Editorial Commentary

PD-L1 expression on tumor cells as a potential predictive biomarker for patients with unresectable stage III non-small cell lung cancer treated with chemoradiotherapy followed by durvalumab

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The tumor microenviroment including the expression of programmed death ligand 1 on tumor cells (PD-L1 TC) has been investigated extensively as a prognostic marker in metastatic non-small cell lung cancer (NSCLC) without oncogenic driver mutation (1). However, the role of PD-L1 TC expression in unresectable stage III NSCLC is still controversial due to heterogenous patient collective, different multimodal treatment sequencing and different PD-L1 antibodies, detection methods and staining cut-offs (2-4) .

Immune-checkpoint inhibition maintenance treatment with durvalumab resulted in a promising benefit regarding progression-free survival (PFS) and overall survival (OS) after platinum-based chemoradiation (cCRT) according to the PACIFIC trial (5). Consequently in 2018, the U.S. Food and Drug Administration (FDA) has approved durvalumab irrespective of PD-L1 status after cCRT for the treatment of inoperable stage III NSCLC. This stands in contrast to the approval by the European Medicines Agency (EMA), where durvalumab use is still restricted to patients with locally advanced, unresectable NSCLC whose tumor cells show at least 1% PD-L1 expression. The cut-off level was defined by a secondary post-hoc OS analysis of the 451 (63%) patients of PACIFIC study after a median follow-up time of 33.3 (range, 0.2–51.3) months, which found an improved OS for all subgroups excluding patients with PD-L1 TC less than 1% [33.1 *vs.* 45.6 months; hazard ratio (HR) =1.14; 95% confidence interval (CI): 0.71–1.84] (6). In addition, several confounding factors in the placebo arm need to be considered such as a younger age, more female patients, and more Caucasian population with pronounced non-squamous, lower disease burden. Patients with PD-L1 TC with ≥25% had a 64.9% probability of survival in the durvalumab arm versus 42.9% in the placebo arm at 36 months (HR =0.50; 95% CI: 0.30–0.83) (6). Likewise, patients with PD-L1 TC expression of 1–24% (59.2% *vs.* 47.3%; HR =0.67; 95% CI: 0.41–1.10) and unknown PD-L1 status (55.5% *vs.* 34.8%; HR =0.60; 95% CI: 0.43–0.84) benefit from durvalumab maintenance treatment. Only patients with PD-L1 TC less than 1% did not profit in this post-hoc analysis (47.4% *vs.* 54.9%; HR =1.14; 95% CI: 0.71–1.84 (6). In contrast, an improved PFS was consequent

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across all subgroups irrespective of PD-L1 TC status (6).

The latest update of the PACIFIC study with 5-year survival outcomes, confirmed the improved PFS and OS benefit for patients treated with immune checkpoint inhibition maintenance compared to the control group irrespective of PD-L1 expression, except for OS in patients with a PD-L1 TC expression <1% (HR =1.15; 95% CI: 0.75–1.75) (7). Since the initial report of the PACIFIC trial (5), several real-word studies have investigated the predictive value of PD-L1 TC expression after implementation of immunotherapy consolidation in stage III NSCLC (2-4,6,8-11) (see *Table 1*). Recently, Bryant *et al.* found an increasing PD-L1 TC expression associated with improved PFS (adjusted HR =0.84 per 25% absolute increase in PD-L1 expression; 95% CI: 0.75–0.94; P=0.003) and OS (adjusted HR =0.86 per 25% absolute increase in PD-L1 expression; 95% CI: 0.74–0.99; P=0.036) based on an analysis of 312 patients from the Veterans Health Administration (VHA) (2). Similarly, no benefit was seen for patients with PD-L1 TC <1% regarding both PFS (adjusted HR =0.84; 95% CI: 0.64–1.10; P=0.19) and OS (adjusted HR =0.81; 95% CI: 0.58–1.13; P=0.22). Besides a meaningful number of patients included in the study, several limitations have to be considered: The VHA database consisted of 985 stage III NSCLC patients treated cCRT plus durvalumab, initial PD-L1 expression was available only in 312 patients (31.6%). In addition, FDA-approved PD-L1 antibodies, detection method, and staining cut-offs varied in the study questioning the statistical analysis of different PD-L1 TC patient subgroups. In the PACIFIC trial, PD-L1 TC testing was restricted to the Ventana SP 263 assay.

Jazieh *et al.* found that PD-L1 TC expression status >50% assessed with the Dako 22C3 PD-L1 clone as the sole predictive biomarker for improved PFS and OS compared to patients with lower expression even after adjusting for age, sex, race, smoking status, histologic subtype, tumor size, and lymph node status (8). Interestingly, the strata PD-L1 TC <1% and PD-L1 TC 1–49% did not significantly differ in PFS and OS questioning the durvalumab approval of the EMA restricted to PD-L1 ≥1%. Furthermore, Desilets *et al.* also reported that patients with PD-L1 TC ≥50% had significantly improved 12-month OS compared to the patients with PD-L1 TC <1% and 1–49% (4). However, median OS wasn't achieved and a longer follow-up is required to provide reliable evidence. In addition, Kartolo *et al.* found an OS benefit associated with high (≥50%) compared to low (<1%) PD-L1 TC expression (HR =0.18; 95% CI: 0.04–0.86; P=0.03) supporting the predictive value of high tumor PD-L1 TC expression (≥50%) on survival outcomes (9). However, median follow-up was also short with only 17.0 months. Again, no significant difference was reported with the cut-off values of 1–49% versus <1% PD-L1 TC-expression (HR =0.36; 95% CI: 0.08–1.63; P=0.18).

Offin *et al.* found no difference between a PD-L1 TC expression of ≥1% *vs.* <1% (HR =0.64; 95% CI: 0.24–1.72; P=0.38) regarding 12-month PFS based on a patient cohort of 62 patients using the E1L3N antibody (10). Likewise, Landman *et al.* (11) reported also no significant difference for OS (HR =2.33; 95% CI: 0.47–11.55; P=0.30) and PFS (HR =1.08; 95% CI: 0.38–3.06; P=0.88) investigating 67 patients and a PD-L1 TC expression of >1% *vs.* <1% after a median follow-up of 20.4 months.

In summary, PD-L1 TC expression seems to be a predictive biomarker for unresectable stage III NSCLC patients treated with cCRT and durvalumab (12). Patients with PD-L1 TC ≥50% may have the most durable and robust OS and PFS benefit from immune checkpoint inhibition consolidation. However, several issues such as the initial detecting method and PD-L1 antibody, lack of prospective data collection and testing prior to multidisciplinary tumorboard-decision, difference in staging modality and in testing fresh *vs.* archived tissue, small patient subgroups, and short follow-up in published real-life studies should be considered. Furthermore, cut-of definitions, especially PD-L1 expression 1–49% seem arbitrary. We recommend harmonization of initial staging including hybrid imaging [positron emission tomography (PET)/computed tomography (CT) + cranial-magnet resonance imaging (MRI)] and PD-L1 testing concerning timing, sample quality, applied assays and its consequent inclusion as a stratification factor in ongoing trials and prospective register studies.

Table 1 Overview about current literature regarding predictive and prognostic value of PD-L1 expression in stage III NSCLC treated with CRT followed by durvalumab [adapted from Manapov *et al.* (12)]

Author [year]	Patient recruitment and number	Study design	PD-L1 assay	PD-L1 expression groups	Median follow-up (months)	Median OS (months)	OS: multivariate CPH (HR, 95% CI, P value)	Median PFS (months)	PFS: multivariate CPH (HR, 95% CI, P value)
Paz-Ares *et al.* [2020] (6)	Recruitment: 05/2014–04/2016 Patient number: 713 (709 assigned intervention)	Prospective, randomised, double-blind, placebo-controlled, international (26 countries), multicenter (235 centers), phase III trial	Ventana PD-L1 (SP263) assay	≥25% (35%, n=159) <25% (65%, n=292) ≥1% (67%, n=303) <1% (33%, n=148) 1–24% (32%, n=144) Unknown (37%, n=262)	OS: 33.0 (range: 0.2–51.3) PFS: 14.5 (range: 0.2–29.9)	Durvalumab *vs.* placebo: - ≥25%: not reached *vs.* 21.1 - <25%: 39.7 *vs.* 37.4 - ≥1%: not reached *vs.* 29.6 - 1–24%: 43.3 *vs.* 30.5 - Unknown: 44.2 *vs.* 23.5 - <1%: 33.1 *vs.* 45.6	Durvalumab *vs.* placebo (HR, 95% CI): - ≥25% (0.50, 0.30–0.83) - <25% (0.89, 0.63–1.25) - ≥1% (0.59, 0.41–0.83) - 1–24% (0.67, 0.41–1.10) - Unknown (0.60, 0.43–0.84) - <1% (1.14, 0.71–1.84)	Durvalumab *vs.* placebo: - ≥25%: 17.8 *vs.* 3.7 - <25%: 16.9 *vs.* 6.9 - ≥1%: 17.8 *vs.* 5.6 - <1%: 10.7 *vs.* 5.6 - 1–24%: not reached *vs.* 9.0 - Unknown: 14.0 *vs.* 6.4	Durvalumab *vs.* placebo (HR, 95% CI): - ≥25% (0.41, 0.26–0.65) - <25% (0.59, 0.43–0.82) - ≥1% (0.46, 0.33–0.64) - <1% (0.73, 0.48–1.11) - 1–24% (0.49, 0.30–0.80) - Unknown (0.59, 0.42–0.83)
Offin *et al.* [2020] (10)	Recruitment: 11/2017–02/2019 Patient number: 62	Retrospective, single institution, RWS	E1L3N anti-PD-L1 antibody assay	≥50% (36%, n=18) ≥1–49% (30%, n=15) <1% (34%, n=17) Unknown: (19%, n=12)	12 (range: 6–20)	Median OS: not reached OS rate at 12 monhts: 85%	Not reached	Median PFS: not reached PFS rate at 12 months: 65%	≥1% *vs.* <1%: (0.64, 0.24–1.72, P=0.38) (univariate)
Desilets *et al.* [2021] (4)	Recruitment: 05/2018–08/2019 Patient number: 147	Retrospective, multicenter (8 centers in Canada and Japan), RWS	PD-L1 IHC 22C3 pharmDx (Dako) kit	≥50% (36.1%, n=53) 1–49% (27.2%, n=40) <1% (21.8%, n=32) Unknown (15.0%, n=22)	15.8 (range: not specified)	Median OS: not reached OS rate at 12 months: - ≥50%: 100% - 1–49%: 87% - <1%: 81%	≥50% *vs.* <50%: (0.25, 0.11–0.58, P=0.007) ≥50 *vs.* <1%: (0.24, 0.07–0.89, P=0.033) 1–49% *vs.* <1%: (0.74, 0.26–2.07, P=0.562)	≥50%: 21.7 1–49%: 10.3 <1%: 9.2	≥50% *vs.* <50%: (0.46, 0.27–0.77, P=0.004)
Jazieh *et al.* [2021] (8)	Recruitment: 07/2017–07/2019 Patient number: 121	Retrospective, single institution (Cleveland Clinic Foundation), RWS	PD-L1 IHC 22C3 pharmDx (Dako) kit	≥50–100% (29.8%, n=36) ≥1–49% (24.8%, n=30) <1% (27.3%, n=33) Unknown (18.2%, n=22)	Not available	Median OS: - ≥50–100%: 17.6 - ≥1–49%: 14.5 - <1%: 14.8 - Unknown: NA	≥50–100% *vs.* <1%: (0.339, 0.104–0.973, P=0.04) ≥1–49% *vs.* <1%: (1.289, 0.535–3.176, P=0.572)	Median PFS: - ≥50–100%: 16.9 - ≥1–49%: 7.0 - <1%: 12.5 - Unknown: NA	≥50–100% *vs.* <1%: (0.205, 0.086–0.491, P=0.0004) ≥1–49% *vs.* <1%: (1.446, 0.752–2.777, P=0.269)
Kartolo *et al.* [2021] (9)	Recruitment: 01/2018–08/2020 Patient number: 63	Retrospective, multicenter (2 centers), RWS	PD-L1 IHC 22C3 pharmDx (Dako) kit	≥50% (43%, n=27) 1–49% (25%, n=16) <1% (13%, n=8) Unknown (19%, n=12)	17.0 (IQR: 11.6–22.7)	≥50: not reached 1–49%: not reached <1%: 25.2 Unknown: not reached	≥50 *vs.* <1%: (0.19, 0.04–0.88, P=0.03) 1–49% *vs.* <1%: (0.37, 0.082–1.65, P=0.19) Unknown *vs.* <1%: (0.16, 0.02–1.03, P=0.05)	≥50: not reached 1–49%: 18.7 <1%: 10.7 Unknown: not reached	≥50 *vs.* <1%: (0.25, 0.07–0.88, P=0.03) 1–49% *vs.* <1%: (0.54, 0.15–1.89, P=0.33) Unknown *vs.* <1%: (0.21, 0.04–0.99, P=0.05)
Landman *et al.* [2021] (11)	Recruitment: 01/2018–06/2020 Patient number: 39	Retrospective, single institution, RWS	Not specified	>1% (46%, n=18) <1% (28%, n=11) Unknown (26%, n=10)	20.4 (range: 1–35.4)	Median OS: not reached OS rate at 12 months: 79%	<1% *vs.* >1%: (2.33, 0.47–11.55, P=0.30) (univariate)	Median PFS: 11.8 PFS rate at 12 months: 49%	<1% *vs.* >1%: (1.08, 0.38–3.06, P=0.88) (univariate)
Bryant *et al.* [2022] (2)	Recruitment: 11/2017–04/2021 Patient number: 312	Retrospective, multi-institutional (US database of all veterans within the Veterans Affairs health care system) study, RWS	Not specified	≥50% (34%, n=107) ≥1–49% (31%, n=96) <1% (35%, n=109)	OS: 19 PFS: 18	Median OS: not reached 24 month-OS-estimates: 54.4% in PD-L1 <1% *vs.* 56.2% in PD-L1 ≥1–49% *vs.* 73.3% in PD-L1 ≥50%, P=0.14)	aHR =0.86 per 25% absolute increase in expression; 95% CI: 0.74–0.99; P=0.036) PD-L1 <1% group *vs.* ≥50% group showed longer OS (aHR =0.57; 95% CI: 0.35–0.94; P=0.028) though the ≥1% to 49% group did not (aHR =0.75; 95% CI: 0.46–1.22; P=0.24)	Median PFS: not reached 24 months-PFS estimates: 29.3% in PD-L1 <1% *vs.* 43.5% in PD-L1 ≥1–49% *vs.* 57.6% in PD-L1 ≥50%, P=0.006	aHR =0.84 per 25% absolute increase in expression; 95% CI: 0.75–0.94; P=0.003). PD-L1 <1% group *vs.* ≥50% group showed longer PFS (aHR =0.51; 95% CI: 0.34–0.76; P=0.001), and the ≥1% to 49% group trended toward longer PFS (aHR =0.70; 95% CI: 0.47–1.03; P=0.07)

NSCLC, non-small cell lung cancer; CRT, chemoradiotherapy; OS, overall survival; CPH, Cox Proportional Hazard Model; HR, hazard ratio; CI, confidence interval; PFS, progression-free survival; RWS, real-world study; IHC, immunohistochemistry; IQR, interquartile range; NA, not available; aHR, adjusted HR.

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