Exploratory analysis of the association of depth of response and survival in patients with metastatic non-small-cell lung cancer treated with a targeted therapy or immunotherapy

Editorial on

"Exploratory analysis of the association of depth of response and survival in patients with metastatic non-small cell lung cancer treated with a targeted therapy or immunotherapy"

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Tumor shrinkage, whether assessed using explicit objective criteria or informally, has always been a useful metric to evaluate treatment results in oncology. Other than measurement error and very rare reports of spontaneous remissions, nothing but effective therapy shrinks tumors. Moreover, clinicians know from experience that patients with objective responses tend to have better outcomes than those without such responses. This observation has been confirmed by a large number of studies, even when the potential bias of comparing survival between responders and non-responders was taken into account [1]. A tempting, but not necessarily correct, conclusion from these observations is that tumor shrinkage is a surrogate for long-term endpoints, such as progression-free survival (PFS) and overall survival (OS).

Given the limitations of both PFS and OS as end points in clinical trials, the search continues for outcome measures that might replace these long-term endpoints, especially with the aim of expediting drug development, approval, and reimbursement [2, 3]. Proper validation of a surrogate endpoint is usually considered to require two conditions: (1) there must be a strong

association between the tentative surrogate endpoint and the true endpoint of interest (*e.g.*, correlation between response and OS) at the patient level, and (2) the treatment effect on the surrogate end point must reliably predict the treatment effect on the true end point at the trial level [4]. The first condition represents the prognostic role of the surrogate (*i.e.*, patients with favourable values of the surrogate also tend to do well on the true end point), whereas the second condition postulates that the surrogate endpoint must have *predictive* value for the true endpoint it is supposed to replace. The latter condition is often confused with the former, yet it is fundamentally different, for it implies that treatment-induced changes in the surrogate predict corresponding changes in the true endpoint.

Depth of response (DoR)—the percent tumor shrinkage at nadir, in comparison with baseline—has recently generated interest as an outcome measure in solid tumors. In advanced colorectal cancer, some authors have found moderate or strong patient-level associations between DoR and OS [5]. Although this comes as no surprise, given the known association between response rate and OS at the patient level in colorectal cancer [6], arguably the use of a continuous metric such as DoR could avoid the information loss due to dichotomization of responses, thus representing a more powerful and informative metric than Response Evaluation Criteria in Solid Tumors (RECIST) responses. Thus, it is certainly of interest to assess the comparative merits of DoR, RECIST response rates, and other dichotomous measures, such as early tumor shrinkage and early objective tumor responses. This interest is raised by the knowledge that several clinical trials are using DoR as an exploratory or secondary endpoint [7, 8]. Moreover, an association between early tumor shrinkage and long-term outcomes has been found in retrospective studies in advanced colorectal cancer [9, 10].

In this issue of *Annals of Oncology*, McCoach *et al*. use target-lesion measurements from individual patients enrolled in four randomized, registration trials in advanced non-small-cell lung cancer (NSCLC), with the aim of assessing the patient-level association between DoR and two long-term endpoints, PFS and OS [11]. Two of the trials tested an ALK inhibitor, and two assessed a programmed cell death (PD)-1 inhibitor; data from the experimental arms of both trials within each drug class (ALK inhibitor and PD-1 inhibitor) were pooled for analysis, even though the four trials had chemotherapy control arms that were not used in the present work. Presumably because only patients with baseline and at least one post-baseline tumor measurement were included in the analysis, between 83% (PD-1 inhibitor) and 88% (ALK inhibitor) of the patients in the original trials were eligible for the current work. McCoach *et al*. computed the hazard ratios (HR) for PFS and OS in four categories of DoR (1 to 25%, 26 to 50%, 51 to 75%, and 76 to 100%), excluding cases with no tumor shrinkage (12 with ALK inhibitors and 168 with PD-1 inhibitor). They found an association between the DoR category and the HRs for both PFS and OS, and for both treatment classes, in the sense that deeper responses were associated with more favorable HRs. The associations appeared to be more "linear" for ALK inhibitors, and more complex with immunotherapy, with the caveat that this study was based on relatively small sample sizes.

These results add to previously published data provided by the same group, who found strong associations between RECIST response rates and both PFS and OS at the patient level in advanced NSCLC treated with chemotherapy and targeted therapy [12]. In the current work, RECIST response rates are not assessed, so their prognostic utility cannot be compared with that of DoR with ALK inhibitors or immunotherapy. A relatively small study from Japan failed to demonstrate that DoR adds to conventional RECIST assessment in terms of predicting OS among patients with NSCLC and complete or partial responses after treatment

with tyrosine-kinase inhibitors of the epidermal growth factor receptor (EGFR) [13]. In the paper by McCoach *et al*., the potentially different associations between targeted therapy and immunotherapy are interesting and worthy of further investigation. In previous studies, we have not found dichotomous response metrics to be valid surrogates for OS in patients with advanced colorectal cancer treated with first-line chemotherapy or antiangiogenics [14, 15]. Moreover, we have found varying associations across three treatment classes—chemotherapy, antiangiogenics, and EGFR inhibitors—when DoR was investigated as a surrogate for OS in the first-line treatment of advanced colorectal cancer, which parallels the results of McCoach *et al.* in NSCLC [16].

As noted above, a strong association at the trial level must be established before a surrogate endpoint is validated. The current work by McCoach *et al*. does not address this issue, thus precluding any tentative conclusions about the worth of DoR as a novel endpoint for clinical trials. Despite this limitation, and others pointed out by the authors in their discussion, this work is a step in the search for other metrics, such as DoR, that can potentially circumvent limitations from the use of RECIST responses as endpoints in clinical trials. Eventually, should such metrics be found to be valid surrogates for PFS or OS at both the patient level and trial level, clinical trials could benefit from using them to capture the effect of treatment in a statistically sensitive and clinically meaningful way.

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