ORIGINAL ARTICLE

The International Association for the Study of Lung Cancer Global Survey on Programmed Death-Ligand 1 Testing for NSCLC

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ABSTRACT

Introduction: Programmed death-ligand 1 (PD-L1) immunohistochemistry (IHC) is required to determine the eligibility for pembrolizumab monotherapy in advanced NSCLC worldwide and for several other indications depending on the country. Four assays have been approved/ Communauté Européene–In vitro Diagnostic (CV-IVD)–marked, but PD-L1 IHC seems diversely implemented across regions and laboratories with the application of laboratory-developed tests (LDTs).

Method: To assess the practice of PD-L1 IHC and identify issues and disparities, the International Association for the Study of Lung Cancer Pathology Committee conducted a global survey for pathologists from January to May 2019, comprising multiple questions on preanalytical, analytical, and postanalytical conditions.

Result: A total of 344 pathologists from 64 countries participated with 41% from Europe, 24% from North America, and 18% from Asia. Besides biopsies and resections, cellblocks were used by 75% of the participants and smears by 11%. The clone 22C3 was most often used (69%) followed by SP263 (51%). They were applied as an LDT by 40% and 30% of the users, respectively, and 76% of the participants developed at least one LDT. Half of the participants reported a turnaround time of less than or equal to 2 days, whereas 13% reported that of greater than or equal to 5 days. In addition, quality assurance (QA), formal training for scoring, and standardized reporting were not implemented by 18%, 16%, and 14% of the participants, respectively.

Conclusions: Heterogeneity in PD-L1 testing is marked across regions and laboratories in terms of antibody clones, IHC assays, samples, turnaround times, and QA measures. The lack of QA, formal training, and standardized reporting stated by a considerable minority identifies a need for additional QA measures and training opportunities.

Keywords: PD-L1; NSCLC; Pathology; International survey

Introduction

Immune checkpoint inhibitors targeting programmed cell death protein-1/programmed death-ligand 1

(PD-L1) axis have drastically changed the treatment landscape in oncology. There are a few anti–programmed cell death protein-1/PD-L1 agents approved for the treatment of patients with advanced NSCLC, either alone or in combination with chemotherapy or an anti–CTLA-4 agent in the first-line setting or second-line and beyond. Notably, pembrolizumab as a monotherapy or in combination with chemotherapy has been approved for the first-line treatment of advanced NSCLC in many countries and changed the standard of care for those patients.[1-5] Pembrolizumab monotherapy is used in many countries[1] to treat patients with tumors with PD-L1 expression by immunohistochemistry (IHC) of at least 50% of tumor cells (tumor proportion score [TPS] of $\geq$50%). A TPS of greater than or equal to 1% has also been approved in this setting in the United States and Japan.[4,5] Although the combination of pembrolizumab and chemotherapy does not require a companion diagnostic, this combination is more likely reserved in current practice for patients with lower PD-L1 expression ($<$50%) or certain clinical factors (e.g., significant tumor or symptom burden). Tumors exhibiting high PD-L1 ($\geq$50%) are often treated with pembrolizumab monotherapy given its less adverse effects.[6] Thus, PD-L1 IHC is now established as a predictive biomarker test to determine pembrolizumab as monotherapy versus in combination with chemotherapy for the first-line treatment of advanced NSCLC. Furthermore, PD-L1 IHC also serves as a companion diagnostic for pembrolizumab monotherapy in the second-line setting and beyond; in the United States, for atezolizumab monotherapy and for a combination of nivolumab and ipilimumab in the first-line setting; and in Europe, for durvalumab therapy after chemoradiation in patients with stage III NSCLC.[7-10] Consequently, PD-L1 IHC has been implemented in most pathology laboratories. However, the implementation of the test and participation in quality assurance (QA) programs and training for PD-L1 scoring seem variable across the regions and laboratories and may influence the test results and, consequently, the clinical care of patients. Therefore, the Immune Biomarker Working Group of the International Association for the Study of Lung Cancer (IASLC) Pathology Committee conducted an international survey for pathologists on PD-L1 testing in NSCLC. The aims of this survey were as follows: (1) to determine the prevalence of PD-L1 testing worldwide; (2) to analyze differences in practice among different regions and laboratories; and (3) to identify the issues that may influence the test results and, consequently, the clinical care of patients.

Materials and Methods

The international online survey for pathologists on PD-L1 IHC testing in NSCLC was conducted from February 1, 2019 to May 31, 2019. The survey was advertised on the IASLC and Pulmonary Pathology Society websites and at the 2019 annual meeting of the United States and Canadian Association of Pathology. To increase the number of participants, we also contacted the president of individual national or regional pathology societies.

The survey consisted of more than 20 questions to encompass preanalytical, analytical, and postanalytical aspects of the PD-L1 IHC testing. They are summarized as follows: (1) the type of samples and tissue handling; (2) the availability/type of PD-L1 IHC assay(s); (3) participation in QA program(s) and training course(s); and (4) reporting of the results.

Regarding statistical analysis, quantitative results are presented as frequency (percentage), with respondents as the unit of analysis. The chi-square test or Fischer's exact bilateral test was used for regional comparisons. All quantitative analyses were conducted using the Statistical Analysis System version 9.4 (SAS Institute, Cary, NV). The p values less than 0.05 were considered statistically significant.

Results

Participants

A total of 344 pathologists from 310 institutions in 64 countries participated in the survey. Of those, 140 (41%) were from Europe (including 45 from France, 14 from the United Kingdom, and 13 from Spain), followed by 83 (24%) from North America (including 64 from the United States and 19 from Canada), 61 (18%) from Asia (including 18 from Japan, 14 from the People's Republic of China, and 10 from India), 25 (7.3%) from Central and South America (including 10 from Argentina, five from Columbia, and four each from Brazil and Mexico), 22 (6.4%) from Africa and the Middle East (including seven from Turkey and five from Saudi Arabia) and 13 (3.8%) from Oceania (including 10 from Australia and three from New Zealand) (Fig. 1). As for the subspecialty, 109 (32%) were specialized in thoracic pathology, 102 (30%) in thoracic pathology and cytology, 22 (6%) in cytology, and 11 (3%) in other fields, whereas 100 (29%) practiced general pathology without specialization.

PD-L1 Testing Status

A total of 10 (2.9%) pathologists from nine countries did not perform PD-L1 IHC for either clinical or research purposes. In addition, two pathologists performed the IHC only for research. Another 34 (9.9%) sent out samples to other laboratories, in particular, 25% of North American participants and 15% of those from Central and South America, with or without scoring the slide on receipt ($p < 0.0001$) (Table 1). Of the 298 pathologists with clinical PD-L1 IHC available in their

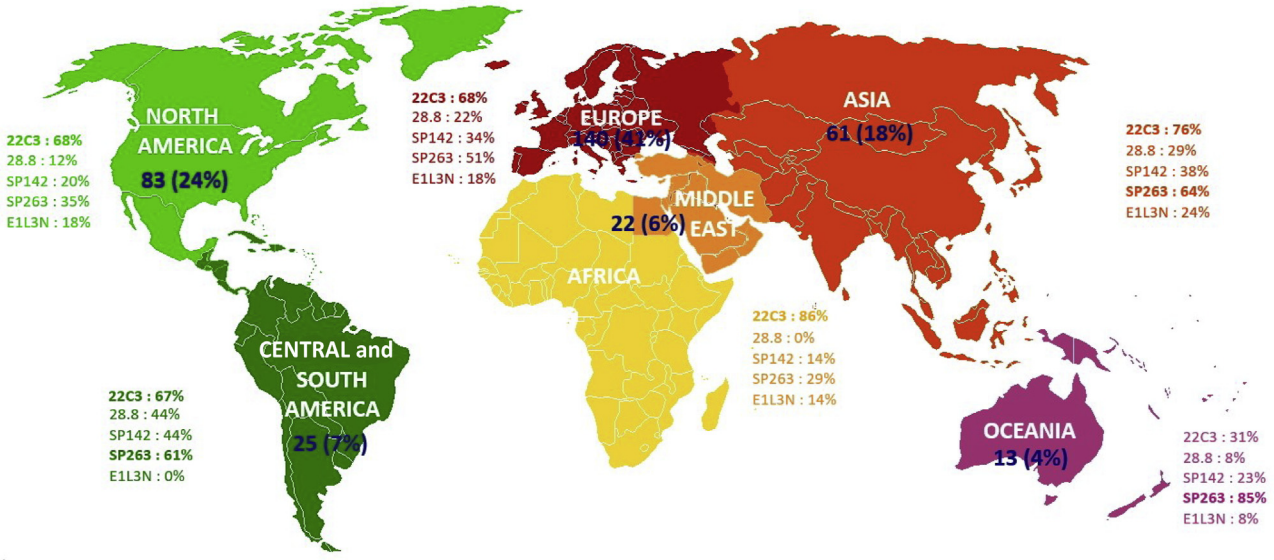

Figure 1. The participation rate of pathologists and use of different PD-L1 clones by region. PD-L1, programmed death-ligand 1.

laboratories, 116 (39%) responded to perform the IHC with internal samples only and 171 (57%) with both internal and referral samples, and 11 (3.7%) belonged to a central or commercial laboratory.

Type of Specimens and Preanalytical Conditions

Of the 332 participants who had clinical PD-L1 testing available and responded to this question, 98% used biopsies, 92% used excision or resection samples, and 75% used cell blocks. Cell blocks were mainly used in North America (88%), Europe (84%), and Oceania (92%), whereas only 20%, 54%, and 63% of the participants from Central and South America, Asia, and Africa and the Middle East, respectively, used them for PD-L1 testing ($p < 0.0001$) (Table 1). The use of cytology smears was limited to 36 participants (11%) including five (6.0%) from North America, 22 (16%) from Europe, four (6.8%) from Asia, and three (16%) from Africa and the Middle East. No participants from Oceania used cytology smears for PD-L1 IHC.

As for the preanalytical conditions, data were available from only 179 of 332 (54%) participants who performed clinical PD-L1 testing. Of those, 42%, 47%, and 72% recorded delay before fixation, fixation duration, and age of unstained slides, respectively, among others. More importantly, the type of fixatives was recorded only by six (3.4%) responders (Supplementary Table 1).

PD-L1 Antibody Clones and Platforms Used

Data relating to IHC platforms were available from 296 participants. The Ventana (Ventana Medical Systems, Oro Valley, AZ) autostainers were most prevalent, with greater than 70% of laboratories equipped in Central and South America, Europe, Asia, and Oceania. Conversely, Dako (Agilent, Santa Clara, CA) and Leica (Leica biosystems, Wetzlar, Germany) autostainers were used in 45% and 19% of the laboratories, respectively. In particular, Dako platforms were available in only 8% of participating laboratories in Oceania and 36% in Europe ($p < 0.0001$), whereas 31% used Leica platforms in Oceania (Table 1).

Of the 302 participants with information about PD-L1 antibody clones available, 155 (51%) used more than one clone. Most (69%) used clone 22C3, followed by clone SP263 (51%), which was used by most laboratories except in North America (35%) and Africa and Middle East (29%) ($p = 0.001$). The clones 28.8, SP142, and 73-10 were used only by 21%, 31%, and 1.7% of participants, respectively (Fig. 1 and Table 2). Interestingly, the clinical trial–validated commercial assay was used in 60% of the laboratories that performed IHC with the 22C3 clone. The SP263 commercial assay was used in 86%, 69%, 64%, and 100% of the laboratories using SP263 clone in Europe, Asia, Oceania, and Africa and the Middle East, respectively, and in only 35% and 45% of laboratories in North America and Central and South America, respectively ($p < 0.0001$) (Table 2). Overall, the 22C3, 28.8, SP142, and SP263 clones were applied as a laboratory-developed test (LDT) by 84 (28%), 21 (7.0%), 36 (12%), and 46 (15%) of the 302 participants. In addition, a minority (18%) used a nonclinical trial clone, E1L3N (Table 2), whereas another Communauté Européene–In vitro Diagnostic (CE-IVD)–marked nonclinical trial clone, QR1, was used by 7.3%, mainly in France. A total of 6% of the laboratories with clinical PD-L1 testing performed only LDTs.

Table 1. Preanalytical, Analytical, and Postanalytical Aspects of PD-L1 Testing Stratified by Region

Region	North America n = 83	Central and South America n = 25	Europe n = 140	Asia n = 61	Oceania n = 13	Africa and Middle East n = 22	Comparison Test	World n = 344
PD-L1 testing status,[a] n (%)	n = 83	n = 20	n = 139	n = 59	n = 13	n = 20	$p^b < 0.0001$	n = 334
In-house	62 (75)	17 (85)	134 (96)	56 (95)	13 (100)	18 (90)		300 (90)
Send-out	21 (25)	3 (15)	5 (4)	3 (5)	0	2 (10)		34 (10)
No. of sample types,[c] n (%)	n = 83	n = 20	n = 138	n = 59	n = 13	n = 19	$p^b < 0.0001$	n = 332
1	2 (3)	5 (25)	5 (4)	5 (9)	1 (8)	6 (32)		24 (7)
2	11 (13)	11 (55)	21 (15)	22 (37)	1 (8)	1 (5)		67 (20)
>3	70 (84)	4 (20)	112 (81)	32 (54)	11 (84)	12 (63)		241 (73)
Sample types used,[c] n (%)								
Biopsy	80 (96)	20 (100)	138 (100)	57 (97)	13 (100)	16 (84)	$p^b < 0.0001$	324 (98)
Surgical	80 (96)	15 (75)	128 (91)	55 (93)	11 (85)	16 (84)	$p^b < 0.0001$	305 (92)
Cell blocks	73 (88)	4 (20)	116 (84)	32 (54)	12 (92)	12 (63)	$p^b < 0.0001$	249 (75)
Cytology smear	7 (8.4)	0	22 (16)	4 (6.8)	0	0		36 (11%)
Platform,[c] n (%)	n = 57	n = 19	n = 133	n = 54	n = 13	n = 18	$p^b = 0.07$	n = 294
Ventana	31 (54)	14 (74)	95 (71)	42 (78)	10 (77)	9 (50)	$p^b = 0.10$	201 (68)
Dako	29 (51)	10 (53)	48 (36)	35 (65)	1 (8)	10 (56)	$p^b < 0.0001$	133 (45)
Leica	13 (23)	1 (5)	23 (17)	14 (26)	4 (31)	1 (6)	$p^b = 0.19$	56 (19)
External QA,[c] n (%)	n = 59	n = 16	n = 134	n = 56	n = 13	n = 18	$p^b = 0.54$	n = 296
No	8 (14)	5 (31)	23 (17)	11 (20)	1 (8)	4 (22)		52 (18)
Yes	51 (86)	11 (69)	111 (83)	45 (80)	12 (92)	14 (78)		244 (82)
If yes, n (%),								
Interlab validation	28 (47)	6 (38)	39 (29)	29 (52)	5 (38)	7 (39)	$p^b = 0.04$	114 (39)
Formal external QA	34 (58)	7 (44)	97 (72)	30 (54)	10 (77)	9 (50)	$p^b = 0.02$	187 (63)
Other	2 (3)	1 (6)	2 (1)	2 (4)	2 (15)	0	$p^b = 0.11$	9 (3)
Training,[c] n (%)	n = 75	n = 21	n = 139	n = 60	n = 13	n = 21	$p^b < 0.0001$	n = 329
No	23 (31)	5 (36)	9 (6)	8 (13)	0	7 (33)		52 (16)
Yes	52 (69)	16 (64)	130 (94)	52 (87)	13 (100)	14 (67)		277 (84)
If yes, organized by, n (%)							$p^b = 0.02$	
Companies	28 (54)	10 (63)	91 (70)	43 (83)	11 (84)	8 (58)		191 (69%)
IASLC	5 (10)	2 (12)	11 (8)	7 (13)	1 (8)	3 (21)		29 (10%)
Other societies	19 (37)	4 (25)	28 (22)	2 (4)	1 (8)	3 (21)		57 (21%)
Guidelines used,[c] n (%)	n = 73	n = 21	n = 140	n = 59	n = 13	n = 20	$p^b = 0.07$	n = 326
No	4 (5)	0	3 (2)	1 (2)	1 (8)	3 (15)		12 (4)
Yes	69 (95)	21 (100)	137 (98)	58 (98)	12 (92)	17 (85)		314 (96)
If yes, n (%)								
Local or national	53 (73)	5 (24)	95 (68)	36 (61)	7 (54)	6 (30)	$p^b < 0.0001$	202 (62)
IASLC	26 (36)	18 (86)	78 (56)	34 (58)	9 (69)	15 (75)	$p^b < 0.0001$	180 (55)
TAT[c]							$p^d = 0.0002$	
Median	1-2 d	2-3 d	1-2 d	2-3 d	1-2 d	3-4 d		1-2 d
Range	[1 to ≥5]	[1 to ≥5]	[1 to ≥5]	[1 to ≥5]	[1 to ≥5]	[1 to ≥5]		[1; ≥5]
Standardized report,[c] n (%)	n = 79	n = 19	n = 138	n = 58	n = 13	n = 18	$p^b = 0.53$	n = 325
No	8 (10)	2 (11)	23 (17)	6 (10)	1 (8)	4 (22)		44 (14%)
Yes	71 (90)	17 (89)	115 (83)	52 (90)	12 (92)	14 (78)		281 (86%)

IASLC, International Association for the Study of Lung Cancer; PD-L1, programmed death-ligand 1; QA, quality assurance; TAT, turnaround time.
[a]The numbers indicate participants whose laboratory offered clinical PD-L1 immunohistochemistry assessment.
[b]The *p* values were obtained using chi-square test or the Fisher's exact bilateral test.
[c]The numbers indicate those of participants who responded to the specific question.
[d]The *p* values were obtained using the Mann-Whitney *U* test.

External Control

Information about on-slide external control was provided by 296 participants. Of those, 99.7% used external (positive) control tissues, and the tonsil was the most prevalent (71%), followed by the placenta (38%) and lung cancer (31%). Commercial cell lines with known levels of PD-L1 expression were also used in 19% and most (52%) applied multiple tissue types as external control.

QA, Training, and Guidelines

A total of 296 participants reported the status of QA in their laboratories. Whereas most (82%) laboratories had external quality assessment (EQA) in place, 18% of participants reported a lack of EQA. More importantly, 63% of the laboratories participated in a formal EQA program(s), including three-quarters of laboratories in Europe and Oceania, but only half of the laboratories in the other regions ($p = 0.02$) (Table 1). Of note, 39% of the laboratories performed only interlaboratory validation.

A total of 329 participants reported scoring PD-L1 on clinical samples. Of those, 84% had undergone some training on the assessment of PD-L1 IHC. The rate was lower in North America (69%), Africa and Middle East (67%), and Central and South America (64%). Of the 277 participants who had undergone training, most (89%) attended a training session(s) organized by vendors, pharmaceutical companies, pathology societies, or the IASLC (Table 1), but 11% had only undergone informal training, such as an intradepartmental session tutored by a colleague who had participated in a formal training session(s).

Some guidelines were applied in most laboratories (96%). National or local guidelines were used by 62% of the participants, mainly in North America, Europe, and Asia (73%, 68%, 61%, respectively) (Table 1), but 76% and 55% of laboratories in Central/South America and Africa and the Middle East, respectively, only referred to the IASLC PD-L1 atlas ($p < 0.0001$).

Turnaround Time and Reporting

Overall, the median turnaround time (TAT) from the acquisition of samples was 1 to 2 days, with a TAT of 2 to 3 days in South and Central America and Asia, and 3 to 4 days in Africa and Middle East ($p < 0.0001$) (Table 1). Most (76%) reported results within 3 days, whereas it took more than 5 days in 21% to 23% of laboratories in Asia, Central and South America, and Africa and the Middle East. TAT was shortest in Europe. In North America, particularly the United States, laboratories that sent out samples to other laboratories and scored them on returning reported longer TAT. For reporting, most laboratories (86%) used a standardized report, but they were less frequently used in Africa and Middle East (78%) (Table 1).

Discussion

PD-L1 IHC is now routinely performed for patients with advanced NSCLC to evaluate their eligibility for immune checkpoint blockade in a few indications. Because of the high running costs of the clinical trial–validated assays, many laboratories use LDTs, leading to the diverse implementation of PD-L1 testing across different regions and across different laboratories. To assess the current prevalence and practice of the PD-L1 testing globally and to identify potential issues and areas for improvement or disparities encountered in some countries, the Immune Biomarker Working Group of the IASLC Pathology Committee conducted an international survey for pathologists on PD-L1 testing in NSCLC.

This is the second survey conducted at the initiative of the IASLC to investigate the implementation of a theragnostic test worldwide. The first survey, recently published by Smeltzer et al.[11] and covering molecular testing in lung cancer, was also descriptive in nature but was aimed at both clinicians and molecular pathologists. We deliberately chose herein to question pathologists only to assess issues related to the test itself in detail and to identify barriers for its implementation, without taking into account the perceptions of clinicians.

Like the survey on molecular testing, the worldwide dissemination was widespread, with most responses coming from Europe, North America, and Asia, whereas only 25 pathologists from Latin America, 22 from Africa and the Middle East, and 13 from Oceania responded. Interestingly, most of the pathologists who responded were specializing in thoracic pathology, but 38% practiced other subspecialties of general pathology, which gave us a global vision of the real-life practice in pathology laboratories. Only 12 of the 344 responders did not conduct or offer clinical PD-L1 IHC for NSCLC, which is very encouraging in terms of test availability, and less than 10% of the laboratories outsourced the test. Most tested biopsies and resection samples and 72% of our survey participants used cellblocks (particularly 92%, 88%, and 84% of those from Oceania, North America, and Europe, respectively) in agreement with the good performance of cell blocks for PD-L1 testing, as compared with surgical samples.[12-17] Although the use of cytology samples for PD-L1 IHC has not been validated in clinical trials, most of those studies reported high concordance in PD-L1 expression with a 50% cutoff between histology and cytology specimen irrespective of assays used.[12-17]

Table 2. PD-L1 Antibody Clones Used Stratified by Region

Region	North America n = 83	Central and South America n = 25	Europe n = 140	Asia n = 61	Oceania n = 13	Africa and Middle East n = 22	Comparison Test	World n = 344
PD-L1 clone								
22C3,[a] n (%)	n = 66	n = 18	n = 136	n = 55	n = 13	n = 14	$p^b = 0.03$	n = 302
Non used	21 (32)	6 (33)	43 (32)	13 (24)	9 (69)	2 (14)		94 (31)
Used	45 (68)	12 (67)	93 (68)	42 (76)	4 (31)	12 (86)		208 (69)
Clinical assay	28 (62)	5 (42)	50 (54)	29 (69)	1 (25)	11 (92)	$p^b = 0.04$	124 (60)
LDT	17 (38)	7 (58)	43 (46)	13 (31)	3 (75)	1 (8)		84 (40)
28.8,[a] n (%)	n = 66	n = 18	n = 136	n = 55	n = 13	n = 14	$p^b = 0.005$	n = 302
Non used	58 (88)	10 (56)	106 (78)	39 (71)	12 (92)	14 (100)		239 (79)
Used	8 (12)	8 (44)	30 (22)	16 (29)	1 (8)	0		63 (21)
Clinical assay	8 (100)	0	22 (73)	12 (75)	0	–	$p^b < 0.0001$	42 (67)
LDT	0	8 (100)	8 (27)	4 (25)	1 (100)	–		21 (33)
SP142,[a] n (%)	n = 66	n = 18	n = 136	n = 55	n = 13	n = 14	$p^b = 0.09$	n = 302
Non used	53 (80)	10 (56)	90 (66)	34 (62)	10 (77)	12 (86)		209 (69)
Used	13 (20)	8 (44)	46 (34)	21 (38)	3 (23)	2 (14)		93 (31)
Clinical assay	8 (62)	5 (63)	31 (67)	10 (48)	1 (33)	2 (100)	$p^b = 0.46$	57 (61)
LDT	5 (38)	3 (37)	15 (33)	11 (52)	2 (67)	0		36 (39)
SP263,[a] n (%)	n = 66	n = 18	n = 136	n = 55	n = 13	n = 14	$p^b = 0.001$	n = 302
Non used	43 (65)	7 (39)	67 (49)	20 (36)	2 (15)	10 (71)		149 (49)
Used	23 (35)	11 (61)	69 (51)	35 (64)	11 (85)	4 (29)		153 (51)
Clinical assay	8 (35)	5 (45)	59 (86)	24 (69)	7 (64)	4 (100)	$p^b < 0.0001$	107 (70)
LDT	15 (65)	6 (55)	10 (14)	11 (31)	4 (36)	0		46 (30)
E1L3N,[a] n (%)	n = 66	n = 18	n = 136	n = 55	n = 13	n = 14	$p^b = 0.28$	n = 302
Non used	54 (82)	18 (100)	111 (82)	42 (76)	12 (92)	12 (86)		249 (82)
Used (LDT only)	12 (18)	0	25 (18)	13 (24)	1 (8)	2 (14)		53 (18)

LDT, laboratory-developed test; PD-L1, programmed death-ligand 1.
[a]The numbers indicate those of participants who responded to the specific question.
[b]The *p* values were obtained using chi-square or the Fisher's exact bilateral test.

Interestingly, 11% of the participants also conducted PD-L1 IHC on cytology smears, although there was a significant difference in the application of smears among regions. The quantification of PD-L1 expression on direct Papanicolaou-stained cytology smears has been reported to be highly concordant with that on formalin-fixed, paraffin-embedded samples,[16,18] and in the study by Noll et al.,[16] Papanicolaou-stained smears performed better than cell blocks as samples for PD-L1 IHC testing. Using smears will likely increase the availability of PD-L1 IHC for advanced NSCLC, in which fine-needle aspiration may be the only sample procured for the diagnosis and biomarker testing; however, there are no recommendations available yet for PD-L1 IHC on this type of sample[5] and large-scale studies are still warranted to confirm the performance of cytology smears in PD-L1 testing. Although cytology samples can be used for PD-L1 IHC, many pathologists, particularly non-cytopathology pathologists, may find scoring PD-L1 expression in cytology samples challenging, partly owing to the fragmented and scarce nature of tumor clusters in such specimens.[19] In the current survey, we failed to ask participants how frequently they received both cytology and biopsy specimens from one procedure that may allow the pathologist to select a sample for PD-L1 IHC. It seems, however, that the practice varies to a large extent across different institutions and clinicians, but a combination of biopsy and cytology specimens are often obtained in one procedure if the patient's condition allows. Of those, biopsies are preferred for PD-L1 IHC, but when biopsies do not contain adequate tumor cells or are not available, cytology samples, in particular, cellblocks are used for PD-L1 testing. Another issue associated with cytology specimens is their small sizes, given that PD-L1 expression is often underscored in small samples.[20,21] Whereas the size of the biopsy was not recorded in the survey, bronchial biopsies are usually approximately 1 mm; thus, combined with cytology specimens, a significant proportion of samples used for PD-L1 IHC are considered small. Awareness of the effect of small sample size on PD-L1 scoring around the 1% threshold is important, emphasizing the need for more or larger biopsies.

Optimal preanalytical conditions are an important element for the standardization of predictive biomarker testing. Unfortunately, only 54% of 332 participants who

perform clinical PD-L1 IHC responded that they were monitoring preanalytical conditions. Cold ischemia seems to have a significant impact on the performance of PD-L1 IHC.[22] Decalcification seems to slightly decrease the yield of staining, particularly when ethylenediaminetetraacetic acid is used in combination with 22C3 clone.[23] Furthermore, avoiding overfixation is of paramount importance because 20% and 10% of samples can be suboptimally stained with IHC using the SP142 and SP263 clones, respectively, when fixation duration is beyond 96 hours, whereas only 3% to 6% of samples may suffer suboptimal staining with 12 to 72-hour fixation.[24] Similarly, cellblock processing protocols affect PD-L1 staining. The Cellient automated system (Hologic, Marlborough, MA) was reported to confer the strongest membranous staining with less cytoplasmic staining, whereas CytoLyt (Cytyc Corporation, Marlborough, MA)-based samples exhibited the poorest staining.[25] Finally, PD-L1 protein can degrade with time; thus, the age of formalin-fixed, paraffin-embedded slides, if not appropriately stored after cutting, has been associated with a decrease in immunoreactivity[26,27] leading to recommendations on the use of freshly cut slides for PD-L1 testing.

Among the antibodies used in practice, two clinical trial–validated clones, 22C3 and SP263, were most often used by 69% and 51% of the participants respectively. However, only 60% of the participants with 22C3 IHC applied the clinical trial–validated commercial assay, probably because the Dako IHC platform, which is required for the assay, is less prevalent across countries and the running costs are significantly higher with the clinical trial–validated assays than LDTs. In contrast, the SP263 commercial assay was more frequently used mainly in Europe and in Asia, but not as frequently in North America owing, in part, to the less prevalent use of the Ventana platform in the region compared with others. In addition, a minority of participants used nonclinical trial clones, such as E1L3N or QR1. This is not surprising, given that the clinical trial–validated clones are generally substantially more expensive and under reimbursement in some countries, and laboratories may not have access to the corresponding IHC platform required for the clinical trial–validated commercial assay.[5] Thus, laboratories may, through choice or budget constraint, run their own PD-L1 IHC assay using an LDT, that has not been validated in a clinical trial. It is important to note, however, that any LDT will not necessarily deliver the same staining results as a commercial assay.[5] The variability in staining performance is not only because of the difference in antibody clones but also in the ancillary chemistry and platform variables.[28] In addition, preanalytical conditions can be critical for IHC standardization, and the IHC protocol may need to be adjusted in accordance with the sample type.[25,29] Thus, thorough optimization and standardization of PD-L1 IHC[30] and quality control monitoring of the test, whether they are for an LDT or a commercial assay, are of paramount importance to achieve a constant staining performance. Unfortunately, the results of this survey have found that a considerable minority (18%) of participating laboratories did not have QA in place, and only 63% of the laboratories participated in a formal EQA program(s) with significant regional disparities. The rate of formal EQA program participation reported was higher in Europe (72%) and Oceania (77%), whereas it was only 50% in the other regions. Of note, the College of American Pathologists has started offering PD-L1 proficiency tests[31] since the end of this survey; thus, it is likely that most laboratories in the United States currently have a formal EQA program(s) in place. Furthermore, Nordic Immunohistochemical Quality Control (NordiQC) has expanded proficiency testing for PD-L1 IHC[32] that may have increased the rate of formal EQA participation.

Another important issue is the reproducibility of PD-L1 scoring, because the assessment of PD-L1 IHC could be susceptible to interobserver and intraobserver variability owing to the semiquantitative nature of assay scoring. Although interobserver agreements on PD-L1 tumor cell scoring have generally reported good interclass correlation coefficient (0.8–0.9)[5,33-38] and intraobserver agreements were excellent (90%–98%) in several studies,[36,37] the question is whether the concordance of 80% to 90% is acceptable for a predictive biomarker testing. Considering the number of patients with advanced NSCLC diagnosed per year (approximately 113,000 in 2018 in the United States) and response rates stratified by PD-L1 TPS on the basis of the clinical trial data,[1,39-41] 10% to 20% of false-positive results for the 50% cutoff could lead to treating 800 to 1500 patients with first-line pembrolizumab alone, when additional chemotherapy might be helpful. Conversely, 10% to 20% of false-negative results for the 50% cutoff could lead to combination therapy in 1000 to 2000 patients, 30% of which would have responded to the first-line pembrolizumab only without the risk of additional adverse effects secondary to chemotherapy administration.[1,41,42]

To provide more reproducible PD-L1 IHC scoring, it is important for pathologists to attend a training session(s) or gain more experience.[5,43] In this survey, 84% of participants reported attendance at some training on the assessment of PD-L1 IHC, but 11% of those had only undergone informal training. Because there are free training programs organized by vendors, pharmaceutical companies, and pathology societies, either as formal hands-on sessions or by means of a website, it is recommended that pathologists who score PD-L1 IHC

participate in such a program(s).[44] Alternatively, if PD-L1 IHC scoring is limited to thoracic pathologists or specific pathologists, they may be able to gain experience and achieve proficiency in a short period and offer consistent scoring.

Adequate TAT and standardized reporting of the results are also important elements of PD-L1 testing. Overall, the median TAT was short (1–2 d), but there were some regional differences. It was longer in South and Central America, Asia, and Africa and the Middle East. Whereas most (76%) reported the results within 3 days, it took 5 or more days in 22% of laboratories in Asia, 21% in Central and South America, and 30% in Africa and the Middle East. More importantly, 25% of the U.S. participants reported sending samples for PD-L1 IHC testing to other laboratories, adding to the TAT. In this survey, we did not ask the participants whether the PD-L1 IHC was performed in a reflex manner because we suspected it was as recommended in the IASLC PD-L1 IHC atlas. However, if it was not a reflex test, additional time spent on identifying the sample, among others, might have contributed to longer TAT. Similarly, whereas most responding pathologists used a standardized report, this was not the case in one-quarter of laboratories from Africa and the Middle East.

To our knowledge, this is the first comprehensive evaluation of the pathologists' perspectives on PD-L1 IHC in NSCLC; however, it is not without limitations. First, responses were received on a voluntary basis and there were multiple responses from the same institutions, albeit rare (data not provided), that may have resulted in duplicate or similar responses. Second, there seemed to be undersampling from Central and South America, Africa and the Middle East, and Oceania. Although it may not be possible to determine whether it is because of a lack of circulation of the questionnaire or a lack of available tests, regional oversampling, and undersampling suggest our results may not accurately reflect the prevalence of PD-L1 testing across the globe. Although we advertised the survey on multiple society websites and contacted several specific pathology societies, we still may have failed to reach a large number of pathologists who assess PD-L1 IHC. However, although these laboratory and regional sampling issues limit our assessments, we believe it is still useful for identifying and understanding the prevalence and barriers to PD-L1 testing in NSCLC. We have now planned to conduct a novel survey that will be distributed to an extended (and exhausting) list of pathologists to involve various levels of organizations/institutes and pathologists across different regions. We will add multiple precise preanalytical and analytical questions along with the size of pathology practice and the number of PD-L1 testing per year. We hope that the novel survey will allow us to understand the preanalytical and analytical issues associated with PD-L1 IHC more in detail and come up with strategies to improve the quality of PD-L1 testing globally with standardization of PD-L1 IHC and high reproducibility of PD-L1 scoring among pathologists.

In conclusion, the results of this survey highlight the heterogeneity in PD-L1 testing practice across international regions and individual laboratories. The regional differences seem significant in PD-L1 testing status, PD-L1 antibody clones/assays used, and TAT. In addition, a minority reported a lack of QA, formal training, or standardized reporting system. Given that PD-L1 IHC is a predictive marker testing, constant and appropriate QA and pathologists' participation in formal training sessions to achieve reproducible scoring are a key to improving the PD-L1 testing practice globally. In addition, despite the limitations of the study, with most participants coming from Europe, North America, and Asia with limited participation from Central and South America, Africa and the Middle East, and Oceania, this survey clearly identified issues and disparities encountered in some countries regarding PD-L1 testing implementation. It highlights the need in some areas to set up actions to improve training and/or technical assistance to offer an optimized and standardized predictive biomarker for immunotherapies in patients with lung cancer worldwide.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2020.12.026

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