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

European Association of Urology

Guidelines

European Association of Urology Guidelines for Clear Cell Renal Cancers That Are Resistant to Vascular Endothelial Growth Factor Receptor–Targeted Therapy

Thomas Powles [a,*], *Michael Staehler* [b], *Börje Ljungberg* [c], *Karim Bensalah* [d], *Steven E. Canfield* [e], *Saeed Dabestani* [f], *Rachel H. Giles* [g], *Fabian Hofmann* [h], *Milan Hora* [i], *Markus A. Kuczyk* [j], *Thomas Lam* [k], *Lorenzo Marconi* [l], *Axel S. Merseburger* [m], *Alessandro Volpe* [n], *Axel Bex* [o]

[a] *The Royal Free NHS Trust and Barts Cancer Institute, Queen Mary University of London, London, UK;* [b] *Department of Urology, Ludwig-Maximilians University, Munich, Germany;* [c] *Department of Surgical and Perioperative Sciences, Urology and Andrology, Umeå University, Umeå, Sweden;* [d] *Department of Urology, University of Rennes, Rennes, France;* [e] *Division of Urology, University of Texas Medical School at Houston, Houston, TX, USA;* [f] *Department of Urology, Skåne University Hospital, Malmö, Sweden;* [g] *Patient Advocate International Kidney Cancer Coalition (IKCC), University Medical Centre Utrecht, Nephrology Department, Utrecht, The Netherlands;* [h] *Department of Urology, Sunderby Hospital, Sunderby, Sweden;* [i] *Department of Urology, Faculty Hospital and Faculty of Medicine in Pilsen, Charles University in Prague, Prague, Czech Republic;* [j] *Department of Urology and Urologic Oncology, Hannover Medical School, Hannover, Germany;* [k] *Academic Urology Unit, University of Aberdeen, Aberdeen, UK;* [l] *Department of Urology, Coimbra University Hospital, Coimbra, Portugal;* [m] *Department of Urology, University Hospital Schleswig-Holstein, Lübeck, Germany;* [n] *Division of Urology, Maggiore della Carità Hospital, University of Eastern Piedmont, Novara, Italy;* [o] *Department of Urology, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands*

Article info

Article history:
Accepted June 7, 2016

Associate Editor:
James Catto

Keywords:
Nivolumab
Cabozantinib
Renal cancer
Guidelines
European Association of Urology

* Corresponding author. The Royal Free NHS Trust and Barts Cancer Institute, Queen Mary University of London, London EC1A7BE, UK. Tel. +44 793 204 81 09; Fax: +44 207 601 85 22.
E-mail address: Thomas.Powles@bartshealth.nhs.uk (T. Powles).

These guidelines give recommendations on the use of nivolumab and cabozantinib in vascular endothelial growth factor receptor (VEGFR)–targeted therapy for refractory clear cell renal cell carcinoma (RCC) after data from two pivotal trials [1,2]. An update is required related to new data that simplify the recommendations (Fig. 1). The most recent data for consideration are the overall survival data for cabozantinib (METEOR) [3]. Median overall survival was 21.4 mo (95% confidence interval [CI], 18.7 to not estimable) with cabozantinib and 16.5 mo (95% CI, 14.7–18.8) with everolimus in vascular endothelial growth factor (VEGF)–resistant RCC. The hazard ratio for death was 0.66 (95% CI, 0.53–0.83; $p = 0.0003$). Consequently, both nivolumab and cabozantinib can be recommended with a survival advantage in this setting. It is advisable to sequence one of these two drugs after initial VEGFR-targeted therapy failure to maximise survival. Impressive quality-of-life data are available for nivolumab. These data are still awaited for cabozantinib. A progression-free survival advantage was seen for cabozantinib; this is not the case for nivolumab.

http://dx.doi.org/10.1016/j.eururo.2016.06.009

Please cite this article in press as: Powles T, et al. European Association of Urology Guidelines for Clear Cell Renal Cancers That Are Resistant to Vascular Endothelial Growth Factor Receptor–Targeted Therapy. Eur Urol (2016), http://dx.doi.org/10.1016/j.eururo.2016.06.009

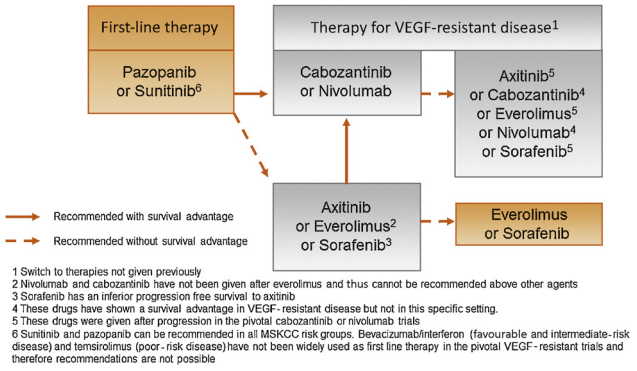

Fig. 1 – Summary of recommendations on the use of nivolumab and cabozantinib in vascular endothelial growth factor receptor–targeted therapy for refractory clear cell renal cell carcinoma.
MSKCC = Memorial Sloan Kettering Cancer Center; VEGF = vascular endothelial growth factor.

Other agents are licenced in VEGF-refractory disease [4]. These include axitinib, everolimus, and sorafenib. All three can be considered for patients, especially if nivolumab or cabozantinib is not available. All three were used after progression in the pivotal cabozantinib and nivolumab trials [2,3]. It is not possible to give recommendations for one of these agents over another in this setting due to a lack of data. In addition, cabozantinib and nivolumab have not been sequenced in large numbers with each other (a small number of patients received cabozantinib after nivolumab). Consequently, although sequencing these drugs appears wise based on efficacy, data are lacking, making strong recommendations over other available agents potentially flawed.

The only prospective study that directly compares two licenced tyrosine kinase inhibitors (axitinib vs sorafenib) in VEGF-refractory disease is the AXIS trial. This study showed axitinib has a progression-free survival advantage but not an overall survival advantage over sorafenib [5]. In VEGF-refractory disease, axitinib has robust data only in the second-line setting, potentially reducing its utility in later lines of therapy.

Conflicts of interest: T. Powles is a company consultant for Novartis, Pfizer, GSK; has received company speaker honoraria from Novartis, Pfizer, GSK, Genentech; performed trial participation for GSK, Pfizer, BMS, Genentech, Genetech; and received grants/research support from GSK, Pfizer, and Novartis. A. Bex has received company speaker honoraria from Pfizer; performed trial participation for Pfizer Europe; participated on advisory boards for GSK and Novartis; is a company consultant for Pfizer and Novartis; and received grants/research support from Pfizer. M. Staehler is a company consultant for Pfizer, Novartis, GSK, Roche, Astellas, Bayer; has received company speaker honoraria from Pfizer, Novartis, GSK, Roche, Astellas, Bayer, Aveo; has performed trial participation for Pfizer, Novartis, GSK, Roche, Bayer, Aveo, Wilex, Immatics; has received fellowships and travel grants from Pfizer, Novartis, GSK, Roche, Bayer; has received grants/research support from Pfizer, Novartis, GSK, Roche, Bayer, and Aveo. B. Ljungberg has received company speaker honoraria from GlaxoSmith Kline, Roche, Pfizer, Novartis; performed trial participation for GlaxoSmithKline, Medivation, Pfizer, Janssen R&D, Inc.; and been on advisory boards for Pfizer and GSK. K. Bensalah has received grants/research support from Pfizer and honoraria or consultation fees from Intuitive Surgical. S. Canfield has received company speaker honoraria from Amgen, Genomic Health, Algeta, and Bayer. M. Hora has received company speaker honoraria from Covidien, Olympus, Janssen, Astellas; performed trial participation for Janssen; and received grants/research support from Ipsen. M.A. Kuczyk is a stock shareholder of Bayer Healthcare, Astellas, Storz, Pfizer, Wyeth, Novartis; is a company consultant for Karl Storz, Coloplast, AstraZeneca, Astellas, Storz, Hexal AG; has received company speaker honoraria from Pfizer, Astellas, Bayer, GSK, Pierre Fabre, Janssen Cilag, Hexal; performed trial participation for the Protect Study, Millenium Study C21004, Millenium Study C21005, Astellas, Ipsen, Janssen; and received grants/research support from Wyeth and Pfizer. T. Lam is a company consultant for and has received company speaker honoraria from Pfizer, GSK, Astellas, and Ipsen. A. Merseburger is a company consultant for Ipsen Pharma, Bayer, Astellas, Janssen Cilag, Novartis, and Pfizer; has received company speaker honoraria from Ipsen Pharma, Wyeth, Astellas, Novartis, Pfizer, SEP; performed trial participation for AstraZeneca, Bayer, Pfizer, TEVA, Novartis, Astellas; received grants/research support from Wyeth; and participated in a company-sponsored speakers bureau for TEVA, Janssen, Pfizer, Astellas, Ferring, and Novartis. S. Dabestani, R.H. Giles, F. Hofmann, L. Marconi, and A. Volpe have nothing to disclose.

References

[1] Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015;373:1814–23.
[2] Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015;373:1803–13.
[3] 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. http://dx.doi.org/10.1016/S1470-2045(16)30107-3, pii: S1470-2045(16)30107-3. [Epub ahead of print].
[4] Powles T, Staehler M, Ljungberg B, et al. Updated EAU guidelines for clear cell renal cancer patients who fail VEGF targeted therapy. Eur Urol 2016;69:4–6.
[5] Motzer RJ, Escudier B, Tomczak P, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. Lancet Oncol 2013;14:552–62.

Please cite this article in press as: Powles T, et al. European Association of Urology Guidelines for Clear Cell Renal Cancers That Are Resistant to Vascular Endothelial Growth Factor Receptor–Targeted Therapy. Eur Urol (2016), http://dx.doi.org/10.1016/j.eururo.2016.06.009