"The first ones now, will later be last"

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EDITORIAL

"The first ones now, will later be last": understanding the importance of historical context when reading ESMO-MCBS scores

A striking phenomenon is identified when reviewing the European Society for Medical Oncology (ESMO)-Magnitude of Clinical Benefit Scale (MCBS) scorecards for first-line therapy trials in renal cell cancer (RCC). The score of 4 (ESMO-MCBS v1.1), for single-agent pazopanib,[1] is the same as the score for immunotherapy and anti-vascular endothelial growth factor tyrosine kinase inhibitor (TKI) combination therapy.[2-5] This equivalence seems absurd, and it would be easy to assume that this indicates something inherently wrong with the ESMO-MCBS scoring for the magnitude of clinical benefit.

Such a conclusion would reflect a common misconception that ESMO-MCBS scores are readily comparable or that the scores are reflective of clinical benefit permanently and independent of context.

The ESMO-MCBS score is a measure of the added benefit compared to the standard of care (SoC) at the particular time of study initiation. In the course of the development history of treatment strategies for any clinical setting, the SoC evolves over time. Consequently, older scores lose contemporary relevance when the SoC has changed. Thus, for any new intervention, the ESMO-MCBS score has relevance pertinent to other contemporary treatments evaluated in the same clinical setting against the same SoC.

The pazopanib versus sunitinib study in the first-line treatment of unresectable or metastatic clear cell RCC[1] demonstrated non-inferior disease control based on progression-free survival (hazard ratio 1.05; 95% confidence interval 0.90-1.22; non-inferiority margin 1.25). In addition, pazopanib reduced grade $\geq$3 toxicities (fatigue, hand-foot syndrome, mucosal inflammation), measured as the relative risk of adverse events or other toxicities affecting daily well-being (constipation, dyspepsia, stomatitis, limb pain, gastrointestinal reflux disease, etc.). Furthermore, pazopanib improved patient tolerability and quality of life, particularly in domains related to fatigue or soreness in the mouth, throat, hands, or feet. When the study was published, this finding indicated that the use of pazopanib could substantially improve the therapeutic index of first-line TKI therapies for metastatic RCC.

Six years later, the context changed. By 2019, immunotherapy had firmly established itself as a salvage treatment for patients with advanced RCC who progressed on TKI combination therapies.[6,7] Nivolumab plus ipilimumab was preferred over TKIs for patients with intermediate- and high-risk RCC.[8] Furthermore, newer TKIs such as axitinib,[9] cabozantinib,[10,11] and lenvatinib[12] were also highly efficacious.

In this new therapeutic era, the relative merits of pazopanib versus sunitinib were no longer relevant for most patients. Now with rapidly evolving strategies to manage RCC, the issue of the day is whether patients, especially those in the immediate- and high-risk groups, should be treated with up-front combination of immune checkpoint inhibitors and a TKI or with an initial TKI, reserving immunotherapy for patients who progressed.[2-5]

This specific example in the first-line therapy of RCC highlights that ESMO-MCBS scores must be contextualized to the relevant SoC at the time the trial was undertaken. For most solid tumors, SoC and therapeutic strategies have evolved substantially over the past 20 years.[13] The ESMO-MCBS score for pazopanib, as first-line therapy for clear cell RCC, indicated the magnitude of benefit over sunitinib, the previous SoC at that time. The relevance of the score is now largely historic, representing a clinical important development at that time.

Another illustrative example is observed in the development of first-line treatment of anaplastic lymphoma kinase (ALK) gene-mutated non-small-cell lung cancer (NSCLC). In 2014, crizotinib received a score of 4 (ESMO-MCBS v1.1), compared with platinum-based chemotherapy,[14] while in 2020, lorlatinib also received a score of 4 when compared with crizotinib.[15] These scores indicate that for each of these two steps in the progressive development of treatment for ALK-mutated NSCLC, there was a similarly scaled and substantial gain in clinical benefit.

ESMO-MCBS scores are more than just a simple scorecard. They are designed to be cancer- and treatment-specific, and are relevant to the current SoC at the time of treatment comparison. Partly for this reason, the ESMO-MCBS scorecards indicate the date of initial scoring (which is usually shortly after regulatory approval).

Understanding ESMO-MCBS scores requires nuance. Firstly, the scores are relevant to the specific SoC at the time of the study. Furthermore, they are prognostically weighted, influenced by the uncertainties from surrogate outcomes, and subject to bias from issues in study implementation and analysis. Consequentially, the appraisal of ESMO-MCBS scores requires an understanding of all of these potentially confounding issues.

Some users have suggested that ESMO-MCBS scores should have an expiration date for relevance when a new SoC is established. However, the rate of change in SoC differs

between countries. Consequently, a score with only historical relevance in one county may still be relevant in another, where the available SoC has not yet evolved. This is part of the challenge in maintaining global relevance, and not only relevance to the most highly resourced health care systems.

When reading ESMO-MCBS scorecards (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards), check the date and the control arm and remember the words of Robert Zimmerman (Bob Dylan):

"And the first one now

Will later be last

For the times they are a-changin"

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REFERENCES

1. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med*. 2013;369:722-731.
2. Motzer R, Alekseev B, Rha SY, et al. Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. *N Engl J Med*. 2021;384:1289-1300.
3. Choueiri TK, Powles T, Burotto M, et al. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2021;384:829-841.
4. 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;21:1563-1573.
5. Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2019;380:1103-1115.
6. Motzer RJ, Rini BI, McDermott DF, et al. Nivolumab for metastatic renal cell carcinoma: results of a randomized phase II trial. *J Clin Oncol*. 2015;33:1430-1437.
7. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med*. 2015;373:1803-1813.
8. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med*. 2018;378:1277-1290.
9. Rini B, 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;378:1931-1939.
10. Choueiri TK, Hessel C, Halabi S, et al. Cabozantinib versus sunitinib as initial therapy for metastatic renal cell carcinoma of intermediate or poor risk (Alliance A031203 CABOSUN randomised trial): progression-free survival by independent review and overall survival update. *Eur J Cancer*. 2018;94:115-125.
11. Choueiri TK, Halabi S, Sanford BL, et al. Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: the Alliance A031203 CABOSUN trial. *J Clin Oncol*. 2017;35:591-597.
12. 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;16:1473-1482.
13. Falzone L, Salomone S, Libra M. Evolution of cancer pharmacological treatments at the turn of the third millennium. *Front Pharmacol*. 2018;9:1300.
14. Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med*. 2014;371:2167-2177.
15. Shaw AT, Bauer TM, de Marinis F, et al. First-line lorlatinib or crizotinib in advanced ALK-positive lung cancer. *N Engl J Med*. 2020;383:2018-2029.