ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN CANCER HORIZONS

EDITORIAL

Dual immune checkpoint inhibition in metastatic renal cell carcinoma

Editorial re.: Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced RCC: extended 4-year follow-up of the phase III CheckMate 214 trial

The introduction of dual immune checkpoint inhibition with nivolumab and ipilimumab (nivo—ipi) represents a paradigm change in the first-line treatment of metastatic renal cell carcinoma (mRCC). As the first upfront treatment to demonstrate a significant improvement in overall survival (OS) when compared with sunitinib (sun), the previous standard of care, the immune combination was also shown to achieve unprecedented rates of complete remission. Benefits were seen in the intent-to-treat (ITT) and intermediate-poor (IP) risk patient populations, regardless of PD-L1 expression. The 4-year update presented by Albiges et al.[1] confirms the initially reported improvements in OS, objective response rates (ORRs) and complete response (CR) rates in the ITT and IP population. The role of nivo—ipi in patients with favourable International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk score, an exploratory endpoint of the study, remains unclear. While ORR and progression-free survival (PFS) were significantly superior with sun, OS was similar at 4 years between nivo—ipi and sun, and CR rates were twice higher with nivo—ipi.

Several factors account for the enthusiasm that has accompanied the study results. First, a median OS of >48 months in IP patients is unprecedented; in the tyrosine kinase inhibitor (TKI) era, the median OS was 22.5 months (95% CI 18.7-25.1) in intermediate-risk and 7.8 months (95% CI 6.5-9.7) in poor-risk patients.[2] Second, the fact that median OS has not yet been reached in responders suggests that the quality of response is superior to that observed with TKIs, where therapy resistance and disease progression eventually occur. Third, the reported CR rate of >10% in IP patients is important, because (sustainable) CR must remain the ultimate treatment goal in oncology; this was not a realistic goal in mRCC before the introduction of nivo—ipi. Fourth, in contrast to sun, the median duration of response with nivo—ipi has not yet been reached in any patient group (ITT, IP and favourable risk). Finally, the chance to discontinue treatment without a requirement for subsequent therapy was twice as high with nivo—ipi versus sun in both patients achieving CR (45.8% versus 21.4%) and those achieving partial response (42.9% versus 23.9%). These findings are highly relevant as they materialize patients' expectations towards cancer treatment. Indeed, in a recent survey on patients' preferences and expectations from mRCC treatment, CR was ranked as the most desirable outcome.[3] Another important expectation addresses durability of response and the possibility to discontinue treatment while maintaining response.

A new treatment is also a game changer, if it has a major impact on worst-case scenarios. Of 1096 patients randomized in CheckMate 214, 139 had tumours with sarcomatoid features (sRCC). Approximately 15% of patients presenting with stage IV RCC have tumours with sarcomatoid features, which are associated with high nuclear grade, aggressive behaviour and short survival.[4] In the era before nivo—ipi, these patients were perceived to be 'lost causes'. A post-hoc analysis of the CheckMate 214 trial revealed an unprecedented ORR of 61% (versus 23% with sun) and a CR rate of 19% (versus 3% with sun) in this subgroup. Moreover, the median OS has not been reached with nivo—ipi in sRCC (versus 14.2 months with sun) and the median PFS was 26.5 months (versus 5.1 months with sun). These results are only surpassed in the subgroup of sRCC patients with PD-L1 expression; ORR and CR rate were 69% and 22%, respectively; OS not reached versus 14.2 months with sun (hazard ratio 0.45) and PFS 26.5 versus 5.1 months (hazard ratio 0.54).[5]

Meanwhile, other immune checkpoint inhibitor combinations have demonstrated OS, PFS and ORR superiority over sun. These combinations address cancer immune escape in a different way than nivo—ipi: while PD-L1 or PD-1 inhibition remains the backbone, the addition of an immune-modulatory and antiangiogenic TKI aims to generate a proimmunogenic tumour microenvironment. Three combinations have been or will be approved based on their superiority over sun. These include the doublets pembrolizumab with VEGFR—TKI axitinib,[6] nivolumab with cabozantinib, a MET—AXL—VEGFR—TKI,[7] and pembrolizumab with lenvatinib, an FGF and VEGFR—TKI (press release only).[8] While nivo—ipi is currently recommended in the IP patient setting, the other combinations are or will be approved for all IMDC risk groups. In this context, it has become increasingly challenging to make treatment decisions and to bring the best treatment to the individual patient. No head-to-head trials have been conducted so far and no reliable predictive factors have been identified. PD-L1 expression was expected to be an ideal marker, because it reflects the mode of action of PD-1/PD-L1 inhibitors. However, different methods of PD-L1 testing, the dynamic of PD-L1 expression during the course of the disease, the

biologic heterogeneity of the tumour[9] and the fact that patients with negative PD-L1 status also benefit from immuno-oncology doublets indicate that the role of PD-L1 expression remains inconclusive.

The abundance of novel treatment options is certainly a major advantage for patients with mRCC. However, we now face the same challenge as in the era in which various TKIs were introduced almost simultaneously combined with the absence of biomarkers. The speed of approval of new treatments is far faster than the growth of our knowledge on how best to use them in the individual patient. Because industry-sponsored trials focus on the largest possible population rather than the individual patient, exploratory substudies and biomarker research lag far behind. It has been encouraging to see that nivo—ipi is superior to sun in patients with and those without PD-L1 expression, but this cannot remain the only effort to find a biomarker in a clinical trial. This pertains to all trials discussed here. Medical societies must emphasize that it should be more than desirable to link the conduct of such trials with ancillary biomarker research programmes.

Although many questions remain unanswered, nivo—ipi has raised the bar for the treatment of mRCC. The robustness of the results at 4 years of follow-up is a confirmation that new and higher treatment goals can be set in mRCC. Among these is the increase in CR rate, the possibility to discontinue treatment while maintaining response and long-term survival. The results of CheckMate 214 underline the importance of simultaneously addressing both cancer escape mechanisms, CTLA4—B7 and PD-1—PD-L1 interaction. Moreover, it is reassuring that the authors report that no new safety signals were observed with longer follow-up.

In the future, extensive biomarker research together with testing of triplet and quadruplet combinations of immunomodulatory drugs may bring another dimension to the treatment of mRCC.

M. Schmidinger[1]*, S. F. Shariat[1,2,3,4,5,6] & H. Fajkovic[1]
[1]*Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria;*
[2]*Departments of Urology, Weill Cornell Medical College, New York;*
[3]*Department of Urology, University of Texas Southwestern, Dallas, USA;*
[4]*Department of Urology, Second Faculty of Medicine, Charles University, Prague, Czech Republic;*
[5]*Institute for Urology and Reproductive Health, I.M. Sechenov First Moscow State Medical University, Moscow, Russia;*
[6]*Division of Urology, Department of Special Surgery, Jordan University Hospital, The University of Jordan, Amman, Jordan*
(*E-mail: manuela.schmidinger@meduniwien.ac.at).

Available online xxx

https://doi.org/10.1016/j.esmoop.2020.100035

FUNDING

No funding declared.

DISCLOSURE

MS has received honoraria for advisory boards or lectures from Pfizer, BMS, Merck, MSD, Ipsen, Exelixis, EUSA, EISAI, Alkermes; SFS has received honoraria from Astellas, Astra Zeneca, Bayer, BMS, Cepheid, Ferring, Ipsen, Janssen, Lilly, MSD, Olympus, Pfizer, Pierre Fabre, Richard Wolf, Roche, Sanochemia, Sanofi, Takeda, UroGen; had/having consulting or advisory roles in Astellas, Astra Zeneca, Bayer, BMS, Cepheid, Ferring, Ipsen, Janssen, Lilly, MSD, Olympus, Pfizer, Pierre Fabre, Richard Wolf, Roche, Sanochemia, Sanofi, Takeda, UroGen; member of speakers' bureau in Astellas, Astra Zeneca, Bayer, BMS, Cepheid, Ferring, Ipsen, Janssen, Lilly, MSD, Olympus, Pfizer, Pierre Fabre, Richard Wolf, Roche, Sanochemia, Sanofi, Takeda, UroGen, Movember Foundation; and has filed the following patents: Method to determine prognosis after therapy for prostate cancer (Granted 6 September 2002); Methods to determine prognosis after therapy for bladder cancer; (Granted 19 June 2003); Prognostic methods for patients with prostatic disease (Granted 5 August 2004); Soluble Fas urinary marker for the detection of bladder transitional cell carcinoma (Granted 20 July 2010); HF has nothing to declare.

REFERENCES

1. 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(6):e001079.
2. Heng DY, Xie W, Regan MM, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. *Lancet Oncol*. 2013;14(2):141-148.
3. Battle D, Bergerot CD, Msaouel P, et al. Patient preferences and expectations of systemic therapy in renal cell carcinoma. *J Clin Oncol*. 2020;38(suppl 15):5083.
4. Shuch B, Amin A, Armstrong AJ, et al. Understanding pathologic variants of renal cell carcinoma: distilling therapeutic opportunities from biologic complexity. *Eur Urol*. 2015;67(1):85-97.
5. Tannir NM, Signoretti S, Choueiri TK, et al. Efficacy and safety of nivolumab plus ipilimumab versus sunitinib in first-line treatment of patients with advanced sarcomatoid renal cell carcinoma. *Clin Cancer Res*. 2020. https://doi.org/10.1158/1078-0432.CCR-20-2063.
6. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2019;380(12):1116-1127.

7. Choueiri TK, Powles T, Burotto 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(suppl 4):S1159.
8. Eisai Co. Ltd. *LENVIMA® Plus KEYTRUDA® Demonstrated Statistically Significant Improvement in Progression-Free Survival, Overall Survival and Objective Response Rate Versus Sunitinib as First-Line Treatment for Patients With Advanced Renal Cell Carcinoma*. Tokyo, Japan: EISAI; 2020. Available at: https://www.eisai.com/news/2020/news202073.html. Accessed December 6, 2020.
9. Gerlinger M, Rowan AJ, Horswell S, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. *N Engl J Med*. 2012;366(10):883-892.