

Conflicts of interest: The authors have nothing to disclose.

Acknowledgements: We thank the radiographer team of the Department of Radiotherapy and Radiooncology of the Medical University of Innsbruck. This work was funded by the Austrian Science Fund (P26799 to F.R.S.) and by the Daniel den Hoed Foundation (Cancer Computation Biology Center).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at <https://doi.org/10.1016/j.eururo.2018.06.002>.

References

- [1] Rycak K, Tang DG. Cancer stem cells and radioresistance. *Int J Radiat Biol* 2014;90:615–21. <https://doi.org/10.3109/09553002.2014.892227>.
- [2] Frame FM, Pellacani D, Collins AT, et al. HDAC inhibitor confers radiosensitivity to prostate stem-like cells. *Br J Cancer* 2013;109:3023–33. <https://doi.org/10.1038/bjc.2013.691>.
- [3] Celià-Terrassa T, Liu DD, Choudhury A, et al. Normal and cancerous mammary stem cells evade interferon-induced constraint through the miR-199a-LCOR axis. *Nat Cell Biol* 2017;19:711–23. <https://doi.org/10.1038/ncb3533>.
- [4] Hyka-Nouspikel N, Desmarais J, Gokhale PJ, et al. Deficient DNA damage response and cell cycle checkpoints lead to accumulation of point mutations in human embryonic stem cells. *Stem Cells* 2012;30:1901–10. <https://doi.org/10.1002/stem.1177>.
- [5] Rachidi W, Harfourche G, Lemaitre G, Amiot F, Vaigot P, Martin MT. Sensing radiosensitivity of human epidermal stem cells. *Radiother Oncol* 2007;83:267–76. <https://doi.org/10.1016/j.radonc.2007.05.007>.

^aDepartment of Urology, Division of Experimental Urology, Medical University of Innsbruck, Innsbruck, Austria

^bCancer Computational Biology Center, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, The Netherlands

^cDepartment of Urology, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, The Netherlands

^dDepartment of Urology and Pediatric Urology, University Medical Center Mainz, Mainz, Germany

^eDepartment of Plastic, Reconstructive and Aesthetic Surgery, Medical University of Innsbruck, Innsbruck, Austria

^fDepartment of Pathology, Medical University of Innsbruck, Innsbruck, Austria

^gDepartment of Radiotherapy and Radiooncology, Medical University of Innsbruck, Innsbruck, Austria

*Corresponding author. Division of Experimental Urology, Department of Urology, Medical University of Innsbruck, Anichstrasse 35, 6020 Innsbruck, Austria. Tel. +43 512 50481801; Fax: +43 512 50424817. E-mail address: frederic.santer@i-med.ac.at (F.R. Santer).

June 1, 2018

<https://doi.org/10.1016/j.eururo.2018.06.002>



A Joint Statement from the European Association of Urology Renal Cell Cancer Guidelines Panel and the International Kidney Cancer Coalition: The Rejection of Ipilimumab and Nivolumab for Renal Cancer by the Committee for Medicinal Products for Human Use Does not Change Evidence-based Guideline Recommendations

Axel Bex^a, Laurence Albiges^b, Michael Staehler^c, Karim Bensalah^d, Rachel H. Giles^{e,f}, Saeed Dabestani^g, Fabian Hofmann^h, Milan Horaⁱ, Markus A. Kuczyk^j, Thomas B. Lam^{k,l}, Lorenzo Marconi^m, Axel S. Merseburgerⁿ, Sergio Fernández-Pello^o, Rana Tahbaz^p, Yasmin Abu-Ghanem^q, Alessandro Volpe^r, Börje Ljungberg^s, Bernard Escudier^t, Thomas Powles^{u,*}

Clear cell kidney cancer is associated with short median overall survival, despite the introduction of vascular endothelial growth factor (VEGF)-targeted therapy a decade ago [1]. These drugs did not achieve a significant overall survival advantage over prior standards of care in previously untreated metastatic disease in the pivotal trials. Nevertheless, patients are living longer, in part due to sequencing of these drugs [2]. A downside to

VEGF-targeted therapy is the toxicity profile that has a major impact on quality of life.

The introduction of immune checkpoint inhibitors has changed the way renal cancer is treated, with nivolumab being established as a standard of care in VEGF-refractory disease [3]. More recently, a large, well-conducted randomised trial comparing the combination of ipilimumab (1 mg/kg) and nivolumab (3 mg/kg) with standard VEGF-targeted

therapy in previously untreated metastatic disease was reported (Checkmate-214) [4].

The combination of ipilimumab and nivolumab showed significant superiority for patients with intermediate- and poor-risk features (42% partial response and 9% complete response rate) over the current standard of care sunitinib (27% and 1%, respectively). The overall survival was significantly better for the immunotherapy arm with a 37% reduced chance of death from kidney cancer. The median survival for sunitinib was 26 mo, but has not yet been reached for the immunotherapy arm with an unprecedented hazard ratio of 0.63. Both the adverse event profile and the quality of life data also favoured the immunotherapy combination. This combination therapy is the most significant achievement in the field of kidney cancer in over a decade.

This trial was ground breaking and has dramatically changed how physicians and patients are managing kidney cancer. The data have already led to rapid changes in European Association of Urology and National Comprehensive Cancer Network guidelines, making the immunotherapy combination the new standard of care for patients with intermediate- and poor-risk features [5]. In April of this year, the combination of ipilimumab and nivolumab was approved as first-line therapy in high- and intermediate-risk patients by the U.S. Food and Drug Administration, and it has since been similarly approved in Canada, Australia, and Switzerland.

On 26 July 2018, the Committee for Medicinal Products for Human Use (CHMP) gave a negative opinion for the use of this combination as first-line therapy. Although improvements in survival were seen in previously untreated patients, the CHMP objected to the lack of evidence showing that ipilimumab contributed to the efficacy of nivolumab.

Nivolumab alone is active in previously treated patients with renal cell carcinoma [3]. Therefore, the CHMP were concerned that the addition of ipilimumab to nivolumab may add toxicity without proven efficacy. There are only limited nivolumab monotherapy data in first-line disease ($n = 24$), which is a shortcoming [6].

The Renal Cell Carcinoma Guidelines Panel of the European Association of Urology agrees with the principle that it is important to determine the contribution of each of the components of the combination, which can be studied in the future. That said, regardless of the outcome of additional research, it still has no bearing on the conclusion of the trial, which shows that the immunotherapy combination is significantly more active and better tolerated than sunitinib.

If the decision of the European Medicines Agency stands, health care providers in Europe will be forced to treat their patients with a drug that has a higher toxicity rate, lower chance of complete remission, and lower overall survival, knowing that another option exists that is potentially curative and could prolong patients' lives.

This decision will have a more profound impact on low-income patients and will create an even wider disparity than what already exists among those who have fewer resources to access treatment. Patients with private health insurance, the ability to travel outside of their respective countries, or pay out of pocket for the combination therapy

will do so based on the overwhelming data and the knowledge that the combination therapy is available in countries outside of the European Union (EU).

Unless things change, patients in the EU will be stuck with shorter overall survival, using less active and more toxic agents, putting them at a disadvantage compared with their counterparts outside the EU.

The decision of the CHMP derives from a struggle to protect patients from unnecessary toxicity and to avoid combinations where monotherapy would be equally effective. With the combination of ipilimumab and nivolumab, the problem is that this ethical principle collides with data of significantly prolonged overall survival and an increased complete response/potential cure rate. These benefits occur concurrently with reduced toxicity compared with sunitinib. The combination of ipilimumab and nivolumab is safer and more effective, and thus the decision of the CHMP is ethically unsound, leaving patients at risk of early death.

In the fight for prolonged overall survival, the combination of ipilimumab and nivolumab is the best treatment available for patients. On occasions when the supporting evidence is so clear, the guidelines required for regulatory approval by the CHMP must be flexible enough to support patients' best interests. Therefore, we will be retaining our recommendation to offer ipilimumab and nivolumab to patients with IMDC intermediate- and poor-risk features based on the high level of evidence from a randomised trial against the previous standard sunitinib.

Conflicts of interest: Professor Dr. Thomas Powles is a company consultant for Novartis, Pfizer, and GlaxoSmithKline; has received company speaker honoraria from Novartis, Pfizer, GlaxoSmithKline, BMS, MSD, and Genentech; has participated in trials for GlaxoSmithKline, Pfizer, BMS, Genentech, and Genetech; and has received grants/research support from GlaxoSmithKline, Pfizer, and Novartis. Professor Dr. Axel Bex has received company speaker honoraria from Pfizer; has participated in trials for Pfizer Europe; has participated in advisory boards for GlaxoSmithKline and Novartis; is a company consultant for Pfizer and Novartis; and has received grants/research support from Pfizer. Professor Dr. 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. Professor Dr. B. Escudier has received honorarium from BMS. Professor Dr. Laurence Albiges has received consulting/advisory fees from BMS, Pfizer, Novartis, Sanofi, Amgen, Bristol-Myers Squibb, Bayer, and Cerulean; and has received research funding from Pfizer and Novartis. Professor Dr. Karim Bensalah has received grants/research support from Pfizer and honoraria or consultation fees from Intuitive Surgical. Professor Dr. Michael Staehler is a company consultant for Pfizer, Novartis, GlaxoSmithKline, Roche, Astellas, and Bayer; has received company speaker honoraria from Pfizer, Novartis, GlaxoSmithKline, Roche, Astellas, Bayer,

and Aveo; has participated in trials for Pfizer, Novartis, GlaxoSmithKline, Roche, Bayer, Aveo, Willex, and Immatics; has received fellowships and travel grants from Pfizer, Novartis, GlaxoSmithKline, Roche, and Bayer; has received grants/research support from Pfizer, Novartis, GlaxoSmithKline, Roche, Bayer, and Aveo; and took part in the S-TRAC trial as an investigator and is an author on the S-TRAC publication. Professor Dr. 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. Professor Dr. Markus A. Kuczyk is a stock shareholder of Bayer Healthcare, Astellas, Storz, Pfizer, Wyeth, and Novartis; is a company consultant for Karl Storz, Coloplast, AstraZeneca, Astellas, Storz, and Hexal; has received company speaker honoraria from Pfizer, Astellas, Bayer, GlaxoSmithKline, Pierre Fabre, Janssen Cilag, and Hexal; has participated in trials for the ProtecT Study, Millenium Study C21004, Millenium Study C21005, Astellas, Ipsen, and Janssen; and has received grants/research support from Wyeth and Pfizer. Dr. Thomas B. Lam is a company consultant for and has received company speaker honoraria from Pfizer, GlaxoSmithKline, Astellas, and Ipsen. Professor Dr. Axel S. 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, and SEP; has participated in trials for AstraZeneca, Bayer, Pfizer, TEVA, Novartis, and Astellas; has received grants/research support from

Wyeth; and has participated in a company-sponsored speakers bureau for TEVA, Janssen, Pfizer, Astellas, Ferring, and Novartis. Professor Dr. Rachel H. Giles, Professor Dr. Alessandro Volpe, Dr. Saeed Dabestani, Dr. Fabian Hofmann, Dr. Lorenzo Marconi, Dr. Sergio Fernández-Pello, Dr. Rana Tahbaz, and Dr. Yasmin Abu-Ghanem have nothing to disclose.

References

- [1] Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007;356:115–24.
- [2] Albiger L, Choueiri T, Escudier B, et al. A systematic review of sequencing and combinations of systemic therapy in metastatic renal cancer. *Eur Urol* 2015;67:100–10.
- [3] Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med* 2015;373:1803–13.
- [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] Powles T, Albiger L, Staehler M, et al. Updated European Association of Urology guidelines recommendations for the treatment of first-line metastatic clear cell renal cancer. *Eur Urol* 2018;74:311–5.
- [6] Choueiri TK, Fishman MN, Escudier B, et al. Immunomodulatory activity of nivolumab in metastatic renal cell carcinoma. *Clin Cancer Res* 2016;22:5461–71.

August 20, 2018

<https://doi.org/10.1016/j.eururo.2018.08.029>

