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Real-world prevalence of programmed death ligand 1 expression in locally advanced or metastatic non–small-cell lung cancer: The global, multicenter EXPRESS study

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ABSTRACT

Objectives: : Tumor programmed death ligand 1 (PD-L1) expression is associated with improved clinical benefit from immunotherapies targeting the PD-1 pathway. We conducted a global, multicenter, retrospective observational study to determine real-world prevalence of tumor PD-L1 expression in patients with NSCLC.

Materials and methods: : Patients ≥18 years with histologically confirmed stage IIIB/IV NSCLC and a tumor tissue block (≤5 years old) obtained before treatment were identified in 45 centers across 18 countries. Tumor samples from eligible patients were selected consecutively, when possible. PD-L1 expression was evaluated at each center using the PD-L1 IHC 22C3 pharmDx kit (Agilent, Santa Clara, CA, USA).

Results: : Of 2617 patients who met inclusion criteria, 2368 (90%) had PD-L1 data; 530 (22%) patients had PD-L1 TPS ≥ 50%, 1232 (52%) had PD-L1 TPS ≥ 1%, and 1136 (48%) had PD-L1 TPS < 1%. The most common reason for not having PD-L1 data (n = 249) was insufficient tumor cells (< 100) on the slide (n = 170 [6%]). Percentages of patients with PD-L1 TPS ≥ 50% and TPS ≥ 1%, respectively were: 22%/52% in Europe; 22%/53% in Asia Pacific; 21%/47% in the Americas, and 24%/55% in other countries. Prevalence of *EGFR* mutations (19%) and *ALK* alterations (3%) was consistent with prior reports from metastatic NSCLC studies. Among 1064 patients negative for both *EGFR* mutation and *ALK* alteration, the percentage with PD-L1 TPS ≥ 50% and TPS ≥ 1%, respectively, were 27% and 53%.

Conclusions: : This is the largest real-world study in advanced NSCLC to date evaluating PD-L1 tumor expression using the 22C3 pharmDx kit. Testing failure rate was low with local evaluation of PD-L1 TPS across a large number of centers. Prevalence of PD-L1 TPS ≥ 50% and TPS ≥ 1% among patients with stage IIIB/IV NSCLC was similar across geographic regions and broadly consistent with central testing results from clinical trial screening populations.

Abbreviations: EMR, electronic medical record; FFPE, formalin-fixed paraffin-embedded; H&E, hematoxylin and eosin; PD-L1, programmed death ligand 1; Q3W, once every 3 weeks; TPS, tumor proportion score

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1. Introduction

The advent of immunotherapy, in particular with agents targeting the programmed death 1 (PD-1) pathway, has improved outcomes for eligible patients with advanced or metastatic non–small-cell lung cancer (NSCLC) [1,2]. The PD-1 receptor is an immune checkpoint protein found on activated lymphocytes and other immune cells that attenuates cytotoxic T-cell responses when bound by its ligands, programmed death ligand 1 and 2 (PD-L1; PD-L2). When expressed by normal tissue or tumor, these ligands allow them to be protected from the ongoing inflammatory process and to escape immunosurveillance [3,4].

Pembrolizumab is a highly selective, humanized monoclonal antibody against the PD-1 receptor that inhibits the interaction between PD-1 and its ligands, PD-L1 and PD-L2 [3]. In pembrolizumab clinical trials, tumor expression of PD-L1 has been utilized as a predictive biomarker to identify those patients most likely to benefit from pembrolizumab monotherapy. PD-L1 expression has been evaluated using an immunohistochemistry assay that uses the 22C3 antibody clone, an approach that was first validated in the KEYNOTE-001 study [5]. To facilitate evaluation of PD-L1 expression for clinical use, the PD-L1 IHC 22C3 pharmDx assay (Agilent, Santa Clara, CA, USA) has been commercialized and is the only companion diagnostic approved by the US Food and Drug Administration to guide pembrolizumab therapy [6]. With this assay (which is performed on tissue samples containing a minimum of 100 viable tumor cells), PD-L1 expression is reported as a tumor proportion score (TPS), which represents the percentage of viable tumor cells that show partial or complete membrane staining irrespective of staining intensity; expression levels can range from 0% to 100% [3,7]. Phase 3 studies evaluating pembrolizumab monotherapy in patients with NSCLC have enrolled patients with tumors expressing PD-L1 with different TPS thresholds. Among patients with previously treated NSCLC, pembrolizumab 2 mg/kg or 10 mg/kg once every 3 weeks (Q3W) improved overall survival (OS) compared with docetaxel in patients with PD-L1 TPS ≥ 1%, and both progression-free survival (PFS) and OS in patients with PD-L1 TPS ≥ 50% in the phase 2/3 KEYNOTE-010 study [8]. In the first-line setting, in advanced NSCLC without sensitizing *EGFR* mutations or *ALK* translocations, pembrolizumab 200 mg Q3W improved OS and PFS compared with platinum-doublet chemotherapy among patients with PD-L1 TPS ≥ 50% in the phase 3 KEYNOTE-024 study [9] and among those with PD-L1 TPS ≥ 1% in the phase 3 KEYNOTE-042 study [10]. In addition, in phase 3 placebo-controlled trials, OS and PFS were improved irrespective of tumor PD-L1 expression when pembrolizumab 200 mg Q3W was combined with platinum-pemetrexed chemotherapy in patients with metastatic non-squamous NSCLC without *EGFR* mutations or *ALK* translocations in the phase 3 KEYNOTE-189 study [11]; and with carboplatin and paclitaxel/nab-paclitaxel in patients with metastatic squamous NSCLC in the KEYNOTE-407 study [12].

The prevalence of PD-L1 expression has largely been evaluated in clinical trial populations. Among all patients screened for enrollment with tumor samples evaluable for PD-L1 expression in the KEYNOTE-001, KEYNOTE-010, and KEYNOTE-024 studies using the PD-L1 IHC 22C3 pharmDx assay, 67% of patients had PD-L1 TPS ≥ 1% and 28% of patients had PD-L1 TPS ≥ 50% [13]. However, to date, little is known about global, real-world prevalence of PD-L1 expression in tumor cells of patients with advanced or metastatic NSCLC. We conducted a global multicenter retrospective study (EXPRESS) across 18 countries to evaluate the real-world prevalence of PD-L1 expression in patients with advanced NSCLC assessed using the PD-L1 IHC 22C3 pharmDx kit on histological material. EXPRESS was designed to evaluate the prevalence of PD-L1 TPS ≥ 1% and ≥ 50% across the overall study population; in subgroups defined by key demographic, clinical, and pathologic characteristics; and across geographic locations.

2. Material and methods

2.1. Study design and procedures

This multicenter, retrospective study conducted at 45 centers in 18 countries examined PD-L1 protein expression levels on histological specimens in patients with advanced or metastatic NSCLC. Asia-Pacific (Japan, Korea, Taiwan, Singapore, and Hong Kong), Europe (Austria, Germany, Sweden, Denmark, Italy, the Netherlands, Spain), the Americas (Canada, Colombia, Argentina), and other (Turkey, Russia, Saudi Arabia) regions participated. Centers were selected based on the availability of suitable NSCLC formalin-fixed paraffin-embedded (FFPE) histological specimens as well as access to Autostainer Link 48 equipment (Agilent, Santa Clara, CA, USA). The primary objectives of the study were to determine the global, regional, and country-specific prevalence of PD-L1 expression in patients with stage IIIB/IV NSCLC using the PD-L1 IHC 22C3 pharmDx kit, and to describe PD-L1 expression by baseline demographic and clinico-pathologic characteristics including other molecular biomarkers (*EGFR/ALK*). The secondary objective was to determine the fraction of patients with stage IIIB/IV NSCLC whose tumor tissue samples were not evaluable for PD-L1 expression testing.

2.2. Patient eligibility

Eligible patients, identified through hospital pathology departments in each participating country, had histologically confirmed stage IIIB/IV primary NSCLC as classified by the American Joint Committee on Cancer staging system (7th edition); were ≥ 18 years of age; provided a tumor tissue sample collected upon stage IIIB/IV or later diagnosis from a site not previously irradiated and before initiation of any systemic treatment for advanced disease; had an available FFPE tumor tissue block ≤ 5 years old; and had no history of malignancy, other than basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, and *in situ* cervical cancer. Patient consent was waived by each center's institutional review board. Tumor samples from eligible patients from the most recent time point and then backward in time were selected. When possible, consecutive tumor samples were selected.

2.3. PD-L1 assessment

Investigators at each site/center determined PD-L1 expression de novo using the PD-L1 IHC 22C3 pharmDx kit (Agilent, Santa Clara, CA, USA). A research use-only kit identical to the commercially available kit was used in all countries, except Colombia, where the commercially available kit was used owing to import regulations. Pathologists at each site were trained in a Merck-sponsored program (Merck & Co., Inc., Kenilworth, NJ, USA) to guide correct scoring and interpretation of PD-L1 TPS. Training sessions involved a presentation overview of the core principles of PD-L1 biology and pathology, the assay development process, optimal strategies to evaluate and score stained images for PD-L1 expression in NSCLC across a range of PD-L1 expression levels evaluated in samples from different patients, and a practical component that included scoring of actual samples [14]. Only resected specimens were available for the training session and small diagnostic biopsies were excluded. A total of five 4-μm FFPE freshly cut sections from biopsies or resected tissues were requested for each patient. Three slides were required at a minimum (two unstained [one for PD-L1 testing and one as a control] and one matched hematoxylin and eosin [H&E]–stained); provision of two additional slides was preferred to allow for rapid reassessment of PD-L1 expression should it be necessary. PD-L1 expression was reported as TPS, which is the percentage of viable tumor cells showing partial or complete membrane staining at any intensity, relative to all viable tumor cells (Figure S1).

2.4. Study variables

Study variables, including demographics, pathology, and other biomarker data, were extracted from each center's electronic medical record (EMR) system (or chart review if no EMR existed) and electronically captured in a central database. Key variables included: diagnosis date, age at diagnosis, sex, smoking status, center/country, specimen type, tumor stage, and histology, metastatic location, and biomarker status (*EGFR* sensitizing mutation status and/or *ALK* translocation). *EGFR* and *ALK* status were not determined de novo. No new data were generated if a variable was missing.

2.5. Statistical analysis plan

It was determined that 100 evaluable samples from each country would provide a precision level of ± 9% to estimate PD-L1 prevalence assuming that TPS ≥ 1% represents 68.5% of the population [5]. Descriptive analyses were conducted by country, by region, and globally. The prevalence of PD-L1 TPS ≥ 50%, TPS ≥ 1%, and TPS < 1% was summarized using counts and percentages. As there were no a priori hypotheses, no *P* values were determined.

3. Results

3.1. Patient screening, selection, and characteristics

Between September 6, 2016, and August 25, 2017, 2673 patients were screened (Fig. 1). Fifty-six tumor samples were excluded because of unconfirmed tissue histology ($n = 2$), FFPE tumor tissue block or tumor sample > 5 years old ($n = 52$), or history of malignancy ($n = 3$). Representative PD-L1 TPS staining patterns are shown in Fig. 2. Among 2617 patients with tumor samples that met all inclusion criteria, 249 had non-evaluable tumor samples or assay failures (most frequently because of insufficient tumor cells (< 100) on the slide; n = 170 [6%]). Overall, 2368 of 2617 patient tumor samples (90%) had PD-L1 expression results and were included in the study analysis. The data cutoff date for this analysis was September 21, 2017.

Of the tissue samples evaluated for PD-L1 expression ($n = 2368$), 1694 (72%) were from tumor biopsies whereas 610 (26%) were from surgical resections. Most specimens were from the primary tumor ($n = 1735$; 73%). Median age at diagnosis for the overall patient population was 66 (range, 24–91) years; 62% were male, 78% had non-squamous histology, and 58% were current/former smokers. Among smokers with available data ($n = 1326$), median pack-years smoked was 15 (range, 0–250). Patients were from centers in Asia-Pacific ($n = 661$); Europe (n = 831); the Americas ($n = 363$) and other countries ($n = 513$). Seventy-four patients (3%) had *ALK* translocations, and 448 (19%) had sensitizing *EGFR* mutations; 1064 patients (45%) were negative for both *ALK* translocation and *EGFR* mutation.

3.2. Prevalence of PD-L1 expression

Among 2368 tumor samples evaluated, 1136 (48%) had PD-L1 TPS < 1%, 1232 (52%) had PD-L1 TPS ≥ 1%, and 530 (22%) had PD-L1 TPS ≥ 50% (Table 1). Tumor samples with PD-L1 TPS ≥ 50% were less common among patients with sensitizing *EGFR* mutations (13%) and those with *ALK* translocations (20%). Conversely, among those who were negative for both *EGFR* mutation and *ALK* translocation, 27% had tumor samples with PD-L1 TPS ≥ 50%; 53% of patients without *EGFR* mutation or *ALK* translation had tumor samples with PD-L1 TPS ≥ 1%.

Based on visual assessment of numerical differences, no other baseline demographic or clinical characteristics appeared to be associated with differences in prevalence of PD-L1 TPS ≥ 1% or PD-L1 TPS ≥ 50%. PD-L1 prevalence was consistent across subgroups defined by age (< 75 vs ≥75 years), sex (male vs female), histology (squamous vs non-squamous), smoking status (never vs former vs current), specimen type (biopsy vs resection), or specimen source (primary vs metastases; Table 1).

3.3. Region-specific prevalence of PD-L1 expression

Prevalence of PD-L1 TPS ≥ 1% and PD-L1 TPS ≥ 50% was similar across regions: PD-L1 TPS ≥ 1% prevalence was 52% in Europe, 53% in Asia-Pacific, 47% in the Americas, and 55% in other countries; and PD-L1 TPS ≥ 50% prevalence was 22% in Europe, 22% in Asia-Pacific, 21% in the Americas, and 24% in other countries (Table 1; Fig. 3A). As in the overall population, prevalence of PD-L1 expression was

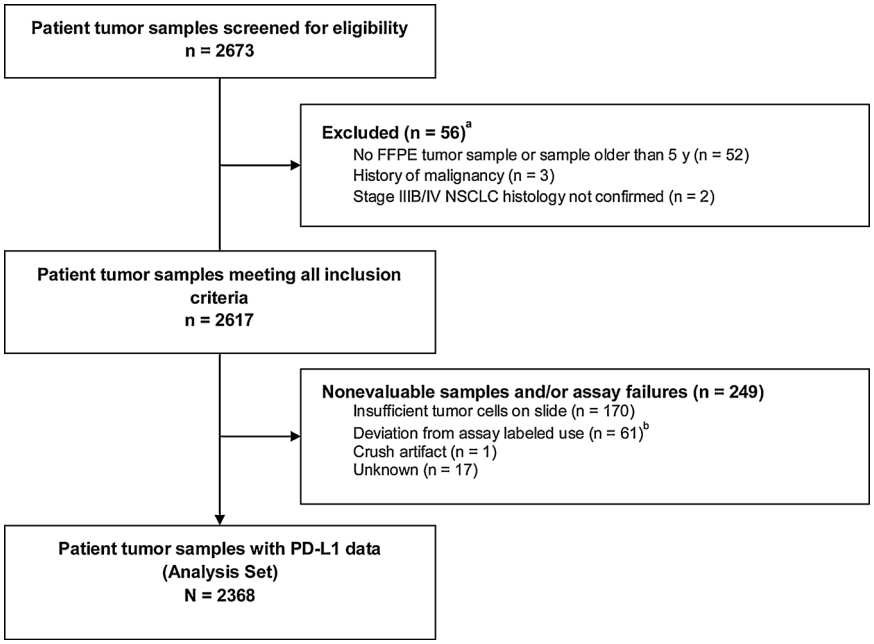

Fig. 1. Patient tumor sample screening and evaluation of PD-L1 expression on tumor cells [a]Reasons for exclusion are not mutually exclusive. [b]Decalcified sample. FFPE, formalin-fixed, paraffin-embedded; NSCLC, non–small-cell lung cancer; PD-L1, programmed death ligand 1.

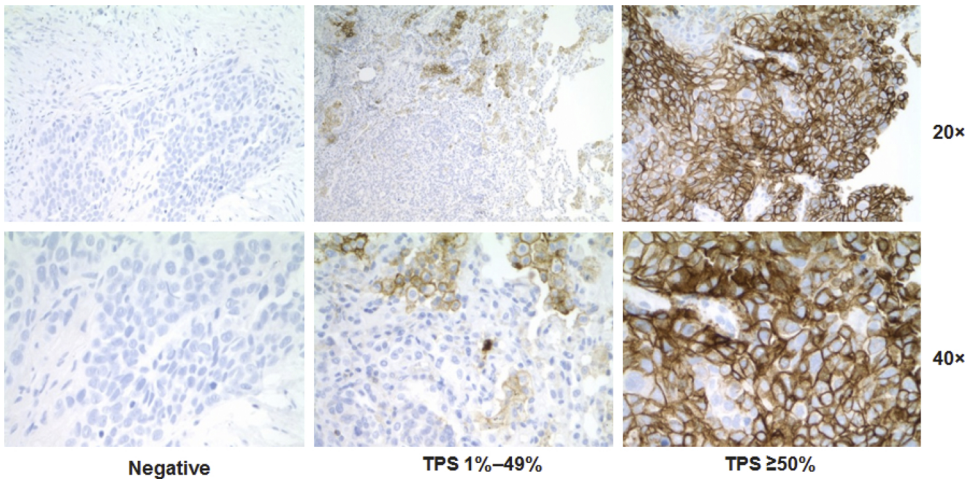

Fig. 2. Evaluation of PD-L1 TPS staining patterns in NSCLC tissue samples using the PD-L1 IHC 22C3 pharmDx assay (Agilent, Santa Clara, CA, USA) at 20× and 40× magnification. PD-L1 staining is shown by presence of the brown chromogen; the blue color is the hematoxylin counterstain (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Table 1
Prevalence of PD-L1 TPS in Tumor Cells by Baseline Demographic and Clinico-Pathologic Characteristics and by Region.

Characteristic, n (%)[a]	*N*	TPS ≥ 50%	TPS ≥ 1%	TPS < 1%
All patients	2368	530 (22)	1232 (52)	1136 (48)
Age, y				
≥75	450	105 (23)	224 (50)	226 (50)
< 75	1917	425 (22)	1008 (53)	909 (47)
Unknown	1	0	0	1 (100)
Sex				
Female	899	189 (21)	471 (52)	428 (48)
Male	1468	340 (23)	760 (52)	708 (48)
Unknown	1	1 (100)	1 (100)	0
Region				
Asia Pacific[b]	661	148 (22)	351 (53)	310 (47)
Europe[c]	831	181 (22)	428 (52)	403 (48)
The Americas[d]	363	77 (21)	172 (47)	191 (53)
Other[e]	513	124 (24)	281 (55)	232 (45)
Specimen type				
Surgical resection	610	127 (21)	327 (54)	283 (46)
Biopsy	1694	394 (23)	880 (52)	814 (48)
Unknown	64	9 (14)	25 (39)	39 (61)
Specimen source				
Primary	1735	377 (22)	892 (51)	843 (49)
Metastases	565	133 (24)	297 (53)	268 (47)
Unknown	68	20 (29)	43 (63)	25 (37)
Histology				
Squamous	500	114 (23)	286 (57)	214 (43)
Non-squamous	1846	410 (22)	934 (51)	912 (49)
Unknown	22	6 (27)	12 (27)	10 (46)
Smoking status				
Never	532	98 (18)	249 (47)	283 (53)
Former	642	154 (24)	349 (54)	293 (46)
Current	740	184 (25)	393 (53)	347 (47)
Unknown	454	94 (21)	241 (53)	213 (47)
ALK translocation status				
Positive	74	15 (20)	48 (65)	26 (35)
Negative	1433	347 (24)	753 (53)	680 (47)
Unknown	861	168 (20)	431 (50)	430 (50)
EGFR mutation status				
Positive	448	60 (13)	197 (44)	251 (56)
Negative	1260	319 (25)	673 (53)	587 (47)
Unknown	660	151 (23)	362 (55)	298 (45)
ALK translocation/*EGFR* mutation negative	1064	283 (27)	569 (53)	495 (47)

PD-L1, programmed death ligand 1; TPS, tumor proportion score.

[a] The number of patients with the specific characteristic (row total) is the denominator for percentages in TPS columns.

[b] Includes Japan, Hong Kong, Korea, Singapore and Taiwan.

[c] Includes Austria, Denmark, Germany, Italy, Spain, Sweden and the Netherlands.

[d] Includes Argentina, Canada, and Colombia.

[e] Includes Russia, Saudi Arabia, and Turkey.

somewhat higher among patients without either *EGFR* mutations or *ALK* translocations: PD-L1 TPS ≥ 1% prevalence of 54% in Europe, 56% in Asia-Pacific, 46% in the Americas, and 60% in other countries; and PD-L1 TPS ≥ 50% prevalence of 25% in Europe, 30% in Asia-Pacific, 20% in the Americas, and 35% in other countries (Fig. 3B).

4. Discussion

EXPRESS is the largest real-world study in patients with advanced NSCLC evaluating PD-L1 expression in tumor cells using the PD-L1 IHC 22C3 pharmDx assay. The study included tumor samples from 2368 patients from 18 different countries, with a broad range of demographic, clinical, and pathologic characteristics. Overall, 52% of patients had PD-L1 TPS ≥ 1% and 22% of patients had PD-L1 TPS ≥ 50%. Among patients without sensitizing *EGFR* mutations or *ALK* translocations, 53% had PD-L1 TPS ≥ 1% and 27% had PD-L1 TPS ≥ 50%. There was no apparent difference in prevalence of PD-L1 by any other baseline demographic or clinico-pathologic characteristic. Overall, these results indicate that 52% of patients with advanced NSCLC express PD-L1 on tumor cells (evaluated on histological material) and are potentially eligible for pembrolizumab monotherapy as first-line or second-or-later–line therapy.

Prevalence of PD-L1 TPS ≥ 50% and PD-L1 TPS ≥ 1% was similar across geographic regions, between surgical specimens and biopsies, and irrespective of whether tissue was from the primary tumor or from metastases. Importantly, PD-L1 expression results were available for > 90% of patients eligible for the study. The consistency in results across geographic regions and high assay success rate are indicative of the high overall reliability and reproducibility of the PD-L1 IHC 22C3 pharmDx assay when performed by experienced trained pathologists. All contributing pathologists in EXPRESS were required to complete a training program, to standardize the technical procedures of staining, scoring, and interpreting PD-L1 expression in NSCLC at the TPS ≥ 1% and ≥50% cut points, as variability between pathologists' assessment of PD-L1 expression can result in lower concordance in PD-L1 TPS classification [14]. Notably, the pathologist interpretation training included ≥25% of cases around the PD-L1 TPS ≥ 1% and ≥50% cut points and covered the range of PD-L1 expression in NSCLC. Additionally, the majority of pathologists in the study had significant experience with PD-L1 testing because pembrolizumab had previously been approved in NSCLC, with obligatory PD-L1 testing, when the study was conducted.

The prevalence of PD-L1 TPS ≥ 1% and PD-L1 TPS ≥ 50% in EXPRESS was broadly consistent with, albeit somewhat lower than, that reported with central testing of clinical trial screening populations in the KEYNOTE-001, KEYNOTE-010, and KEYNOTE-024 studies. [13] Because no assay variability was apparent, the pathologist training

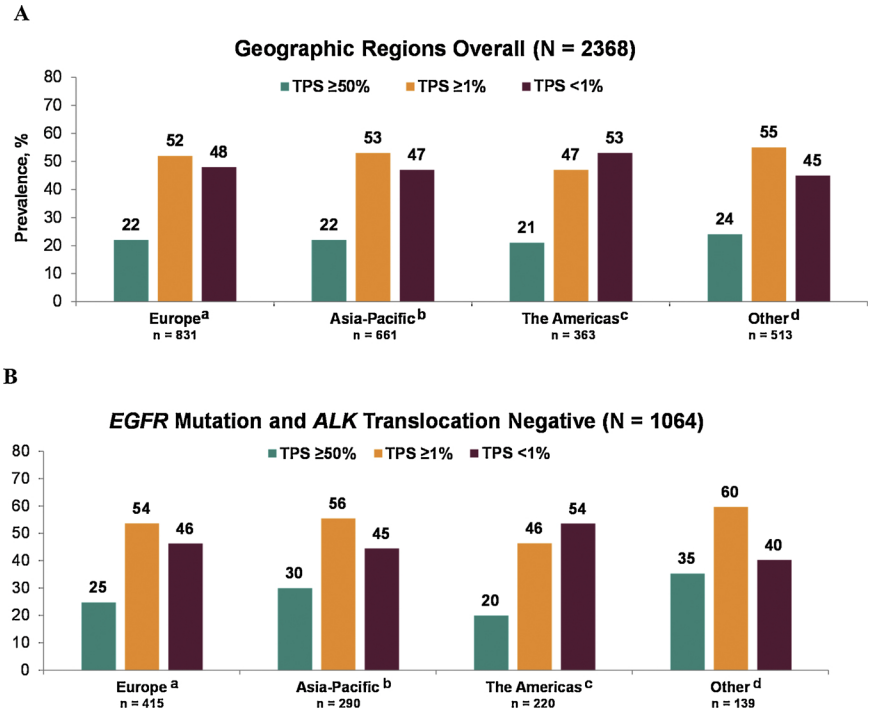

Fig. 3. PD-L1 prevalence in tumor cells by TPS stratum (A) across geographic regions and (B) among patients without genetic driver mutations. Prevalence is defined as the proportion (%) of a population with a particular characteristic at a given time. Rounding may result in total percentage > 100%. [a]Austria, Denmark, Germany, Italy, Spain, Sweden, the Netherlands. [b]Japan, Hong Kong, Korea, Singapore, Taiwan. [c]Argentina, Canada, Colombia. [d]Russia, Saudi Arabia, Turkey. PD-L1, programmed death ligand 1; TPS, tumor proportion score.

program was rigorous, and PD-L1 expression prevalence was consistent across regions, other potential factors may have contributed to this slightly lower prevalence, such as the inclusion of patients with sensitizing *EGFR* mutations and *ALK* translocations, who were either excluded from pembrolizumab clinical trials (KEYNOTE-024) and/or infrequently enrolled in these trials (KEYNOTE-001, KEYNOTE-010). Notably, we observed higher PD-L1 expression prevalence among patients without *EGFR* mutations or *ALK* translocations. Thus, given that PD-L1 expression is lower among patients with these genetic aberrations, inclusion of this patient group in our study may partially explain the difference in PD-L1 prevalence between EXPRESS and clinical trial populations. Notably, although the presence of driver mutations has been hypothesized to result in differences in tumor PD-L1 expression, a number of previous studies have evaluated associations between PD-L1 expression and *EGFR* mutations with equivocal results [15]. The potential for referral bias, whereby patients with histologically/cytologically confirmed PD-L1–expressing tumors are more likely to be enrolled in clinical trials, might also partially explain the moderately higher PD-L1 prevalence reported in clinical trials.

Notably, immunohistochemistry assays that use antibodies other than the 22C3 clone have been developed to evaluate PD-L1 expression and are commercially available (ie, 28-8, SP263, and SP142). An evaluation of these assays showed results that were typically (though not always) concordant with those from PD-L1 IHC 22C3 pharmDx kit [6]. Laboratory-developed tests (LDTs) that employ one of these existing antibodies have also been shown to provide reliable assessments of PD-L1 expression when properly implemented [16]. As demonstrated by Ilie and colleagues, high concordance can be achieved between LDTs and the PD-L1 IHC 22C3 pharmDx assay, at both the PD-L1 TPS ≥ 50% and TPS ≥ 1% cutpoints [17,18]. Together with the low testing failure rate in EXPRESS, these data demonstrate the feasibility of evaluating PD-L1 expression with 22C3 antibody-based assays in the real world to support treatment decisions.

Limitations of this study include that samples may not have been obtained from consecutively enrolled patients in all cases, PD-L1 expression was determined retrospectively from already available tumor samples, and quality and completeness of demographic and clinicopathologic characteristic data varied across centers. For example, race was included in the demographic variable fields, but was not reported or reportable by many countries due to local regulation/practice. However, as noted above, no significant variation in PD-L1 prevalence was observed between geographic regions; therefore, to the extent that geography and ethnicity are correlated, these results suggest that ethnicity has no impact on PD-L1 prevalence. Additionally, although this study was large, certain subgroups had small numbers of patients (eg, those with *ALK* translocations), limiting the reliability of PD-L1 prevalence estimates in these subgroups. Finally, cytological cell block specimens were not included in this study. Because > 40% of all patients with NSCLC are diagnosed based on cytology alone, evaluation of PD-L1 in such material would be of interest. Several recent studies have demonstrated that PD-L1 expression can be assessed on such material, and that concordance with PD-L1 expression in tumor biopsy samples is high [17,19].

5. Conclusions

In conclusion, this is the largest real-world study in advanced NSCLC evaluating PD-L1 tumor expression using the 22C3 pharmDx kit. Testing failure rate was low with local evaluation of PD-L1 TPS across a large number of sites. Prevalence of PD-L1 TPS ≥ 50% and TPS ≥ 1% among patients with stage IIIB/IV NSCLC was similar across geographic regions and generally consistent with (although somewhat lower than) central testing results from clinical trial screening populations.

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Declaration of Competing Interest

Manfred Dietel declares no conflict of interest. Nikita Savelov declares no conflict of interest. Ruben Salanova, Patrick Micke, Jose Antunez, Birgit Guldhammer Skov, Georg Hutarew, Luz F. Sua declare no conflicts of interest. Gilbert Bigras has served as an advisory board

member for Merck, Roche, BMS and Pfizer and has received research grants from Merck and Roche. Toyoaki Hida has received grants and honoraria from Merck Sharp & Dohme, Ono Pharmaceutical Co., Ltd., AstraZeneca, Chugai Pharmaceutical Co., Ltd., Bristol-Myers Squibb, Novartis, Nippon Boehringer Ingelheim, Eli Lilly, Taiho Pharmaceutical Co., Ltd., Pfizer, Clovis Oncology, Kissei, and Ignyta; grants from Eisai, Takeda Pharmaceutical Co., Ltd., Dainippon Sumitomo Pharma, Abbvie, Merck Serono, Kyowa Hakko Kirin, Daiichi Sankyo, Astellas, and Servier. Hirotoshi Dosaka-Akita has received grants from Merck & Co., Inc., Taiho Parmaceutical Co. Ltd., Ono Pharmaceutical Co. Ltd., Eisai Co. Ltd., and Eli Lilly Japan Co. Ltd.; and has received grants and honoraria from AstraZeneca Japan Co. Ltd. Oscar Siu-Hong Chan has received honoraria for speaking activities from Merck Sharp & Dohme, Bristol-Myers Squibb, and AstraZeneca. Bilal Piperdi, Thomas Burke, Shirin Khambata-Ford, and Anne Deitz are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ USA.

Data sharing statement

MSD's data sharing policy, including restrictions, is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the EngageZone site or via email to dataaccess@merck.com.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.06.012.

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