Editorial Commentary

Surrogate endpoints in immunotherapy trials for solid tumors

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In a systematic review published in *European Journal of Cancer*, Nie *et al.* analyzed the role of objective response (ORR), disease control and progression-free survival (PFS) as surrogate endpoints in phase II and III studies with immunotherapy [anti-PD(L)1 agents] in solid tumors (1). As expected, across 43 trials available for inclusion, no surrogate endpoint was validated using standard statistical criteria, because neither RECIST-based ORR, nor PFS were able to capture the final overall survival (OS) gain used generally for authority approval. As stated by authors, anti-PD-1/PD-L1 drugs may induce an initial increase in the tumor volume, and the delayed antitumor activity can, thereafter, produce a late shrinkage of the tumor volume. This may cause pseudo-progression and explains why ORR and PFS correlate weakly with survival.

Evaluation of surrogates for survival is an old story. The ideal surrogate should satisfy the following three criteria: (I) there should be a direct association between the disease mechanism, the surrogate endpoint, and the clinical endpoint; (II) a change in the surrogate endpoint should cause a clear demonstration of a change in disease status for individual patients, and (III) a clear association between a change in surrogate endpoint caused by a therapeutic intervention and the ultimate clinical outcome within a trial should be found. Traditionally, using a more easy to capture endpoint compared to OS would permit to spare time spent for conducting clinical trials, costs and allow a more rapid drug approval in case of surrogates satisfied in that specific trial. Up to now, only a few surrogates have been validated by the means of comprehensive systematic reviews and meta-analyses of individual patient data. For example, DFS at 3 years has been evaluated and approved as a surrogate for 5-year OS in resected stage C colorectal cancer (2). Similarly, in early breast cancer, DFS is an established surrogate for OS with adjuvant, anti-HER2 therapies. For this reason, a breakthrough therapy as trastuzumab was initially approved as adjuvant therapy for resected HER2-positive breast cancer (3). In the setting of advanced disease, PFS was only moderately correlated with OS in gastric cancer (4). Conversely, In head and neck cancer, event-free survival was considered a reasonable surrogate of OS in randomized studies (5).

At present no validated surrogates have yet been validated in cancer patients treated with immune checkpoint inhibitors (ICIs). Roviello *et al.* analyzed if ORR could be a valid surrogate for OS with ICIs but found coherently a weak correlation (R^2=0.32) (6). Similarly, a moderate correlation was found between PFS and OS (R^2=0.47). In an initial evaluation of surrogacy through a published level meta-analysis, Petrelli and colleagues observed that the correlation between treatment effect on 1- and 2-year OS is a reliable surrogate of effect on OS in 13 studies including the currently used ICIs (7). Ito *et al.* recently published an analysis of lung cancer studies and found that a milestone endpoint as 1-year OS was strongly correlated with hazard ratio for OS (8). Finally, Ritchie *et al.* found that 6-month PFS is a good surrogate of 1-year OS in phase II studies with ICIs (9). Explanations of these ambiguous results are

various. Type of disease (course of melanoma and lung cancer are usually shorter after progression compared to breast or colorectal cancer where various lines of therapy are usually available), type of agents (ICIs have a typical delayed response of several weeks or months compared to cytotoxic agents), type of combinations (in the first months, treatment with ICIs alone is sometimes associated with worse survival curves as compared with control arms of chemotherapy indicating that a proportion of patients experience a rapid disease progression), length of follow-up (sometimes too short to permit a survival gain to be demonstrated) and post-progression therapies (e.g., crossover) are potential reasons for these findings. However, in the paper of Nie *et al.*, the elimination of the potential effect of crossover, with restriction to trials without the crossover rate and trials with the crossover rate lower than 50%, led to similar results, with no confirmed correlation between PFS and OS.

In some cases, Food and Drug Administration (FDA) granted an accelerated approval of drugs in early clinical trials (single-arm phase II studies), adopting ORR as a criterion for acceptance of approval. In these circumstances (e.g., avelumab approval for Merkel cell carcinoma) an orphan drug designation or a disease with a specific molecular profile [e.g., pembrolizumab for microsatellite instability (MSI) cancers] led FDA to an accelerate market admission.

Accurate evaluation of surrogate endpoints is crucial for clinical research. Their acceptation from industries and health authorities require a formal validation through large scale meta-analyses on individual patient data of all trials included. Such analyses differ from published based meta-analyses in that we have full access to clinically relevant data of enrolled patients in terms of demographic and clinical data (e.g., race and performance status), radiological ORR timing of disease evaluation, and post progression therapies. Furthermore, in order to demonstrate validity, a high correlation between effects on the surrogate and the relevant endpoint is usually required (0.9 is considered as a potential threshold). A surrogate endpoint is generally defined by FDA as a marker, such as a laboratory measurement, radiographic image, physical sign, or another measure, that is not itself a direct measurement of clinical benefit, but (I) is known to predict clinical benefit and could be used to support traditional approval of a drug or biological product; or (II) is reasonably likely to predict clinical benefit and could be used to support the accelerated approval of a drug or biological product. Other than ORR and PFS, other potential surrogates could be evaluated in clinical practice when using ICIs. Immune-related adverse events are specific (organ defined) toxicities observed with ICIs and are the consequence of immune system activation (e.g., colitis or pneumonitis). Some observations already available in the literature, describe a correlation between the development of specific toxicities (e.g., thyroid dysfunction) and survival in patients treated with ICIs (10-13). Present authors defined that immune-related adverse events were highly correlated with OS and PFS (reduction in the risk of death and progression by 50%) in a meta-analysis of published studies (Petrelli's personal communication).

Outstanding research progresses have provided new insights into the clinical scenario with the extensive adoption of new effective treatments for several lethal diseases (melanoma, urothelial, lung and kidney cancers). Consequently, patient expectations have increased but also financial toxicity. Surrogate endpoints are widely adopted in particular in those diseases where a longer follow-up is required to observe the outcome, due to increasingly effective treatments resulting in endpoints being reached later (as for adjuvant breast cancer setting). In metastatic disease, RECIST-based ORR and maybe PFS are not yet validated as surrogates for trials that adopt ICIs for solid tumors. Milestone survival analysis could become the ideal candidate for OS in ICIs trials (14). It may represent a time point beyond which the researchers believe that the treatment benefit is likely to remain stable (usually 2 years as derived from many ICIs trials). In fact, different phase II and III studies have demonstrated that OS among patients treated with ICIs (e.g., ipilimumab) begins to chronicize at least 2 years after random assignment. So far, clinical researchers may decide to choose this 2-year milestone as the time point of interest for surrogacy with OS.

In conclusion, until milestones or other potential surrogates for OS will be confirmed as such, the primary endpoint of phase III studies comparing ICIs with or without standard of care, should remain OS.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Nie RC, Chen FP, Yuan SQ, et al. Evaluation of objective response, disease control and progression-free survival as surrogate end-points for overall survival in anti-programmed death-1 and anti-programmed death ligand 1 trials. Eur J Cancer 2019;106:1-11.
2. Sargent DJ, Patiyil S, Yothers G, et al. End points for colon cancer adjuvant trials: observations and recommendations based on individual patient data from 20,898 patients enrolled onto 18 randomized trials from the ACCENT Group. J Clin Oncol 2007;25:4569-74.
3. Saad ED, Squifflet P, Burzykowski T, et al. Disease-free survival as a surrogate for overall survival in patients with HER2-positive, early breast cancer in trials of adjuvant trastuzumab for up to 1 year: a systematic review and meta-analysis. Lancet Oncol 2019;20:361-70.
4. Paoletti X, Oba K, Bang YJ, et al. Progression-free survival as a surrogate for overall survival in advanced/recurrent gastric cancer trials: a meta-analysis. J Natl Cancer Inst 2013;105:1667-70.
5. Michiels S, Le Maître A, Buyse M, et al. Surrogate endpoints for overall survival in locally advanced head and neck cancer: meta-analyses of individual patient data. Lancet Oncol 2009;10:341-50.
6. Roviello G, Andre F, Venturini S, et al. Response rate as a potential surrogate for survival and efficacy in patients treated with novel immune checkpoint inhibitors: A meta-regression of randomised prospective studies. Eur J Cancer 2017;86:257-65.
7. Petrelli F, Coinu A, Cabiddu M, et al. Early analysis of surrogate endpoints for metastatic melanoma in immune checkpoint inhibitor trials. Medicine (Baltimore) 2016;95:e3997.
8. Ito K, Miura S, Sakaguchi T, et al. The impact of high PD-L1 expression on the surrogate endpoints and clinical outcomes of anti-PD-1/PD-L1 antibodies in non-small cell lung cancer. Lung Cancer 2019;128:113-9.
9. Ritchie G, Gasper H, Man J, et al. Defining the Most Appropriate Primary End Point in Phase 2 Trials of Immune Checkpoint Inhibitors for Advanced Solid Cancers: A Systematic Review and Meta-analysis. JAMA Oncol 2018;4:522-8.
10. Lisberg A, Tucker DA, Goldman JW, et al. Treatment-Related Adverse Events Predict Improved Clinical Outcome in NSCLC Patients on KEYNOTE-001 at a Single Center. Cancer Immunol Res 2018;6:288-94.
11. Owen DH, Wei L, Bertino EM, et al. Incidence, Risk Factors, and Effect on Survival of Immune-related Adverse Events in Patients With Non-Small-cell Lung Cancer. Clin Lung Cancer 2018;19:e893-900.
12. Teraoka S, Fujimoto D, Morimoto T, et al. Early Immune-Related Adverse Events and Association with Outcome in Advanced Non-Small Cell Lung Cancer Patients Treated with Nivolumab: A Prospective Cohort Study. J Thorac Oncol 2017;12:1798-805.
13. Haratani K, Hayashi H, Chiba Y, et al. Association of Immune-Related Adverse Events With Nivolumab Efficacy in Non-Small-Cell Lung Cancer. JAMA Oncol 2018;4:374-8.
14. Chen TT. Milestone Survival: A Potential Intermediate Endpoint for Immune Checkpoint Inhibitors. J Natl Cancer Inst 2015. doi: 10.1093/jnci/djv156.

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