ipilimumab plus nivolumab confirmed the OS benefit with a PFS plateauing after 30 months. The RCC Guidelines Panel recommends three tyrosine kinase inhibitors + ICI combinations of axitinib plus pembrolizumab, cabozantinib plus nivolumab, and lenvatinib plus pembrolizumab across all IMDC risk groups in advanced first-line RCC, and dual immunotherapy of ipilimumab and nivolumab in IMDC intermediate- and poor-risk groups.

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Patient summary: New data from combination trials with immune checkpoint inhibitors for advanced kidney cancer confirm a survival benefit for lenvatinib plus pembrolizumab, cabozantinib plus nivolumab (with improved quality-of-life), axitinib plus pembrolizumab, and ipilimumab plus nivolumab. These combination therapies are recommended as first-line treatment for advanced kidney cancer.

Therapy for treatment-naive metastatic clear-cell renal cell carcinoma (cc-mRCC) has changed to doublets with an immune checkpoint inhibitor (ICI) backbone targeting the programmed death-receptor (PD)-1 or its ligand (PD-L1). These doublets are either complemented by a tyrosine kinase inhibitor or a second ICI directed against the cytotoxic T-lymphocyte–associated Protein 4 (CTLA-4). In total, six phase III randomised controlled trials (RCTs) have been conducted to investigate ICI doublets against sunitinib, a previous standard of care [1–6].

The randomised phase 3 trial (RCT) CLEAR in cc-mRCC patients is the most recent trial to report (Table 1). CLEAR randomised patients in a 1:1:1 ratio to receive lenvatinib plus pembrolizumab ($n = 355$), lenvatinib plus everolimus ($n = 357$), or sunitinib ($n = 357$) [2]. The trial reached its primary endpoint of independently assessed progression-free survival (PFS) with 23.9 mo for lenvatinib plus pembrolizumab versus 9.2 mo for sunitinib (hazard ratio [HR]: 0.39, 95% confidence interval [CI]: 0.32–0.49, $p < 0.001$). Overall survival (OS) was significantly improved with lenvatinib plus pembrolizumab versus sunitinib (HR: 0.66, 95% CI: 0.49–0.88, $p = 0.005$), with a median follow-up of 26.6 mo. Objective response for lenvatinib plus pembrolizumab was 71%, with 16% of the patients achieving a complete remission; efficacy was observed across all International Metastatic Database Consortium (IMDC) risk groups, and was independent of PD-L1 status. The median duration of response for lenvatinib plus pembrolizumab in patients with a response was 25.8 mo (95% CI: 22.1–27.9). In the lenvatinib plus everolimus arm, PFS was also significantly improved compared with sunitinib with a median PFS of 14.7 mo (HR: 0.65, 95% CI: 0.53–0.80, $p < 0.001$) and the median OS was not reached (HR: 1.15, 95% CI: 0.88–1.50, $p = 0.30$). Treatment-related adverse events of grade ≥ 3 with lenvatinib plus pembrolizumab were reported in 72% of the participants. Treatment-related deaths occurred in four patients in the lenvatinib plus pembrolizumab arm and in one patient in the sunitinib arm.

In CheckMate-9ER, treatment-naïve cc-mRCC patients ($n = 651$) were randomised to nivolumab plus reduced-dose cabozantinib ($n = 323$) or sunitinib ($n = 328$) [1]. Recently, results were updated with a median follow-up of 23.5 mo [7]. The primary endpoint of PFS, as assessed by a central independent review in the intention-to-treat (ITT) population, was improved significantly for nivolumab plus cabozantinib (17.0 mo) versus sunitinib (8.3 mo; HR: 0.52, 95% CI: 0.43–0.64, $p < 0.0001$). The secondary endpoint of OS was also significantly prolonged for nivolumab plus cabozantinib (not reached) versus sunitinib (29.5 mo; HR: 0.66, 95% CI: 0.50–0.87, $p = 0.0034$). The independently assessed objective response rate (ORR) was 54.8% for nivolumab plus cabozantinib versus 28.4% for sunitinib, with a complete response rate of 9% versus 4.3%. The efficacy was observed independent of the IMDC group and PD-L1 status. Unique among these trials, CheckMate-9ER considered health-related quality of life as a secondary endpoint; two validated tools strongly indicated that the nivolumab plus cabozantinib combination was better at maintaining quality of life than sunitinib [1]. Treatment-related adverse events (grade ≥ 3) occurred in 61% of patients receiving cabozantinib and nivolumab versus 51% of patients receiving sunitinib. Treatment-related deaths occurred in one patient in the nivolumab plus cabozantinib arm and in two patients in the sunitinib arm.

The Keynote-426 RCT investigated pembrolizumab plus axitinib versus sunitinib in 861 patients with treatment-naïve cc-mRCC [5]. OS and PFS assessed by a central independent review in the ITT population were the primary endpoints; a recent update of Keynote-426 with a minimum follow-up of 23.4 mo (median follow-up 30.6 mo) demonstrated an on-going OS benefit for pembrolizumab plus axitinib in the ITT population (HR: 0.68, 95% CI: 0.55–0.85, $p < 0.001$) [8]. A PFS benefit (HR: 0.71, 95% CI: 0.60–0.84, $p < 0.0001$) was seen across all IMDC subgroups. However, in the favourable-risk group, OS was similar for pembrolizumab plus axitinib and sunitinib. In addition, patients who completed 2 yr of axitinib plus pembrolizumab treatment had excellent long-term OS of 95% and PFS of 75% at 36 mo [9].

Owing to the positive data of the trials CLEAR, CheckMate-9ER, and Keynote-426, the European Association of Urology (EAU) Renal Cell Cancer Guidelines Panel now recommends lenvatinib plus pembrolizumab, cabozantinib plus nivolumab, or axitinib plus pembrolizumab for all IMDC subgroups for treatment-naïve cc-mRCC.

A 48-mo follow-up for the phase III trial CheckMate-214 reported a continued benefit for this ICI combination in the IMDC intermediate- and poor-risk groups with median OS of 48.1 mo over sunitinib (26.6 mo; HR: 0.65, 95% CI: 0.54–0.78, $p < 0.001$) [8,10]. The PFS for nivolumab plus ipilimumab plateaued at approximately 35% after 30 mo, which indicates exceptional durability of a response. For the IMDC favourable-risk group, sunitinib continued to perform better than nivolumab plus ipilimumab, although the HR for OS is evolving over time toward the immune doublet in the 48-mo follow-up update (HR: 0.93, 95% CI: 0.62–1.40), while PFS remains in favour of sunitinib (HR: 1.84, 95% CI: 1.29–2.62). For these reasons, the EAU Renal Cell Cancer Guidelines Panel continues to recommend nivolumab and ipilimumab in the IMDC intermediate- and poor-risk patient populations only.

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Table 1 – First line immune checkpoint inhibitor combination trials for metastatic clear-cell RCC
Cross trial comparison is not recommended and should occur with caution

Phase III trials of TKI + PD-1/PD-L1 doublets						
Study	N	Experimental arm	Primary endpoint	Risk groups	PFS (mo) Median (95% CI) HR	OS (mo) Median (95% CI) HR
CheckMate-9ER **NCT03141177** Median follow-up of 23.5 mo [1,7]	651	Nivolumab 240 mg fixed-dose IV every 2 wk plus cabozantinib 40 mg PO daily vs sunitinib 50 mg PO QD 4/2 wk	PFS in the ITT by BICR	**IMDC** FAV 22% IMD 58% POOR 20% **MSKCC** Not determined	(ITT) NIVO + CABO: 17.0 (12.6–19.4) SUN: 8.3 (6.9–9.7) HR: 0.52 (95% CI: 0.43–0.64) $p < 0.0001$	(ITT) NIVO + CABO: NR (NE) SUN: 29.5 (28.4.6–NE) HR: 0.66 (98.9% CI: 0.50–0.87) $p = 0.0034$
CLEAR **NCT02811861** Median follow-up of 26.6 mo [2]	712	Pembrolizumab 200 mg IV Q3W plus lenvatinib 20 mg PO QD vs sunitinib 50 mg PO QD 4/2 wk	PFS in the ITT by BICR	**IMDC** FAV 31% IMD 59% POOR 9% n.e 1% **MSKCC** FAV 27% IMD 64% POOR 9%	(ITT) PEMBRO + LEN: 23.9 (20.8–27.7) SUN: 9.2 (6.0–11.0) HR: 0.39 (95% CI: 0.32–0.49) $p > 0.001$	(ITT) PEMBRO + LEN: NR (33.6–NE) SUN: NR (NE–NE) HR: 0.66 (95% CI: 0.49–0.88) $p = 0.005$
Immotion151 **NCT02420821** Median follow-up 24 mo [6]	915	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 wk	PFS in the PD-L1+ population and OS in the ITT by IR	**IMDC** Not determined **MSKCC** FAV 20% IMD 69% POOR 12%	(PD-L1+) ATEZO + BEV: 11.2 (8.9–15.0) SUN: 7.7 (6.8–9.7) HR: 0.74 (95% CI: 0.57–0.96) $p = 0.0217$	(ITT) ATEZO + BEV: 33.6 (29.0–NE) SUN: 34.9 (27.8–NE) HR: 0.93 (95% CI: 0.76–1.14) $p = 0.4751$
JAVELIN 101 **NCT02684006** Median follow-up 19 mo [3,11]	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	**IMDC** FAV 22% IMD 62% POOR 16% **MSKCC** FAV 23% IMD 66% POOR 12%	(PD-L1+) AVE + AXI: 13.8 (10.1–20.7) SUN: 7.0 (5.7–9.6) HR: 0.62 (95% CI: 0.49–0.78) $p < 0.0001$	(PD-L1+) AVE + AXI: NR SUN: 28.6 (27.4–NE) HR: 0.83 (95% CI: 0.60–1.15) $p = 0.1301$
KEYNOTE-426 **NCT02853331** Median follow-up 30.6 mo [5,8]	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	**IMDC** FAV 31% IMD 56% POOR 13% **MSKCC** Not determined	(ITT) PEMBRO + AXI: 15.4 (12.7–18.9) SUN: 11.1 (9.1–12.5) HR: 0.71 (95% CI: 0.60–0.84) $p < 0.0001$	(ITT) PEMBRO + AXI: NR SUN: 35.7 (33.3–NE) HR: 0.68 (95% CI: 0.55–0.85) $p = 0.0003$
Phase III trial of CTLA-4 + PD-1 doublets						
Study	N	Experimental arm	Primary endpoint	Risk groups	PFS (mo) Median (95% CI) HR	OS (mo) Median (95% CI) HR
CheckMate214 **NCT02231749** Minimum follow-up of 48 mo [4,10]	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 and OS in the IMDC intermediate and poor population by BICR	**IMDC** FAV 23% IMD 61% POOR 17% **MSKCC** Not determined	(IMDC IMD/POOR) NIVO + IPI: 11.2 (8.4–16.1) SUN: 8.3 (7.0–10.8) HR: 0.74 (95% CI: 0.62–0.88)	(IMDC IMD/POOR) NIVO + IPI: 48.1 (35.6–NE) SUN: 26.6 (22.1–33.5) HR: 0.65 (95% CI: 0.54–0.78) $p \leq 0.0001$

ATEZO = atezolizumab; AVE = avelumab; AXI = axitinib; BEV = bevacizumab; BICR = blinded independent central review; BID = twice a day; CABO = cabozantinib; CI = confidence interval; CTLA-4 = cytotoxic T-lymphocyte-associated Protein 4; FAV = favourable; HR = hazard ratio; IPI = ipilimumab; IMD = intermediate; IMDC = Metastatic Renal Cancer Database Consortium; IR = investigator review; ITT = intention-to-treat; IV = intravenous; LEN = lenvatinib; mo = months; MSKCC = Memorial Sloan Kettering Cancer Center; NE = non-estimable; NR = not reached; NIVO = nivolumab; OS = overall survival; PD-1 = programmed death-receptor 1; PEMBRO = pembrolizumab; PFS = profession-free survival; PO = by mouth; BID = twice a day; QD = once a day; Q2W = every 2 weeks; Q3W = every 3 weeks; SUN = sunitinib; wk = weeks; TKI = tyrosine kinase inhibitor.

In the phase III RCT JAVELIN RENAL 101, axitinib and avelumab were compared with sunitinib in 866 patients [3]. While the primary endpoint of PFS was met in the PD-L1–positive population, an OS advantage has not been observed in the primary efficacy population of PD-L1–positive patients (19-mo median follow-up; HR: 0.83 [95% CI: 0.60–1.15, $p = 0.1301$]) at the second interim analysis [11]. The final analysis is still pending, and this combination is not currently recommended without a significant survival signal. Similarly, the combination of atezolizumab and bevacizumab versus sunitinib met its primary endpoint of investigator-assessed PFS in the PD-L1–positive population in the IMmotion151 phase III trial [6]. However, a significant OS advantage has not been shown; without a significant

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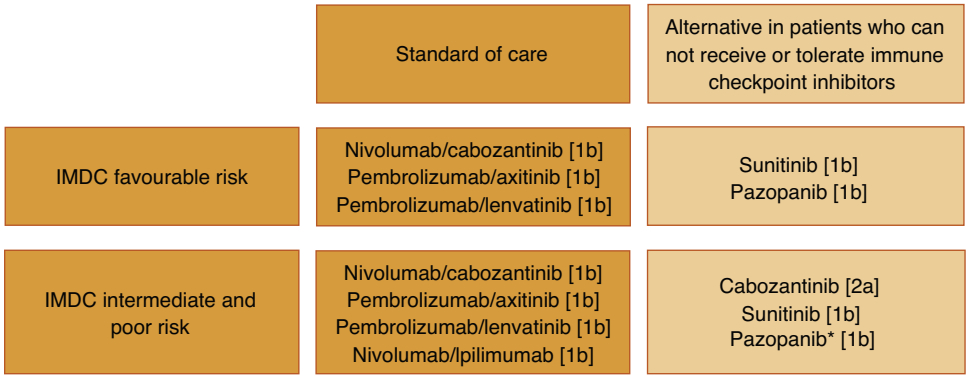

Fig. 1 – Updated European Association of Urology guidelines recommendations for the first-line treatment of metastatic clear-cell renal cancer.
IMDC = The International Metastatic Renal Cell Carcinoma Database Consortium.
***pazopanib for intermediate-risk disease only.**
[1b] = based on a randomised controlled phase III trial.
[2a] = based on a well-designed study without randomisation, or a subgroup analysis of a randomised controlled trial.

survival advantage, this combination is not currently recommended.

Collectively, four ICI combinations with proven OS benefit form the new standard of care for first-line cc-mRCC patients (Fig. 1). Pembrolizumab plus lenvatinib, nivolumab plus cabozantinib, and pembrolizumab plus axitinib show benefit irrespective of IMDC risk group and PD-L1 status. These combinations achieved all three endpoints of PFS, OS, and ORR. In addition, the 32–34% reductions in the risk of death in CLEAR, Keynote-426, and CheckMate 9ER, together with acceptable safety profiles, are reasons for recommending these three combinations as the new standard of care in all IMDC risk groups. Of the patients, <5–11% have progression of disease as the best response to these agents, which demonstrates excellent initial efficacy. For treatment-naïve IMDC intermediate- and poor-risk patients, nivolumab and ipilimumab is a fourth option, with favourable response rates and OS endpoints. The reduction in risk of death by 35%, and impressive long-term PFS plateauing at approximately 35% after 30 mo as well as superior quality of life data versus sunitinib make this combination attractive. However, immune-related adverse events are prominent when nivolumab is combined with ipilimumab, and high-dose steroids were used in 35% of patients.

In patients who cannot receive or tolerate immune checkpoint inhibition, monotherapies with sunitinib, pazopanib, and cabozantinib (intermediate- and poor-risk disease) are alternative treatment options in this setting.

Drug choice in the second- and third-line settings, after ICI combinations and subsequent vascular endothelial growth factor (VEGF)-targeted therapy, is currently unknown. The vast majority of the regimen explored was tested after sequential use of VEGF receptor tyrosine kinase inhibitors (TKIs) and single-agent PD-1 inhibition. Limited data are available to date after the failure of first-line combination regimens. The panel recommends a subsequent agent that is approved in the VEGF-refractory disease setting, with the exception of rechallenge with immune checkpoint blockade as a monotherapy [12]. Combination regimens are actively being investigated in second line or beyond. The lenvatinib plus everolimus combination was approved based on superiority versus everolimus in a small randomised phase II trial [13]. This combination has additional data in a second phase II trial of 343 patients, which also included patients with prior ICIs [14]. In addition, first data of the combination of lenvatinib plus pembrolizumab in the second-line setting demonstrated activity of this ICI + TKI combination after the use of ipilimumab plus nivolumab or TKI + ICI in the first line [15]; however, the panel advocates awaiting randomised data before recommending on-going ICI therapy.

***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.
Conception and design: J. Bedke, T. Powles, B. Ljungberg, A. Bex.
Acquisition of data: J. Bedke, T. Powles, A. Bex.
Analysis and interpretation of data: J. Bedke, T. Powles, A. Bex.
Drafting of the manuscript: J. Bedke.
Critical revision of the manuscript for important intellectual content: L. Albiges, U. Capitanio, R.H. Giles, M. Hora,T.B. Lam, B. Ljungberg,L. Marconi, T. Klatte, A. Volpe, Y. Abu-Ghanem, S. Dabestani, S. Fernández-Pello, F. Hofmann, T. Kuusk, R. Tahbaz.
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References

[1] Choueiri TK, Powles T, Burotto M, et al. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 2021;384:829–41.
[2] Motzer R, Alekseev B, Rha SY, et al. Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. N Engl J Med 2021;384:1289–300.
[3] Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 2019;380:1103–15.
[4] Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 2018;378:1277–90.
[5] Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 2019;380:1116–27.
[6] Rini BI, Powles T, Atkins MB, et al. Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): a multicentre, open-label, phase 3, randomised controlled trial. Lancet (Lond Engl) 2019;393:2404–15.
[7] Motzer RJ, Choueiri TK, Powles T, et al. Nivolumab + cabozantinib (NIVO+CABO) versus sunitinib (SUN) for advanced renal cell carcinoma (aRCC): outcomes by sarcomatoid histology and updated trial results with extended follow-up of CheckMate 9ER. J Clin Oncol 2021;39:308.
[8] Powles T, Plimack ER, Soulières D, et al. Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial. Lancet Oncol 2020;21:1563–73.
[9] Plimack ER, Powles T, Bedke J, et al. Outcomes for patients in the pembrolizumab + axitinib arm with advanced renal cell carcinoma (RCC) who completed two years of treatment in the phase III KEYNOTE-426 study. J Clin Oncol 2021;39:327.
[10] Albiges L, Tannir NM, Burotto M, et al. Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial. ESMO Open 2020;5:e001079.
[11] Choueiri TK, Motzer RJ, Rini BI, et al. Updated efficacy results from the JAVELIN Renal 101 trial: first-line avelumab plus axitinib versus sunitinib in patients with advanced renal cell carcinoma. Ann Oncol 2020;31:1030–9.
[12] Bedke J, Albiges L, Capitanio U, et al. Updated European Association of Urology guidelines on renal cell carcinoma: nivolumab plus cabozantinib joins immune checkpoint inhibition combination therapies for treatment-naive metastatic clear-cell renal cell carcinoma. Eur Urol 2021;79:339–42.
[13] 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.
[14] Pal SK, Puente J, Heng DYC, et al. Phase II trial of lenvatinib (LEN) at two starting doses + everolimus (EVE) in patients (pts) with renal cell carcinoma (RCC): results by independent imaging review (IIR) and prior immune checkpoint inhibition (ICI). J Clin Oncol 2021;39:307.
[15] Lee C-H, Shah AY, Hsieh JJ, et al. Phase II trial of lenvatinib (LEN) plus pembrolizumab (PEMBRO) for disease progression after PD-1/PD-L1 immune checkpoint inhibitor (ICI) in metastatic clear cell renal cell carcinoma (mccRCC). J Clin Oncol 2020;38:5008.

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