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The clinical utility of PD-L1 testing in selecting non-small cell lung cancer patients for PD1/PD-L1 directed therapy

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Lung cancer is the leading cause of cancer mortality in the United States and worldwide. Long thought to be non-immunogenic, immunotherapy in lung cancer has historically been met with disappointing results. Programmed death-1 (PD-1), and the PD-1 ligand, PD-L1, are immune checkpoint proteins which fine-tune the antigen specific T-cell response after stimulation of the T-cell receptor and are crucial for self-tolerance. This pathway in particular is co-opted by tumors through expression of PD-L1 on the tumor cell surface and within the tumor microenvironment, allowing for direct suppression of anti-tumor cytolytic T-cell activity by the tumor. Indeed, induction of the PD1/PD-L1 pathway represents an adaptive immune resistance mechanism exerted by tumor cells in response to endogenous anti-tumor activity. In 2015, the Food and Drug Administration (FDA) approved two immuno-oncology agents, the PD-1 inhibitors nivolumab and pembrolizumab, for the treatment of previously treated advanced non-small cell lung cancer (NSCLC). Coincident with the clinical trials that led to these regulatory approvals has been the development of several immunohistochemistry (IHC) tests of PD-L1 expression, which may serve to select patients who will derive the most benefit from PD1 or PD-L1 directed therapy. The PD-L1 IHC assays are distinct in their methods and interpretation, which poses a challenge to clinicians selecting patients for these therapies.

Two clinical trials were central to the regulatory approval of nivolumab (Table 1), in which a clear survival benefit was noted in previously treated advanced NSCLC patients compared with docetaxel, a benefit that was noted in both squamous (Checkmate-017) and non-squamous histology (Checkmate-057) and regardless of PD-L1 positivity, as determined by any degree of IHC staining of the tumor cell membrane utilizing the 28-8 antibody (Dako). (1, 2) While PD-L1 positivity did not impact efficacy in squamous NSCLC, PD-L1 positivity in patients with non-squamous histology was associated with enhanced efficacy with longer overall survival (OS), progression-free survival (PFS) and higher objective

response rates (ORRs) with nivolumab versus docetaxel across PD-L1 expression cut-points (1%, 5% or 10% expression). Pembrolizumab was evaluated in Keynote-010, which enrolled patients with PD-L1 positive NSCLC, as determined by membranous staining in at least 1% of tumor cells or intercalated mononuclear inflammatory cells within tumor nests or stroma surrounding the tumor nests, by the 22C3 antibody (Dako).(3) While the benefit of pembrolizumab over docetaxel was noted in all patients included in this trial regardless of histology, in a pre-specified analysis, PD-L1 expression $\geq 50\%$ enhanced the ORR, OS and PFS benefit of pembrolizumab over docetaxel considerably (Table 1).

Atezolizumab and durvalumab are inhibitors of PD-L1, which are also being evaluated in NSCLC in the context of distinct companion diagnostics. POPLAR was a phase II randomized clinical trial which compared the PD-L1 inhibitor atezolizumab with docetaxel in advanced NSCLC patients, in whom PD-L1 positivity was assessed using the SP142 antibody IHC assay (Ventana) and scored on tumor-infiltrating immune cells (ICs) and tumor cells (TCs) as IC0, 1, 2 or 3 and TC0, 1, 2 or 3, respectively(4). Atezolizumab was associated with an OS benefit in the entire population, however the benefit of atezolizumab over docetaxel was more pronounced in patients when classified as medium to high PD-L1 expressers (TC2/3 or IC 2/3) or any PD-L1 expressers (TC1/2/3 or IC 1/2/3) as compared with patients that were non-PD-L1 expressers (TC0 or IC0) (Table 1). The clinical activity of the PD-L1 inhibitor durvalumab was studied in a phase I dose expansion cohort in treatment-naïve and previously untreated NSCLC patients (ARTIC), in which a higher level of activity was associated with PD-L1 positivity, as determined by membranous staining of $\geq 25\%$ tumor cells at any intensity using the SP263 antibody IHC assay (Ventana) (5).

While the clinical activity of the agents targeting the PD1/PD-L1 pathway is impressive, the question still remains how best to select patients based on the PD-L1 status of their tumor and associated immune infiltrate. Each of the aforementioned agents was tested along with discrete IHC assays, and the criteria for defining PD-L1 positivity were distinct. The difference in criteria between the assays includes differences in the assessments (tumor cells versus tumor associated immune cells or both), the scoring methods (percentage versus H-score), and differences in clinical decision cut-points (1% versus $\geq 50\%$, etc). There is no indication as of yet of the comparability of the antibody clones with regard to sensitivity and specificity or whether the reactivity of these clones differs between tumor cells and tumor infiltrating immune cells. Each antibody was developed with a specific protocol and platform, and on a practical level it is neither pragmatic nor cost effective for individual laboratories to maintain multiple assays and platforms for PD-L1. From the patient perspective, multiple PD-L1 tests demands patient tissue with the possible consequence of exhaustion of patient tumor biopsies, which might otherwise be used for genomic testing.

In the regulatory review of nivolumab, the FDA approved the use in previously treated NSCLC patients of both squamous and non-squamous history regardless of PD-L1 positivity. The 28-8 antibody assay (Dako) was approved as a complimentary diagnostic. As such, the use of the 28-8 assay is not needed to select patients for nivolumab therapy, but may be useful in determining how well patients, in particularly the non-squamous subset, may respond to therapy. In comparison, pembrolizumab was specifically developed in the context of a PD-L1 expressing population. As such, the FDA approved pembrolizumab

specifically in PD-L1 expressing patients as determined by the companion diagnostic, the 22C3 antibody assay. This renders the 22C3 antibody, from the regulatory standpoint, essential in selecting patients for pembrolizumab therapy. As the clinical development of atezolizumab and durvalumab progress, so will the complexity of the PD-L1 assay landscape with the likely addition of the SP142 and SP263 antibody assays into the diagnostic mix. Of concern, most clinicians in routine practice are not communicating regularly with their pathologists with regards to the specifics of a diagnostic test. If laboratories select a single antibody to perform their PD-L1 testing for pragmatic issues, the issue then arises of the possibility of a mismatched diagnostic assay for the PD1 or PD-L1 therapeutic that is being considered for a particular patient by the clinician.

These issues have been paid particular attention by the FDA, who in a public workshop in collaboration with the American Society of Clinical Oncology (ASCO) and the American Association for Clinical Research (AACR), announced efforts geared toward harmonizing companion diagnostics across PD1/PD-L1 directed therapies. The Blueprint Proposal involves collaboration between six pharmaceutical and diagnostic companies involved in the development of the PD1/PD-L1 inhibitors and assays. NSCLC samples will be tested on the different platforms in order to compare the analytical performance of the individual assays. The overarching goals of this proposal are to lay the foundation for post-market standardization and/or the development of practice guidelines. This collaboration between companies developing commercially competing compounds and diagnostics is unprecedented, as is the interface at the regulatory level with the FDA and non-commercial entities like ASCO and AACR. If successful, this project may lay the groundwork for future collaboration between multiple private and public entities in the rationale development of targeted therapeutic approaches in oncology.

In using PD-L1 to select patients for PD1/PD-L1 directed therapies, it is important to note the clinical activity of these agents in the PD-L1 negative population. In Checkmate-017, nivolumab was associated with a response rate of about 10% in patients with PD-L1 expression <1%, <5% and <10%, which was comparable to the response rate to docetaxel. Similarly in POPLAR, atezolizumab was associated with a RR of 8% in PD-L1 negative (TC0/IC0) patients compared with 10% with docetaxel. In these comparative trials, the PD1 and PD-L1 directed therapies were much better tolerated from the standpoint of treatment-related adverse side effects relative to docetaxel, which places the immune checkpoint inhibitors in a favorable light even in the PD-L1 negative population given its comparable efficacy and better tolerability compared with single agent cytotoxic therapy.

Another consideration is that PD-L1 expression is a dynamic, rather than static process, varying both temporally and spatially in what is an adaptive immune resistance exerted by the tumor. Consideration of alternative predictive biomarkers will be important in optimizing patient selection for these types of therapies. Response to pembrolizumab has been associated with a higher nonsynonymous mutation burden, a molecular smoking signature, higher neo-antigenic burden, and DNA repair pathway mutations (6), which suggests that limiting the development of predictive biomarkers to PD-L1 expression may be underestimating the complexity of determinants of PD1/PD-L1 therapeutic benefit.

The demonstration of a survival benefit from PD1 directed therapies compared single agent chemotherapy in the previously treated NSCLC population has revolutionized the treatment paradigm of lung cancer. Attendant with this is the appropriate compulsion to personalize cancer therapies; selecting patient populations that are most likely to respond, while sparing potential toxicity in patients who are unlikely to derive significant therapeutic benefit from a particular therapy. The challenge in the development of the PD1/PD-L1 directed therapies is the heterogeneity in the co-development of the PD-L1 assays. Hopefully, the collaborative efforts by the FDA, ASCO and AACR along with pharmaceutical and diagnostic companies will provide insight into the standardization of these diagnostics. The question still remains if PD-L1 expression poses any clinical utility in selecting patients for these therapies, given the reasonable percentage of patients who are PD-L1 negative who respond to PD1/PD-L1 directed therapy. Finally, incorporation of other candidate biomarkers, such as a molecular smoking signature or neo-antigenic burden, in prospective clinical trials evaluating these therapies will be helpful in fine-tuning patient selection.

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Table 1

Selected clinical trials and the predictive benefit of PD-L1 testing.

Study	Study Arms	Primary Endpoint(s)	PD-L1 Assay	Predictive Benefit?			
PD1 inhibitors							
CheckMate-017 Phase III Previously treated squamous NSCLC Any PD-L1 status	Nivolumab	OS (mos) 9.2 *	IHC 28-8 antibody assay (Dako) PD-L1 positivity: tumor-cell membrane (at any intensity).	No.			
	Docetaxel	6.0					
CheckMate-057 Phase III Previously treated non-squamous NSCLC Any PD-L1 Status	Nivolumab	OS (mos) 12.2 *	IHC 28-8 antibody assay (Dako) PD-L1 positivity: tumor-cell membrane (at any intensity).	Yes, a pre-specified analysis demonstrated nivolumab associated longer OS and PFS and higher RRs across PD-L1 expression cut-points 1%, 5% or 10% compared with docetaxel.			
	Docetaxel	9.4					
Keynote-010 Phase II/III Previously treated NSCLC PD-L1 positive			IHC 22C3 antibody assay (Dako) PD-L1 positivity: membranous staining in at least 1% of cells of tumor cells and intercalated mononuclear inflammatory cells) within tumor nests or surrounding stroma.	Yes, OS and PFS by PD-L1 expression 50% were assessed as co-primary endpoints.			
		OS (mos)			PFS (mos)	OS (mos)	PFS (mos)
	Pembrolizumab 2 mg/kg	10.4 *			3.9	14.9 *	5.6 *
	Pembrolizumab 10 mg/kg	12.7 *			4.0	17.3 *	5.2 *
	Docetaxel	8.5			4.0	8.2	4.1
PD1 inhibitors							
POPLAR Phase II Previously treated NSCLC Any PD-L1 Status		OS (mos)	IHC SP 142 antibody assay (Ventana) PD-L1 expression on tumor-infiltrating immune cells (ICs) and tumor cells (TCs) scored as TC0, 1, 2 or 3 and IC0, 1, 2 or 3, respectively.	Yes, OS by IC PD-L1 expression assessed as co-primary endpoint.			
					OS (mos)		
					TC2/3	TC1/2/3	TC0
					IC 2/3	IC 1/2/3	IC0
	Atezolizumab	12.6 *				15.1 *	15.5 *
	Docetaxel	9.7		7.4	9.2	9.7	
ARTIC Phase I Advanced NSCLC Any PD-L1 Status	Durvalumab	ORR 16%	IHC SP 263 antibody assay (Ventana)	Yes, ORR 27% * versus 5% in PD-L1 positive and PD-L1 negative tumors, respectively.			

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Study	Study Arms	Primary Endpoint(s)	PD-L1 Assay	Predictive Benefit?
			PD-L1 positivity: membranous staining of ~25% tumor cells at any intensity	

Abbreviations: mos, months; PFS, progression-free survival; OS, overall survival; ORR, objective response rate; IHC, immunohistochemistry.

* Statistical significance.