Editorial Commentary

The benefit of the doubt: PD-L1 status in unresectable stage III NSCLC management

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Programmed death ligand-1 (PD-L1) tumor proportion score (TPS), although imperfect, is the best biomarker identified so far to guide the treatment of metastatic non-small cell lung cancer (NSCLC) with immune checkpoint inhibitors (ICI). Landmark trials in the first-line metastatic setting support its predictive value for response to immunotherapy in this population (1,2). As such, international guidelines recommend single agent anti-PD-1/PD-L1 treatment in the PD-L1 ≥50% population, while those agents should be combined with either chemotherapy, anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) or both in PD-L1 1–49% and <1% patients (3,4). The role of PD-L1 as a biomarker for consolidation durvalumab after chemoradiotherapy (CRT) in unresectable stage III NSCLC, however, remains controversial. The European Medicines Agency approved adjuvant durvalumab for PD-L1 ≥1% NSCLC (5), while North American health authorities did not make this distinction (6,7).

In this study, Bryant *et al.* conducted a retrospective analysis of 312 patients treated with adjuvant durvalumab after CRT in 2017–2021 (8). Every absolute increase of 25% in PD-L1 TPS was associated with significant improvement of both progression-free survival (PFS) and overall survival (OS). There were also significant benefit in PFS for the PD-L1 ≥50% and 1–49% subgroups compared to the <1% subgroup. OS followed the same trend, although the difference between the 1–49% and <1% was not statistically significant. The cohort of durvalumab patients was compared to a historical cohort from 2015–2016 which did not receive durvalumab. PD-L1 expression was unknown in this second cohort. Subgroups of durvalumab patients with PD-L1 ≥50% and 1–49% both had improved PFS and OS compared to the no-durvalumab patients, but not the <1% subgroup.

Bryant *et al.* results suggest a predictive role of PD-L1 TPS in patient receiving durvalumab. Findings from PACIFIC-R, a retrospective study including 1,399 patients started on durvalumab through an extended access program in 2017–2018, point in the same direction (9). Real-world PFS was longer in PD-L1 ≥1% (22.4 months) versus <1% (15.6 months) patients. Published OS data remain preliminary and do not address PD-L1 expression. Two prior, smaller retrospective analyses of patients who received durvalumab between 2017 and 2020 demonstrated improved outcomes in PD-L1 ≥50% compared to PD-L1 <1% patients, but there was no significant difference between the 1–49% and <1% groups (10,11).

Do PD-L1 negative CRT patients actually benefit from adjuvant durvalumab? No conclusions can be drawn from Bryant *et al.* comparative analysis, since PD-L1 expression was unknown in the no-durvalumab cohort. A posthoc, unplanned analysis of 451 PD-L1 assessable patients from

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PACIFIC provides some insight (12). Compared to placebo, durvalumab seemed to improve PFS in both PD-L1 ≥1% [hazard ratio (HR) 0.46; 95% confidence interval (CI): 0.33–0.64, n=303] and PD-L1 <1% patients (HR 0.73; 95% CI: 0.48–1.11, n=148), although the confidence interval crossed unity in the latter. For OS, benefits were seen in the PD-L1 ≥1% subgroup (HR 0.59; 95% CI: 0.41–0.83, n=303) but not in the PD-L1 <1% subgroup (HR 1.14; 95% CI: 0.71–1.84, n=148). However, the trial was not powered for this analysis and randomization was not stratified for PD-L1, which put the PD-L1 <1% subgroup of the durvalumab arm at a disadvantage for demographics and stage. The sample size was also fairly small, with few events (n=60) in the PD-L1 <1% subgroup.

Bryant *et al.* referred to the prognostic role of PD-L1, but did not investigate this question specifically as PD-L1 expression was unknown in the cohort of patients who did not receive durvalumab. Previous studies had conflicting results, with the most data concerning resectable NSCLC. A recent meta-analysis of 15 studies comprising 3,790 patients with early-stage, resected NSCLC suggested PD-L1 positivity was associated with shorter disease-free survival (DFS) and OS (13). However, the included studies used widely different PD-L1 assays and positivity cutoffs, ranging from 1–100% of tumor cells. Moreover, PD-L1 expression was associated with other disadvantageous characteristics such as male sex, squamous histology, nodal metastases and higher stage, all of which could have been confounders. In patients with unresectable, locally advanced NSCLC treated with CRT alone, without durvalumab, no significant relationship has been demonstrated between PD-L1 expression and PFS or OS (14-16).

Of course, in order to evaluate the predictive and/or prognostic value of PD-L1 TPS, reliable testing is key. When it comes to immunohistochemistry (IHC), considering the type of assay is of the essence, since SP142 has poorer sensitivity compared to SP263, 28-8 or 22C3 (1,17,18). Perhaps another important aspect is the timing of testing, as discussed by the authors. It may be that the PD-L1 status of tumor prior to CRT treatment initiation does not matter as much as the influence of the preceding concurrent chemotherapy and radiotherapy. The interplay between radiotherapy and the immune microenvironment have long been acknowledged, with increased cancer antigen release and visibility, upregulation of MHC-1 expression and priming tumor specific T cells (19). This activation accounts for the abscopal effect and is the impetus for trials utilizing ICI as a radiosensitizer. Chemotherapy promotes immune responses by similar mechanisms in addition to altering whole body physiology to augment immune competence (20). Biomarkers are important and useful but the treatment context is also highly relevant when trying to understand treatment effects. CRT can upregulate PD-L1 expression, questioning the reliability of pre-CRT PD-L1 TPS to guide consolidation immunotherapy treatment (21,22).

Identifying the most effective way to utilize the respective tools for managing unresectable stage III NSCLC is the focus of current clinical trials. A number of different strategies are being explored including induction immunotherapy, concurrent immunotherapy with CRT and the use of doublet checkpoint inhibition (23). What will be critical to advance the field is the collection of biomarker status, with respect to PD-L1 TPS and driver mutations, as treatment of curative intent NSCLC becomes more sophisticated with our understanding of biology.

Bryant *et al.* demonstrate a correlation between increasing PD-L1 TPS and improved patient outcome paralleling the association of high PD-L1 TPS and benefit in metastatic NSCLC. The effects of radiotherapy and chemotherapy on the immune milieu may serve to augment the beneficial effects of ICI in the PD-L1 TPS <1% population and requires further investigation. With the potential for achieving a cure, it behooves the oncology community to seek better ways to use our treatment tools to improve outcomes for our patients.

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