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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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