available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Brief Correspondence

Updated European Association of Urology Guidelines on Renal Cell Carcinoma: Nivolumab plus Cabozantinib Joins Immune Checkpoint Inhibition Combination Therapies for Treatment-naïve Metastatic Clear-Cell Renal Cell Carcinoma

Jens Bedke [a,b], *Laurence Albiges* [c], *Umberto Capitanio* [d,e], *Rachel H. Giles* [f,g], *Milan Hora* [h], *Thomas B. Lam* [i,j], *Börje Ljungberg* [k], *Lorenzo Marconi* [l], *Tobias Klatte* [m,n], *Alessandro Volpe* [o], *Yasmin Abu-Ghanem* [p], *Saeed Dabestani* [q], *Sergio Fernández Pello* [r], *Fabian Hofmann* [s], *Teele Kuusk* [t], *Rana Tahbaz* [u], *Thomas Powles* [v], *Axel Bex* [w,x,y,*]

[a] *Department of Urology, University Hospital Tuebingen, Tuebingen, Germany;* [b] *German Cancer Consortium (DKTK) and German Cancer Research Center (DKFZ), Heidelberg, Germany;* [c] *Department of Cancer Medicine, Gustave Roussy, Université Paris-Saclay, Villejuif, France;* [d] *Department of Urology, San Raffaele Scientific Institute, Milan, Italy;* [e] *Division of Experimental Oncology/Unit of Urology, Urological Research Institute, IRCCS San Raffaele Hospital, Milan, Italy;* [f] *Department of Nephrology and Hypertension, University Medical Center Utrecht, Utrecht, The Netherlands;* [g] *Patient Advocate, International Kidney Cancer Coalition, Utrecht, The Netherlands;* [h] *Department of Urology, University Hospital Pilsen and Charles University Faculty of Medicine in Pilsen, Pilsen, Czech Republic;* [i] *Academic Urology Unit, University of Aberdeen, Aberdeen, UK;* [j] *Department of Urology, Aberdeen Royal Infirmary, Aberdeen, UK;* [k] *Department of Surgical and Perioperative Sciences, Urology and Andrology, Umeå University, Umeå, Sweden;* [l] *Department of Urology, Coimbra University Hospital, Coimbra, Portugal;* [m] *Department of Urology, Royal Bournemouth Hospital, Bournemouth, UK;* [n] *Department of Surgery, University of Cambridge, Cambridge, UK;* [o] *Department of Urology, University of Eastern Piedmont, Maggiore della Carità Hospital, Novara, Italy;* [p] *Department of Urology, Chaim Sheba Medical Center, Tel-Hashomer, Ramat-Gan, Israel;* [q] *Department of Translational Medicine, Division of Urological Cancers, Lund University, Malmö, Sweden;* [r] *Department of Urology, Cabueñes University Hospital, Gijón, Spain;* [s] *Department of Urology, Sunderby Sjukhus, Umeå University, Luleå, Sweden;* [t] *Department of Urology, Darent Valley Hospital, Dartford and Gravesham NHS Trust, Dartford, UK;* [u] *Department of Urology, Elbe Kliniken, Stade, Germany;* [v] *The Royal Free NHS Trust and Barts Cancer Institute, Queen Mary University of London, London, UK;* [w] *The Royal Free London NHS Foundation Trust, London, UK;* [x] *UCL Division of Surgery and Interventional Science, University College London, London, UK;* [y] *Department of Urology, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands*

Article info

Article history:
Accepted December 1, 2020

Associate Editor:
James Catto

Keywords:
Nivolumab
Cabozantinib
Systemic therapy
First line

Abstract

Longer follow-up and new trial data from phase 3 randomised controlled trials investigating immune checkpoint blockade (PD-1 or its ligand PD-L1) in advanced clear-cell renal cell carcinoma (RCC) have recently become available. The CheckMate 9ER trial demonstrated an improved progression-free survival (PFS) and overall survival (OS) benefit for the combination of cabozantinib plus nivolumab. A Keynote-426 update demonstrated an ongoing OS benefit for pembrolizumab plus axitinib in the intention-to-treat population, with a PFS benefit seen across all International Metastatic Database Consortium (IMDC) subgroups, while an update of CheckMate 214 confirmed the long-term benefit of ipilimumab plus nivolumab in IMDC intermediate and poor risk patients. The RCC Guidelines Panel continues to recommend these tyrosine kinase inhibitors + immunotherapy (IO) combination across IMDC risk groups in advanced first-line RCC and dual immunotherapy of ipilimumab and nivolumab in IMDC intermediate and poor risk.

* Corresponding author. UCL Division of Surgery and Interventional Science, Pond Street, London NW3 2QG, UK.
E-mail address: a.bex@ucl.ac.uk (A. Bex).

https://doi.org/10.1016/j.eururo.2020.12.005

Treatment-naïve
Clear cell
Renal cell carcinoma

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

Six phase 3 randomised controlled trials (RCTs) have investigated immune checkpoint blockade (PD-1 or its ligand PD-L1) in advanced clear-cell renal cancer. The treatment consisted of PD-1/PD-L1 inhibition in combination with therapy targeting CTLA-4 signalling or VEGF. The comparator arm was sunitinib in all of the studies. The most recent study was the CheckMate 9ER study (Table 1). CheckMate 9ER randomised 651 patients to nivolumab plus cabozantinib ($n = 323$) or sunitinib ($n = 328$) in treatment-naïve clear-cell metastatic renal cell carcinoma (cc-mRCC). The primary endpoint of progression-free survival (PFS) assessed by central independent review in the intention-to-treat (ITT) population was significantly prolonged for nivolumab + cabozantinib (16.6 mo) compared to sunitinib (8.3 mo; hazard ratio [HR] 0.51, 95% confidence interval [CI] 0.41–0.64; $p < 0.0001$). Nivolumab plus cabozantinib also demonstrated a significant overall survival (OS) benefit in the secondary endpoint compared with sunitinib (HR 0.60, 95% CI 0.40–0.89; $p = 0.0010$) after median follow-up of 18.1 mo. The independently assessed objective response rate was 56% versus 27%, with a complete response (CR) rate of 8% for nivolumab + cabozantinib versus 4% with sunitinib. The efficacy was observed independently of International Metastatic RCC Database Consortium (IMDC) risk group or PD-L1 status. Treatment-related adverse events (AEs) of grade ≥3 occurred in 61% of the patients receiving

Table 1 – First-line immune checkpoint inhibitor combination trials for clear-cell RCC[a]

Study	*N*	Experimental arm	Primary endpoint	Risk groups	Median PFS, mo (95% CI)	Median OS, mo (95% CI)
KEYNOTE-426 **NCT02853331** **Median follow-up 30.6 mo** [3,5]	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) $p = 0.0003$
JAVELIN 101 **NCT02684006** **Median follow-up 19 mo** [6,7]	886	Avelumab 10 mg/kg IV Q2W + AXI 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) $p = 0.1301$
IMmotion 151 **NCT02420821** **Median follow-up 24 mo** [8]	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) $p = 0.4751$
CheckMate214 **NCT02231749** **Minimum follow-up of 48 months** [2,4]	1096	Nivolumab 3 mg/kg + 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 (0.54–0.78) $p < 0.0001$
CheckMate 9ER **Median follow-up of 18.1 months** **NCT03141177** [1]	651	Nivolumab 240 mg fixed dose IV every 2 wk + cabozantinib 40 mg PO daily vs sunitinib 50 mg PO QD4/2 wk	PFS in the ITT by BICR	IMDC FAV 22% IMD 58% POOR 20% **MSKCC** Not determined	(ITT) NIVO + CABO: 16.6 (12.5–24.9) SUN: 8.3 (7.0–9.7) HR 0.51 (95% CI 0.41–0.64) $p < 0.0001$	(ITT) NIVO + CABO: NR SUN: NR (22.6–NE) HR 0.60 (98.9% CI 0.40–0.89) $p = 0.0010$

ATEZO = atezolizumab; AVE = avelumab; AXI = axitinib; BEV = bevacizumab; BICR = blinded independent central review; BID = twice a day; CABO = cabozantinib; CI = confidence interval; FAV = favourable; HR = hazard ratio; IPI = ipilimumab; IMD = intermediate; IMDC = Metastatic Renal Cancer Database Consortium; IR = investigator review; ITT = intention-to-treat; IV = intravenous; mo = months; MSKCC = Memorial Sloan Kettering Cancer Center; NE = non-estimable; NR = not reached; NIVO = nivolumab; OS = overall survival; 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.

[a] Cross trial comparison is not recommended and should occur with caution.

Please cite this article in press as: Bedke J, et al. Updated European Association of Urology Guidelines on Renal Cell Carcinoma: Nivolumab plus Cabozantinib Joins Immune Checkpoint Inhibition Combination Therapies for Treatment-naïve Metastatic Clear-Cell Renal Cell Carcinoma. Eur Urol (2020), https://doi.org/10.1016/j.eururo.2020.12.005

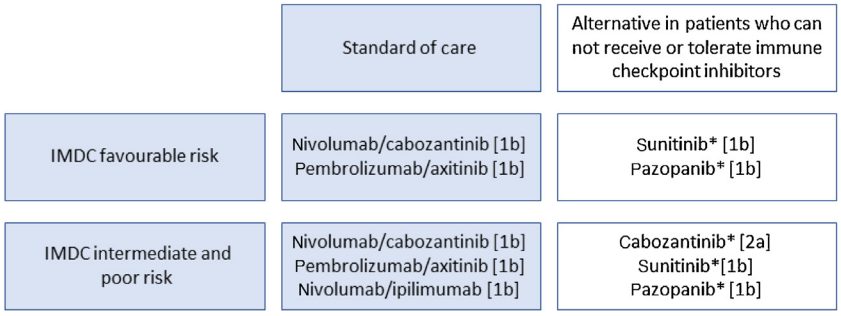

Fig. 1 – Updated European Association of Urology guideline recommendations for the first-line treatment of metastatic clear-cell renal cancer. IMDC = International Metastatic Renal Cell Carcinoma Database Consortium. [1b] = based on a randomised controlled phase 3 trial. [2a] = based on a well-designed study without randomisation, or a subgroup analysis of a randomised controlled trial. * Pazopanib for intermediate-risk disease only.

cabozantinib and nivolumab versus 51% of the patients receiving sunitinib [1].

The CheckMate214 and Keynote-426 trials were updated with longer-follow up [2,3]. CheckMate214 was the first of these trials, showing superiority of nivolumab and ipilimumab over sunitinib in patients with IMDC intermediate and poor risk [4]. A recent update with 48-mo data showed ongoing benefits for the immune checkpoint inhibition combination, with an OS HR of 0.65 (95% CI 0.54–0.78) in the IMDC intermediate- and poor-risk group. The 48-mo OS probability was 50% with ipilimumab and nivolumab versus 39% with sunitinib. The PFS for nivolumab and ipilimumab at 48 mo was >30%, indicating exceptional durability of response. The IMDC good-risk group continues to perform better with sunitinib, although this appears less marked than in earlier analyses (HR for OS 0.93, 95% CI 0.62–1.40) [2]. For these reasons, the European Association of Urology Renal Cell Cancer Guidelines Panel continues to recommend nivolumab and ipilimumab for patients with IMDC intermediate and poor risk.

The Keynote-426 RCT investigated pembrolizumab plus axitinib versus sunitinib in 861 patients with treatment-naïve cc-mRCC [5]. OS and PFS in the ITT population were the primary endpoints assessed by central independent review. The response rate, PFS, and OS for the PD-L1–positive patient population were secondary endpoints.

A recent update of Keynote-426 with a minimum follow-up of 23.4 mo (median follow-up 30.6 mo) demonstrated an ongoing OS benefit for pembrolizumab plus axitinib in the ITT population (HR 0.68, 95% CI 0.55–0.85; $p < 0{\cdot}001$). A PFS benefit (HR 0.71, 95% CI 0.60–0.84; $p < 0{\cdot}0001$) was seen across all IMDC subgroups. In the favourable-risk group, OS was similar for pembrolizumab plus axitinib versus sunitinib [3]. The Guidelines Panel continues to recommend this combination across all IMDC risk groups as first-line treatment in advanced RCC.

The JAVELIN Renal 101 trial is a 886-patient phase 3 RCT of avelumab and axitinib versus sunitinib with primary endpoints of PFS and OS in the PD-L1–positive population [6]. At the second interim analysis, an OS advantage has not been shown in the primary efficacy population of PD-L1–positive patients (19-mo median follow-up, HR 0.83, 95% CI 0.60–1.15; $p = 0.1301$) [7]. While the final analysis is awaited, this combination is not recommended without a significant survival signal.

The IMmotion 151 trial explored atezolizumab and bevacizumab versus sunitinib and it met its PFS endpoint in the PD-L1–positive population, but a significant OS has not yet been shown [8]. This combination is not recommended without a significant survival signal.

This leaves three immune checkpoint inhibitor combinations with proven OS benefit as the new standard of care for first-line treatment of cc-mRCC (Fig. 1). Pembrolizumab plus axitinib and nivolumab plus cabozantinib are active irrespective of IMDC risk group and PD-L1 status. These combinations achieved all three endpoints of RR, PFS, and OS. In addition, the 48–32% and 40% reduction in the risk of death in Keynote-426 and CheckMate 9ER, respectively, with acceptable AE rates are reasons to recommend both combinations as the new standard of care in all IMDC risk groups. Fewer than 15% of patients have progression of disease as the best response to these agents, which demonstrates excellent initial efficacy. For treatment-naïve patients with IMDC intermediate and poor risk, nivolumab plus ipilimumab is a third option with favourable response rates and OS endpoints. The reduction in risk of death by 35% and impressive long-term PFS, superior quality-of-life data, and OS advantage in the PD-L1–positive population (HR 0.41) make this combination attractive. However, immune-related AEs are prominent when nivolumab is combined with ipilimumab, and high-dose steroids were used in 35% of patients.

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

Drug choice in the second- and third-line settings, after immune checkpoint inhibitor combinations and subsequent VEGF-targeted therapy, is unknown. The panel recommends a subsequent agent that is approved in the VEGF-refractory disease setting, with the exception of re-challenge with immune checkpoint blockade. Cabozantinib is the only agent in VEGF-refractory disease having shown a survival advantage in an RCT (against everolimus) and may be used preferentially [9]. Axitinib has positive PFS data in VEGF-refractory disease (vs sorafenib) [10]. Both sorafenib

Please cite this article in press as: Bedke J, et al. Updated European Association of Urology Guidelines on Renal Cell Carcinoma: Nivolumab plus Cabozantinib Joins Immune Checkpoint Inhibition Combination Therapies for Treatment-naïve Metastatic Clear-Cell Renal Cell Carcinoma. Eur Urol (2020), https://doi.org/10.1016/j.eururo.2020.12.005

and everolimus have been outperformed by other agents in VEGF-refractory disease and therefore are less attractive. The lenvatinib plus everolimus combination appears superior to everolimus alone and has been granted European Medicines Agency regulatory approval based on randomised phase 2 data. This is an alternative treatment option despite the availability of only phase 2 data [11]. Tivozanib has PFS superiority over sorafenib in VEGF-refractory disease, as shown in a study that also included patients with prior immune checkpoint inhibitors [12]. However, there was no difference in OS [13].

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: Bedke, Powles, Ljungberg, Bex.
Acquisition of data: Bedke, Powles, Bex.
Analysis and interpretation of data: Bedke, Powles, Bex.
Drafting of the manuscript: Bedke.
Critical revision of the manuscript for important intellectual content: Albiges, Capitanio, Giles, Hora, Lam, Ljungberg, Marconi, Klatte, Volpe, Abu-Ghanem, Dabestani, Fernández Pello, Hofmann, Kuusk, Tahbaz.
Statistical analysis: None.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Bedke, Powles, Bex, Ljungberg.
Other: None.

Financial disclosures: Axel Bex certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Jens Bedke has received institutional research funding from AstraZeneca, Astellas, BMS, Eisai, Ipsen, MSD, Novartis, Nektar, Pfizer, Roche, and Seattle Genetics; and has received honoraria from BMS and MSD on an institutional basis and from AstraZeneca, Astellas, BMS, Eisai, EUSA Pharma, Ipsen, MSD, Merck Serono, Novartis, Pfizer, and Roche on a personal basis. Laurence Albiges has received consulting/advisory fees from BMS, Pfizer, Novartis, Sanofi, Amgen, Bristol-Myers Squibb, Bayer, and Cerulean; and research funding from Pfizer and Novartis. Thomas Powles has received institutional research funding from AstraZeneca, Roche, BMS, Exelixis, Ipsen, Merck/MSD, Novartis, Pfizer, Seattle Genetics, Merck Serono, Astellas, Johnson & Johnson, and Eisai; has received honoraria from AstraZeneca, BMS, Exelixis, Incyte, Ipsen, Merck/MSD, Novartis, Pfizer, Seattle Genetics, Merck Serono, Astellas, Johnson & Johnson, Eisai, and Roche on a personal basis; and has received travel, accommodation, and other expenses from Roche, Pfizer, MSD, AstraZeneca, and Ipsen. Milan Hora has received company speaker honoraria from Covidien, Olympus, Janssen, and Astellas; has participated in trials for Janssen; and has received grants/research support from Ipsen. Thomas B. Lam is a company consultant for and has received company speaker honoraria from Pfizer, GlaxoSmithKline, Astellas, and Ipsen. Teele Kuusk has received company speaker honorarium and a travel grant from Ipsen. Börje Ljungberg has received company speaker honoraria from GlaxoSmithKline, Roche, Pfizer, and Novartis; has participated in trials for GlaxoSmithKline, Medivation, Pfizer, and Janssen R&D; and has been on advisory boards for Pfizer and GlaxoSmithKline. Axel Bex has received company speaker honoraria from Pfizer; has participated in trials for Pfizer Europe; has participated in advisory boards for BMS, GlaxoSmithKline, and Novartis; is a company consultant for Pfizer and Novartis; and has received grants/research support from Pfizer. The remaining authors have nothing to disclose.

Funding/Support and role of the sponsor: None.

References

[1] Choueiri TK, Powles T, Burottto M, et al. 696O_PR Nivolumab + cabozantinib vs sunitinib in first-line treatment for advanced renal cell carcinoma: first results from the randomized phase III CheckMate 9ER trial. Ann Oncol 2020;31:S1159.
[2] Albiges L, Tannir N, Burotto M, et al. 711P Nivolumab + ipilimumab (N+I) vs sunitinib (S) for first-line treatment of advanced renal cell carcinoma (aRCC) in CheckMate 214: 4-year follow-up and subgroup analysis of patients (pts) without nephrectomy. Ann Oncol 2020;31:S559–60.
[3] 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(12):1563–73.
[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] 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.
[7] 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.
[8] 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 2019;393:2404–15.
[9] Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. Lancet Oncol 2016;17:917–27.
[10] 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.
[11] 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.
[12] Rini BI, Pal SK, Escudier BJ, et al. Tivozanib versus sorafenib in patients with advanced renal cell carcinoma (TIVO-3): a phase 3, multicentre, randomised, controlled, open-label study. Lancet Oncol 2020;21:95–104.
[13] Pal SK, Escudier BJ, Atkins MB, et al. Final overall survival results from a phase 3 study to compare tivozanib to sorafenib as third- or fourth-line therapy in subjects with metastatic renal cell carcinoma. Eur Urol 2020;78(6):783–5.

Please cite this article in press as: Bedke J, et al. Updated European Association of Urology Guidelines on Renal Cell Carcinoma: Nivolumab plus Cabozantinib Joins Immune Checkpoint Inhibition Combination Therapies for Treatment-naïve Metastatic Clear-Cell Renal Cell Carcinoma. Eur Urol (2020), https://doi.org/10.1016/j.eururo.2020.12.005