Perspective

Programmed cell death ligand-1 (PD-L1) as a biomarker for non-small cell lung cancer (NSCLC) treatment—are we barking up the wrong tree?

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Abstract: Immunotherapy with monoclonal antibodies targeting programmed cell death-1 (PD-1) and programmed cell death ligand-1 (PD-L1) has become a standard of care treatment for patients with advanced or metastatic non-small cell lung cancer (NSCLC) in first and later treatment lines with durable responses seen in approximately 10–20% of patients treated. However, the optimal selection of eligible patients who will benefit most, is far from being clear and the best biomarker has not yet been established. PD-L1 expression as a predictive biomarker for immunotherapy in NSCLC patients has shown some value for predicting response to immune checkpoint inhibitors in some studies, but not in others, and its use has been complicated by a number of factors which has prompted many researchers to establish better predictive biomarkers for immunotherapy of NSCLC. Most recently, two phase III first-line NSCLC studies have provided evidence that tumour mutational burden (TMB) correlates with the clinical response to the combination of nivolumab and ipilimumab (CheckMate-227; NCT02477826), whereas atezolizumab response was correlated with T effector gene signature expression (IMPower 150; NCT02366143). Both studies demonstrated a significant primary endpoint [progression-free survival (PFS)] benefit in the TMB group and in the group of patients expressing a T effector cell signature, respectively. However, PFS benefit in both studies was seen regardless of the PD-L1 status of all patients suggesting that TMB and T effector cell signatures may be more robust to predict clinical response following treatment with checkpoint inhibitors. The role of putative novel predictive biomarkers evaluated in the CheckMate-227 and the IMPower 150 trials may, if confirmed in future prospective studies, offer a new perspective for predicting immunotherapy treatment outcomes of NSCLC patients in the near future.

Keywords: Non-small cell lung cancer (NSCLC); programmed cell death ligand-1 expression (PD-L1 expression); novel biomarkers

Submitted Apr 18, 2018. Accepted for publication Apr 18, 2018.
doi: 10.21037/tlcr.2018.04.18
View this article at: http://dx.doi.org/10.21037/tlcr.2018.04.18

Immunotherapy with monoclonal antibodies targeting programmed cell death-1 (PD-1) and programmed cell death ligand-1 (PD-L1) has become a standard of care treatment for patients with advanced or metastatic non-small cell lung cancer (NSCLC) in first and later treatment lines. Prolonged and durable responses are seen in approximately 10–20% of patients treated, however, the efficacy of these checkpoint inhibitors requires an optimal selection of eligible patients who will benefit most. Clearly, there is a huge clinical need to establish validated biomarkers which are suitable to predict immunotherapy outcome in NSCLC patients (1).

PD-L1 expression has been extensively evaluated as a predictive biomarker for immunotherapy in NSCLC

patients and has shown some value for predicting response to immune checkpoint inhibitors in some studies, but not in others. The use of PD-L1 as a biomarker remains to be complicated by a number of factors including the variability in tissue collection timing, the antibody and methodology used for staining (including the definition of positivity and the non-standardised test design), the heterogeneity and dynamic of PD-L1 expression within different tumours, and the role of PD-L1 expression on tumour-infiltrating lymphocytes and other immune cells versus the malignant cell population. In addition, PD-L1 is regarded to be a biological continuum and therefore might be of limited value as a biomarker in this subset of patients (2).

Pembrolizumab (Keytruda®, Merck, USA: targeting PD-1) is approved (EMA, FDA) for first-line treatment of NSCLC patients with advanced or metastatic cancers (with PD-L1 expression ≥50% using the Dako 22C3 IHC assay), whereas for second-line treatment a PD-L1 expression of ≥1% is required (1). Both, nivolumab (Opdivo®, Bristol-Myers Squibb, USA: targeting PD-1) and atezolizumab (Tecentriq®, Roche, Switzerland: targeting PD-L1) are also approved (EMA, FDA) in the second-line setting, but PD-L1 screening is not mandatory, however, complementary PD-L1 diagnostics are approved for NSCLC (1). Durvalumab (Imfinzi®, AstraZeneca, UK: targeting PD-L1) and avelumab (Bavencio®, MerckSerono, Germany: targeting PD-L1) are currently evaluated in first- or second-line treatment studies for NSCLC and are not approved for NSCLC treatment yet. However, it should be noted that durvalumab has demonstrated a significant progression-free survival (PFS) benefit [16.8 versus 5.6 months, hazard ratio (HR) =0.52] as maintenance therapy in stage IIIA/B NSCLC patients following radio-chemotherapy and two cycles of platinum-based therapy (PACIFIC trial) (3). Interestingly, PFS benefit was independent of PD-L1 expression. Details of this relevant phase III study is given in *Table 1*.

Some clinical trials (*Table 1*) have demonstrated that PD-L1 expression appears to be significantly correlated with clinical outcomes in NSCLC, but not in all trials, although some patients treated in these trials who had PD-L1-negative lung cancers, clinical benefit from PD-1/PD-L1 inhibitors was also observed. This observation adds therefore weight to the proposal that PD-L1 is a weak biomarker which prompted researchers to look beyond PD-L1 expression levels in order to identify more robust predictive biomarkers which then could help to better identify the immune status and the pre-existing tumour microenvironment of a given tumour.

To date, many groups of oncologists are attempting to establish better predictive biomarkers in NSCLC for monoclonal antibodies targeting the PD-1/PD-L1 axis to select patients who might have a greater benefit from immune checkpoint therapies. Initial preclinical and clinical studies have revealed that tumour mutational burden

Table 1 Results of positive phase II/III immuno-oncology studies for NSCLC

Study	Phase	Design	Results	Biomarker results	Reference
OAK trial (NCT02008227)	III	Atezolizumab versus docetaxel (second-line after platinum-failure) (N=1,225)	OS: 15.7 versus 10.3 months, HR=0.74 (PD-L1 ≥1%) OS: 12.6 versus 8.9 months, HR=0.75 (PD-L1 not detectable)	Benefit regardless of PD-L1 expression (threshold: ≥1%)	Rittmeyer *et al.* 2017 (4)
IMPower 150 trial (NCT02366143)	III	Atezolizumab + bevacizumab + carboplatin/ paclitaxel versus bevacizumab + carboplatin/ paclitaxel (N=1,202)	PFS: 8.3 versus 6.8 months (HR=0.62) overall PFS: 11.3 versus 6.8 months (HR=0.62) for T effector cell signature expression	Benefit correlated with T effector gene signature expression, but was regardless of PD-L1 expression levels (threshold: ≥1%)	Reck *et al.* 2017 (5) Kowanetz *et al.* 2018 (6)
POPLAR trial (NCT01903993)	II	Atezolizumab versus docetaxel (second-line after platinum failure) (N=287)	OS: 12.6 versus 9.7 months, HR=0.73	OS correlated with PD-L1 expression (HR=0.49 for PD-L1 ≥50%)	Fehrenbacher *et al.* 2016 (7)

Table 1 (*continued*)

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Study	Phase	Design	Results	Biomarker results	Reference
KeyNote-024 trial (NCT02142738)	III	Pembrolizumab versus SoC (first-line) (N=305)	PFS: 10.3 versus 6.0 months (HR=0.50) OS at 6 months: 80.4% versus 72.8%	Benefit seen in patients expressing PD-L1 ≥50%	Reck *et al.* 2016 (8)
KeyNote-010 trial (NCT01905657)	III	Pembrolizumab versus docetaxel (second-line after platinum failure) (N=1,034)	OS: 14.9 versus 8.2 months (HR=0.54) (pembrolizumab: 2 mg/kg) OS: 17.3 versus 8.2 months (HR=0.50) (pembrolizumab: 10 mg/kg)	Benefit seen in patients with PD-L1 ≥50%	Herbst *et al.* 2016 (9)
KeyNote-189 trial (NCT02578680)	III	Pembrolizumab plus pemetrexate/platinum drug versus placebo plus pemetrexate/platinum drug (non-squamous) (N=616)	OS at 12 months: 69.2% versus 49.4% (HR=0.49, P<0.001) PFS: 8.8 versus 4.9 months (HR=0.52, P<0.001)	PFS and OS benefits were seen across all PD-L1 categories	Gandhi *et al.* 2018 (10)
PACIFIC trial (NCT 02125461)	III	Durvalumab versus placebo (stage IIIA/B: maintenance after radiotherapy and 2 cycles of platinum-based chemotherapy) (N=713)	PFS: 16.8 months versus 5.6 months (HR=0.52)	PFS benefit regardless of PD-L1 expression: PD-L1 <25%: HR=0.59 (95% CI: 0.43–0.82); PD-L1 ≥25%: HR=0.41 (95% CI: 0.26–0.65)	Antonia *et al.* 2017 (3)
ATLANTIC trial (NCT 02087423)	II	Durvalumab (third or later treatment lines after platinum failure) (N=333)	ORR was 16.4% and 30.9% in patients with ≥25% and ≥90% of PD-L1-positive tumour cells, respectively	ORR correlated strongly with PD-L1 expression	Garassino *et al.* 2016 (11)
CheckMate-227 trial (NCT02477826)	III	Nivolumab + ipilimumab versus nivolumab versus platinum-based chemotherapy (first-line) for patients with PD-L1 ≥1%; nivolumab + ipilimumab versus nivolumab + platinum-based chemotherapy versus platinum-based chemotherapy for patients with PD-L1 <1% (N=1,980)	Significant PFS benefit for nivolumab + ipilimumab versus platinum-based chemotherapy for patients with high TMB (≥10 mutations/1 Mbase): 7.2 versus 5.5 months (HR=0.58, P<0.001); ORR: 45.3% versus 26.9%	PFS benefit was independent of PD-L1 expression, but correlated with TMB levels. No PFS benefit was seen in the overall population	Hellmann *et al.* 2018 (12)
CheckMate-017 trial (NCT01642004)	III	Nivolumab versus docetaxel (squamous cell, second-line after platinum-failure) (N=272)	OS: 9.2 versus 6.0 months, HR=0.59, P<0.001	OS benefit regardless of PD-L1 expression (range, 1–10%)	Brahmer *et al.* 2015 (13)
CheckMate-057 trial (NCT01673867)	III	Nivolumab versus docetaxel (non-squamous, second-line after platinum failure) (N=582)	OS: 12.2 versus 9.4 months, HR=0.73, P=0.002	PD-L1 expression (range, 1–10%) predictive of benefit	Borghaei *et al.* 2015 (14)

OS, overall survival; PFS, progression-free survival; HR, hazard ratio; TMB, tumour mutational burden; PD-L1, programmed cell death-ligand 1; ORR, overall response rate.

(TMB) or gene signatures may be an ideal strategy guiding treatment decisions for checkpoint inhibitors (15,16). Yarchoan *et al.* (15) reported a clear correlation between TMB and overall response rate (ORR) (P<0.001) following checkpoint inhibitor treatment in many cancers suggesting that a significant relationship between TMB and anti-PD-1/anti-PD-L1 treatment exists. On the other hand, Leal and Ramalingham (1) found that in NSCLC patients responding to immune checkpoint inhibitor treatment early PD-L1-positive CD8-positive T cell responses were seen suggesting that these proliferating CD8-positive T cells may have an effector-like phenotype which could generate cytotoxicity [see also (16) for a review].

Most recently, two phase III studies (CheckMate-227 and IMPower 150) have provided evidence that TMB correlates with the clinical response to the combination of nivolumab and ipilimumab (Yervoy®, Bristol-Myers Squibb, USA: targeting CTLA-4) (CheckMate-227) (12), whereas atezolizumab response was correlated with T effector gene signature expression (IMPower 150) (5,6,16). Both studies were conducted as first-line trials in NSCLC (*Table 1*). The CheckMate-227 trial is the first to our knowledge to evaluate TMB as a predictive biomarker for immunotherapy in NSCLC (co-primary endpoint). The study demonstrated a significant PFS benefit in the nivolumab + ipilimumab group in first-line NSCLC patients with a TMB level of ≥10 mutation/Mbase regardless of PD-L1 expression (7.2 versus 5.5 months, HR=0.58, P<0.001) (12). Interestingly, the reported median PFS benefit was only seen in the TMB subgroup, but not the overall population (12) suggesting that TMB may be a predictive novel biomarker for checkpoint inhibitor treatment. Objective response rates were found to be 45.3% versus 26.9%, respectively (12).

The IMPower 150 trial is the first phase III study to demonstrate a clinically meaningful and significant PFS benefit with atezolizumab plus bevacizumab and chemotherapy (paclitaxel and carboplatin) versus bevacizumab plus chemotherapy in the first-line stetting of advanced or metastatic NSCLC (8.3 versus 6.8 months, HR=0.62, P<0.0001) and the PFS benefit was seen regardless of the PD-L1 status in all patients (5,11). The PFS benefit, however, was even more pronounced in patients expressing a T effector gene signature (11.3 versus 6.8 months, HR=0.51, P<0.0001) (5,6) indicative that the expression of gene signatures may be more robust to predict clinical response following treatment with PD-L1 inhibitors.

Although PD-L1 testing has clearly some limitations as a predictive biomarker, it is currently widely used (17). Despite progress made so far in terms of novel immunotherapy strategies for NSCLC, the major challenge still remains to identify those patients with advanced or metastatic NSCLC who will benefit the most following treatment with immune checkpoint inhibitors. In this regard the role of the putative novel predictive biomarkes evaluated in the CheckMate-227 and in the IMPower 150 trials may, if confirmed in further prospective clinical trials, offer a new perspective for predicting immunotherapy treatment outcomes of NSCLC patients in the near future.

Acknowledgements

None.

Footnote

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

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Cite this article as: Dempke WC, Fenchel K, Dale SP. Programmed cell death ligand-1 (PD-L1) as a biomarker for non-small cell lung cancer (NSCLC) treatment—are we barking up the wrong tree? Transl Lung Cancer Res 2018;7(Suppl 3):S275-S279. doi: 10.21037/tlcr.2018.04.18

