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Annals of Oncology 30: 1653–1659, 2019
doi:10.1093/annonc/mdz288
Published online 21 August 2019

ORIGINAL ARTICLE

Outcomes to first-line pembrolizumab in patients with non-small-cell lung cancer and very high PD-L1 expression

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Background: In non-small-cell lung cancers with programmed death-ligand 1 (PD-L1) expression on ≥50% of tumor cells, first-line treatment with the PD-1 inhibitor pembrolizumab improves survival compared with platinum-doublet chemotherapy. Whether higher PD-L1 levels within the expression range of 50%–100% predict for even greater benefit to pembrolizumab is currently unknown.

Patients and methods: In this multicenter retrospective analysis, we analyzed the impact of PD-L1 expression levels on the overall response rate (ORR), median progression-free survival (mPFS), and median overall survival (mOS) in patients who received commercial pembrolizumab as first-line treatment of non-small-cell lung cancer (NSCLC) with a PD-L1 expression of ≥50% and negative for genomic alterations in the *EGFR* and *ALK* genes .

Results: Among 187 patients included in this analysis, the ORR was 44.4% [95% confidence interval (CI) 37.1% to 51.8%], the mPFS was 6.5 months (95% CI 4.5–8.5), and the mOS was not reached. The median PD-L1 expression level among patients who experienced a response to pembrolizumab was significantly higher than among patients with stable or progressive disease (90% versus 75%, $P < 0.001$). Compared with patients with PD-L1 expression of 50%–89% ($N = 107$), patients with an expression level of 90%–100% ($N = 80$) had a significantly higher ORR (60.0% versus 32.7%, $P < 0.001$), a significantly longer mPFS [14.5 versus 4.1 months, hazard ratio (HR) 0.50 (95% CI 0.33–0.74), $P < 0.01$], and a significantly longer mOS [not reached versus 15.9 months, HR 0.39 (95% CI 0.21–0.70), $P = 0.002$].

Conclusion: Among patients with NSCLC and PD-L1 expression of ≥50% treated with first-line pembrolizumab, clinical outcomes are significantly improved in NSCLCs with a PD-L1 expression of ≥90%. These findings have implications for treatment selection as well as for clinical trial interpretation and design.

Key words: pembrolizumab, PD-L1, NSCLC

Introduction

The incorporation of programmed death-1 (PD-1) pathway inhibitors in the first-line treatment of metastatic non-small-cell lung cancer (NSCLC) has recently revolutionized care for this population. Because only a subset of NSCLCs will respond to immunotherapy, the identification of biomarkers that predict

benefit from PD-1 inhibitors is of great interest. In the KEYNOTE-001 study, NSCLCs with immunohistochemical expression of the PD-1 ligand, PD-L1, on at least half of tumor cells (a tumor proportion score of ≥50%) had improved clinical outcomes after treatment with the PD-1 inhibitor pembrolizumab compared with tumors with lower PD-L1 levels [1].

As a result, a PD-L1 expression level of ≥50% was selected for further clinical development in the KEYNOTE-024 study, a randomized phase III trial which demonstrated prolonged overall survival (OS) in patients treated with first-line pembrolizumab compared with those treated with platinum doublet chemotherapy for advanced NSCLCs with a PD-L1 expression level of ≥50% and lacking mutations in the epidermal growth factor receptor (*EGFR*) or rearrangements in anaplastic lymphoma kinase (*ALK*) [2]. In the pembrolizumab arm of this study, the overall response rate (ORR) was 44.8%, the median progression-free survival (mPFS) was 10.3 months, and the median OS (mOS) was 30.0 months [2, 3]. These results were immediately practice-changing and now PD-L1 expression is routinely tested in patients with newly diagnosed NSCLC. In addition, platinum doublet chemotherapy plus pembrolizumab is now also a standard option for advanced NSCLC in the first-line setting regardless of PD-L1 expression levels based on the KEYNOTE-189 and KEYNOTE-407 studies [4, 5]. However, an unresolved question is whether to use pembrolizumab monotherapy or pembrolizumab plus chemotherapy in patients with NSCLC and a PD-L1 level ≥50%. Biomarkers that can even more successfully enrich for patients who respond to pembrolizumab may help further refine the use of monotherapy and spare patients the added toxicities of chemotherapy.

As PD-L1 expression is a continuous biomarker that correlates with immunotherapy efficacy in NSCLC [1–3], we hypothesized that among patients with NSCLC and a PD-L1 expression level of 50%–100%, those with the highest levels of PD-L1 expression would experience improved clinical outcomes to treatment with first-line pembrolizumab. Therefore, we conducted a multicenter retrospective analysis of patients with advanced NSCLC and PD-L1 expression of ≥50% treated with first-line commercial pembrolizumab and examined the relationship between PD-L1 expression levels and clinical outcomes.

Methods

Study population

We retrospectively analyzed data from four participating academic centers: the Dana-Farber Cancer Institute, the Memorial Sloan Kettering Cancer Center, MD Anderson Cancer Center, and the Massachusetts General Hospital. Patients were included if they had consented to institutional review board-approved medical record review protocols at each institution and had advanced NSCLC without *EGFR* mutations or *ALK* rearrangements and a PD-L1 expression level of ≥50% who were treated with at least one dose of commercial pembrolizumab monotherapy in the first-line setting. Patients who had previously received cytotoxic chemotherapy and/or radiation therapy for early-stage NSCLC were eligible for this study if they had completed prior therapy ≥6 months before the start of pembrolizumab.

Clinical outcomes

The ORR and PFS were determined by blinded radiologists at each participating institution using Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. PFS was defined as the time from the start of pembrolizumab to the date of disease progression or death, whichever occurred first. Patients who were alive without disease progression were censored on the date of their last disease assessment. OS was defined as the time from the start of immunotherapy to death. Patients who were still alive at the time of data analysis were censored at the date of last contact.

PD-L1 testing and tumor mutational burden assessment

PD-L1 expression was reported as a percentage of tumor cells with positive membranous staining using a variety of immunohistochemical antibodies and platforms depending on local institutional practice. Tumor mutational burden (TMB) was calculated at two institutions using the OncoPanel (Dana-Farber Cancer Institute) and MSK-Impact (Memorial Sloan Kettering Cancer Center) platforms, as previously described [6, 7].

Statistical analysis

Categorical and continuous variables were summarized using descriptive statistics. The Wilcoxon rank sum test was used to test for differences in continuous variables between groups, and Fisher's exact test was used to test for associations between categorical variables. A recursive partitioning algorithm was used to investigate an optimal grouping of PD-L1 expression levels with respect to ORR, PFS, and OS using the Rpart function in R [8] and identified a primary split at a PD-L1 expression level of 87.5%, which was rounded up to 90% for further investigation in this study. Furthermore, as objective response rates to pembrolizumab in NSCLC have previously been evaluated according to increasing PD-L1 expression quartiles [1], we also investigated the efficacy of pembrolizumab by increasing PD-L1 expression quartiles of 50%–74% versus 75%–100%.

Event-time distributions were estimated using Kaplan–Meier methodology, and the Greenwood formula was used to estimate the standard errors of the estimates. Log-rank tests were used to test for differences in event-time distributions, and Cox proportional hazards models were fitted to obtain estimates of hazard ratios in univariate and multivariate models. All *P*-values are 2-sided and CIs are at the 95% level, with significance pre-defined to be at the 0.05 level.

Results

Patient characteristics and PD-L1 expression

Clinicopathologic characteristics of the 187 patients with advanced NSCLC (*EGFR* and *ALK* negative) and a PD-L1 expression level of ≥50% who received first-line commercial pembrolizumab are shown in supplementary Table S1, available at *Annals of Oncology* online. The median age of patients in this study was 68 (range 35–92), 93.6% of patients had a history of tobacco use, and 73.8% had adenocarcinoma histology. Among the 162 (86.6%) patients with available genomic testing, an activating *KRAS* mutation was identified in 44.4% of patients. A variety of PD-L1 immunohistochemical antibodies were used to determine PD-L1 expression levels, including E1L3N (66.3%), 22C3 (32.1%), SP263 (1.1%) and 28-8 (0.5%). In the entire cohort of patients, the median PD-L1 level was 80% (range 50–100) and the mean PD-L1 level was 76.1% (SD ±16.7). The distribution of

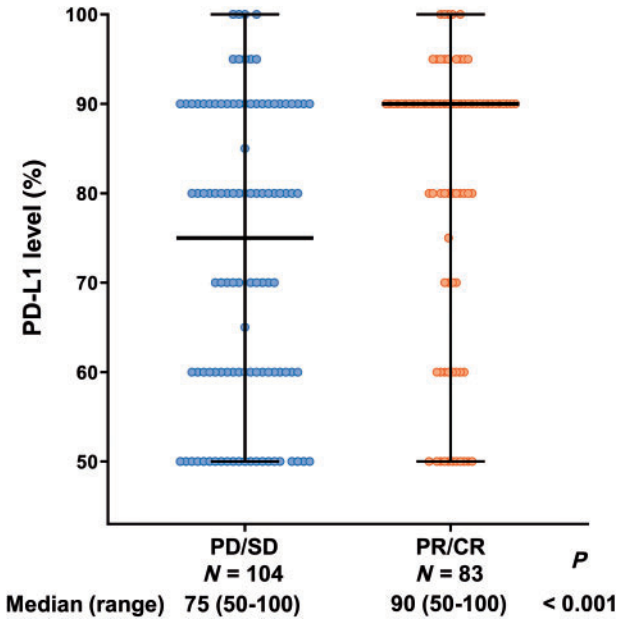

Figure 1. Distribution of programmed death-ligand 1 (PD-L1) expression values in patients who achieved a partial or complete response (PR/CR) to pembrolizumab monotherapy compared with those with a best objective response of progressive or stable disease (PD/SD). Shown are the median and interquartile range for each group.

Table 1. Characteristics of patients with non-small-cell lung cancer (NSCLC) and a programmed death-ligand 1 (PD-L1) expression level of 50%–89% versus 90%–100%

Clinical characteristic	PD-L1 level 50%–89% *N* = 107 (%)	PD-L1 level 90%–100% *N* = 80 (%)	*P* value
Age, median (range)	68 (35–92)	68 (43–88)	0.70
Sex			
Male	57 (53.3)	38 (47.5)	0.46
Female	50 (46.7)	42 (52.5)	
Smoking status			
Current/former	97 (90.7)	78 (97.5)	0.07
Never	10 (9.3)	2 (2.5)	
Histology			
Adenocarcinoma	77 (72.0)	61 (76.3)	
Squamous cell carcinoma	20 (18.7)	8 (10.0)	0.20
NSCLC NOS	10 (9.3)	11 (13.8)	
KRAS mutation status			
Present	38 (41.3)	34 (48.6)	0.42
Absent	54 (58.7)	36 (51.4)	
Not assessed	15	10	
ECOG performance status			
0–1	86 (80.4)	67 (83.8)	0.57
≥2	21 (19.6)	13 (16.2)	

ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified.

PD-L1 expression in the entire cohort of patients according to deciles is represented in supplementary Figure S1, available at *Annals of Oncology* online.

Efficacy of pembrolizumab according to PD-L1 expression

In the cohort of 187 NSCLC patients treated with first-line commercial pembrolizumab, the ORR was 44.4% (95% CI 37.1% to 51.8) (supplementary Figure S2A, available at *Annals of Oncology* online). At a median follow-up of 12.6 months (95% CI 11.6–13.6), the mPFS was 6.5 months (95% CI 4.5–8.5, supplementary Figure S2B, available at *Annals of Oncology* online), and the mOS was not reached (supplementary Figure S2C, available at *Annals of Oncology* online), calculated from the start date of immunotherapy. Patients who experienced a partial response to pembrolizumab had a significantly higher median PD-L1 expression level than patients with a best objective response of stable or progressive disease (expression 90% versus 75%, $P < 0.001$, Figure 1).

A recursive partitioning algorithm was used to investigate an optimal grouping of PD-L1 expression levels with respect to ORR, PFS, and OS, which identified a primary split at a PD-L1 expression level of 87.5%. Additionally, because the median PD-L1 expression among responders to pembrolizumab was 90%, we explored clinical outcomes in patients with NSCLC and a PD-L1 expression of 50%–89% ($N = 107$, representing 57.2% of the entire cohort) compared with a PD-L1 expression of 90%–100% ($N = 80$, representing 42.8% of the entire cohort). Baseline clinicopathological characteristics were generally balanced between the two cohorts in terms of age, sex, histology, smoking status, *KRAS* mutation status, and Eastern Cooperative Oncology Group (ECOG) performance status (PS) (Table 1).

In patients with a PD-L1 expression level of 90%–100%, the ORR to pembrolizumab was 60.0% (95% CI 48.4% to 70.8%), which was significantly higher than the ORR of 32.7% (95% CI 23.9% to 42.4%) observed in patients with a PD-L1 expression of 50% to 89% ($P < 0.001$, Figure 2A and B). The mPFS was significantly longer in the PD-L1 expression 90%–100% group compared with the PD-L1 50%–89% group [14.5 versus 4.1 months, HR 0.50 (95% CI 0.33–0.74), $P < 0.01$, Figure 3A). The mOS was also significantly longer in the PD-L1 expression 90%–100% group compared with the PD-L1 expression 50%–89% group [not reached versus 15.9 months, HR: 0.39 (95% CI 0.21–0.70), $P = 0.002$, Figure 3B). The median duration of treatment (mDOT) was 6.3 months (95% CI 4.30–8.31) and 3.2 months (95% CI 1.37–5.00) among patients with a PD-L1 expression of 90%–100% and 50%–89%, respectively. After adjusting for ECOG performance status, a PD-L1 expression level of 90%–100% was significantly associated with improved PFS [HR 0.50 (95% CI 0.34–0.75), $P < 0.01$] and OS [HR 0.39 (95% CI 0.23–0.70), $P = 0.002$] (supplementary Table S2, available at *Annals of Oncology* online).

We also investigated the clinical outcomes in patients according to increasing PD-L1 expression quartiles 50%–74% ($N = 75$; 40.1% of the entire cohort) versus 75%–100% ($N = 112$; 59.9% of the entire cohort). Baseline clinicopathological characteristics

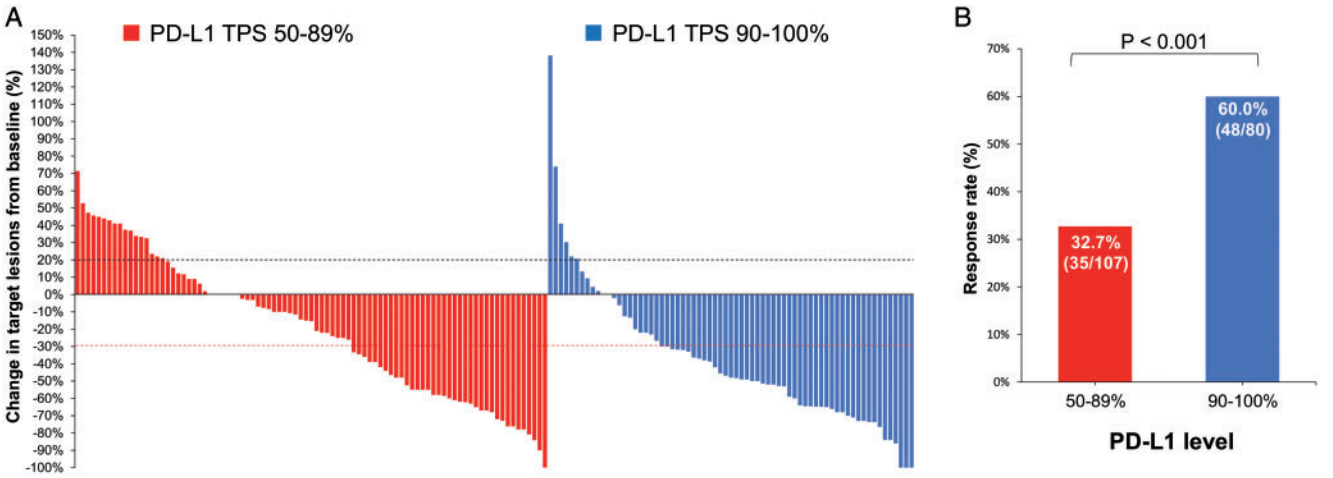

Figure 2. (A) The best objective response to pembrolizumab is shown as a percent change of target lesions from baseline in evaluable patients in patients with a non-small-cell lung cancer programmed death-ligand 1 (PD-L1) expression level of 50%–89% versus 90%–100%. (B) Histograms showing the response rate to first-line pembrolizumab in the PD-L1 expression 50%–89% versus 90%–100% groups.

were again well balanced between the two cohorts in terms of age, sex, histology, smoking status, and Eastern Cooperative Oncology Group (ECOG) performance status (PS) (supplementary Table S3, available at *Annals of Oncology* online). However, patients with a PD-L1 expression level of 75%–100% were more likely to have a *KRAS* mutation (51.5% versus 32.8%, $P = 0.02$). Patients with a PD-L1 expression level of 75%–100% had a significantly higher response rate compared with patients with a PD-L1 expression level of 50%–74% [ORR 53.6% (95% CI 43.9–63.0) versus 30.7% (95% CI 20.5–42.4), $P = 0.003$, supplementary Table S3A and B, available at *Annals of Oncology* online). The mPFS was significantly longer in the PD-L1 expression 75%–100% group than in the 50%–74% group [7.8 versus 4.3 months, HR 0.63 (95% CI 0.43–0.92), $P = 0.02$, supplementary Figure S4A, available at *Annals of Oncology* online). There was no significant difference in mOS between the PD-L1 expression 75%–100% group and the expression 50%–74% group [not reached versus 20.3 months, HR 0.62 (95% CI 0.37–1.03), $P = 0.07$, supplementary Figure S4B, available at *Annals of Oncology* online). The mDOT was 5.5 months (95% CI 4.12–6.92) and 2.7 months (95% CI 1.74–3.78) among patients with a PD-L1 expression level of 75%–100% and 50%–74%, respectively. After adjusting for ECOG performance status, PD-L1 expression of 75%–100% was significantly associated with improved PFS [HR 0.62 (95% CI 0.42–0.91), $P = 0.01$] but not OS (supplementary Table S4, available at *Annals of Oncology* online).

We lastly investigated whether TMB impacted outcomes to pembrolizumab in the entire cohort of patients with a PD-L1 expression ≥50%. Data from two different platforms were available in 91 patients (48.6% of the cohort). To determine whether there was a significant difference in clinical outcomes by TMB, we fit a multivariate Cox model with TMB as a continuous measurement and adjusted for institution. Among NSCLCs with a PD-L1 expression level ≥50%, we found no association of TMB with prolonged PFS [HR 0.98 (95% CI 0.95–1.02), $P = 0.29$] or OS [HR 0.96 (95% CI 0.91–1.01), $P = 0.14$].

Discussion

In this report, we demonstrate that among patients with NSCLC and a PD-L1 expression level ≥50% treated with first-line pembrolizumab, clinical outcomes are improved with increasing PD-L1 expression levels ≥75% and particularly ≥90%. Among the full cohort of 187 patients in our study, the ORR was 44.4%, which is similar to that observed in the KEYNOTE-024 study [2, 3]. The shorter mPFS in our study compared with KEYNOTE-024 may reflect that this was a non-clinical trial population, in which 18.2% of patients had an ECOG PS ≥2. The ORR to pembrolizumab in our study among patients with a PD-L1 expression level of 50%–89% was 32.7%, which is similar to the response rate of first-line platinum doublet chemotherapy [9–11].

Current treatment decisions in the first-line setting for patients with NSCLC lacking targetable genomic alterations are often impacted by PD-L1 expression levels; patients with PD-L1 levels ≥50% typically receive pembrolizumab monotherapy and those with low or absent PD-L1 expression are treated with a combination of a PD-(L)1 inhibitor plus platinum doublet chemotherapy. However, there has been no direct comparison of pembrolizumab with or without chemotherapy in patients with a PD-L1 level ≥50%, and this is a source of ongoing debate about which regimen is optimal for this population. Our results suggest that patients with NSCLC and very high PD-L1 expression levels might be well-suited for receive treatment with pembrolizumab monotherapy rather than in combination with chemotherapy.

Recently, in the KEYNOTE-042 study, pembrolizumab monotherapy significantly prolonged OS compared with standard chemotherapy in patients with a PD-L1 expression level of ≥50%, ≥20%, and ≥1%. However, in a prespecified exploratory

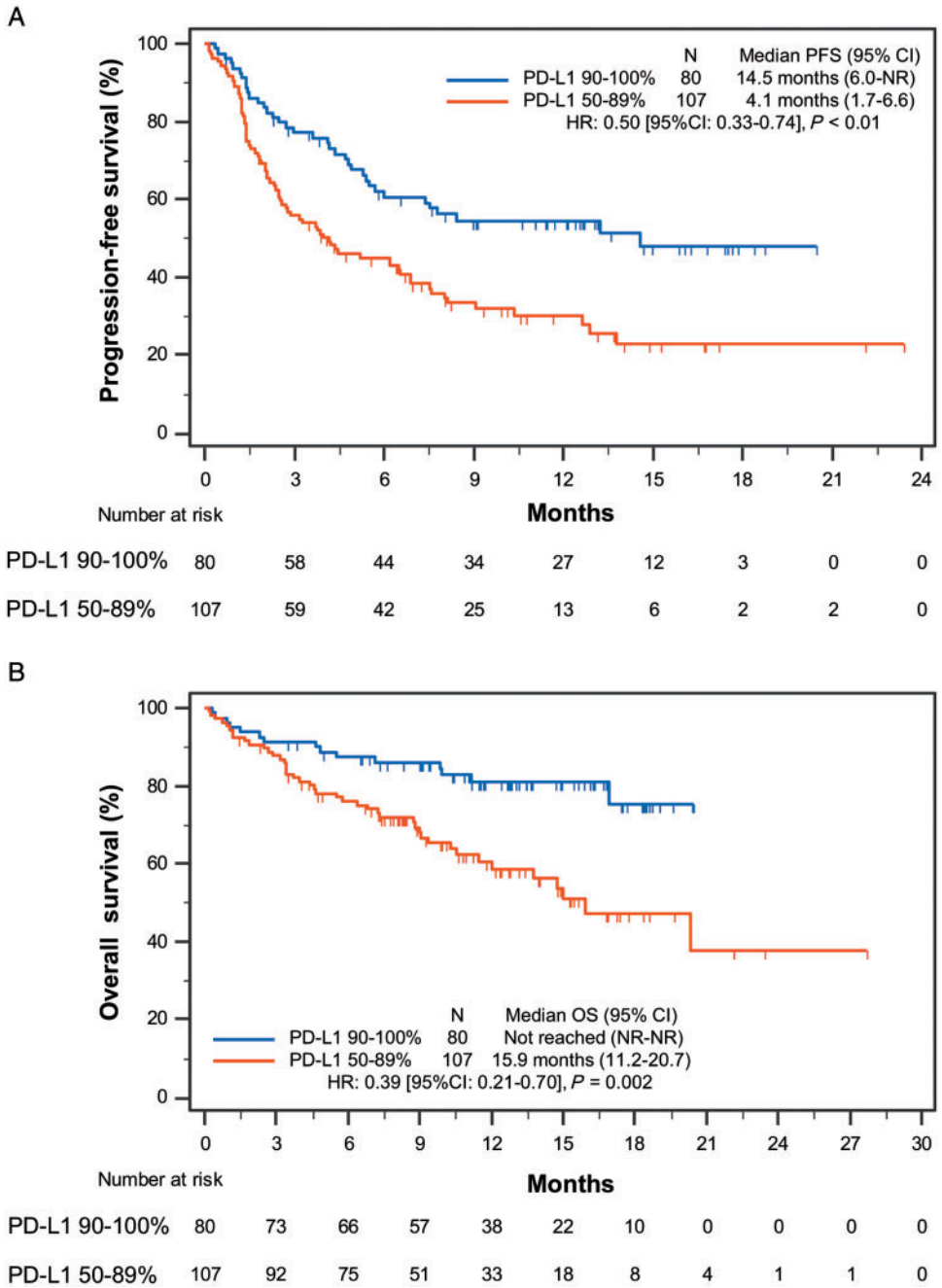

Figure 3. Kaplan–Meier curves for (A) progression-free survival and (B) overall survival to first-line pembrolizumab in the programmed death-ligand 1 (PD-L1) expression 50%–89% and 90%–100% groups. HR, hazard ratio; CI, confidence interval; NR, not reached.

analysis of patients with NSCLC and a PD-L1 expression level of 1%–49%, there was no significant difference in mOS, suggesting that the survival benefit observed in the entire cohort of patients with a PD-L1 expression level of ≥1% was primarily driven by patients whose cancers expressed high PD-L1 levels [12]. Similarly, in the JAVELIN Lung 200 trial comparing the PD-L1 inhibitor avelumab to docetaxel in previously treated NSCLC, clinical outcomes to immunotherapy appeared to improve with increasing PD-L1 expression cutoffs of ≥1%, ≥50%, and ≥80% [13]. Additional analyses from completed first-line immunotherapy clinical trials of outcomes in patients with NSCLC and PD-L1 expression levels ≥75% and ≥90% may help to validate the findings in our non-clinical trial population.

There are number of ongoing or planned first-line randomized phase II and III trials exploring novel treatment strategies in combination with PD-1 pathway inhibitors either in NSCLCs with PD-L1 expression ≥50% or in all-comers with NSCLC regardless of PD-L1 level. These studies should employ stratification measures to ensure that randomized groups are evenly balanced by various PD-L1 levels; otherwise, differences in outcomes may be

the result of imbalances in PD-L1 distribution rather than the treatment intervention. In addition, retrospective analyses have explored factors such as TMB [14], concurrent STK11/LKB1 mutations [15], or prior radiation [16] in predicting response and resistance to immunotherapy in NSCLC. Future analyses of such factors should adjust for PD-L1 expression on a continuous scale from 0% to 100%.

Our study is limited by its retrospective nature. Furthermore, different PD-L1 immunohistochemical antibodies were used in this study other than Food and Drug Administration-approved 22C3 diagnostic test; however, studies have shown good concordance among the E1L3N, 22C3, and 28-8 antibodies which were used in 99% of cases in the present study [17, 18].

While we currently select targeted therapies with kinase inhibitors based on the binary presence or absence of alterations in genes such as *EGFR*, *ALK*, *ROS1*, *BRAF*, and others, an increasing number of continuous biomarkers, including PD-L1 expression, TMB [19, 20], gene expression profile [21], infiltrating immune cells, and T-cell receptor clonality [22], appear to influence outcomes to immune checkpoint inhibitors in NSCLC. An emerging challenge in oncology will be developing rapid diagnostics to integrate these multiple, complex biomarkers in order to select the safest and most effective therapies for patients with cancer.

Acknowledgements

This study has been presented in part at the 2019 Annual American Society of Clinical Oncology (ASCO) Meeting and at the 2018 International Association for the Study of Lung Cancer (IASLC) World Conference on Lung Cancer (WCLC).

Funding

None declared.

Disclosure

MMA is a consultant in Merck, Bristol-Myers Squibb, Genetech, AstraZeneca, Nektar, Ariad. Research Funding: Bristol-Myers Squibb. LMS performs consulting for LOXO Oncology, Foghorn Therapeutics; received honorarium from AstraZeneca; received travel grant from Bristol Myers Squibb; and received research support from Roche. MA received research funding from Bristol Myers Squibb and Lilly. JS: Pfizer, Merck, Thermo Fisher Scientific. JFG is a consultant or received honoraria from Bristol-Myers Squibb, Genentech/Roche, Ariad/Takeda, Loxo, Pfizer, Incyte, Novartis, Merck, Agios, Amgen, Regeneron, Oncorus, Array, Jounce and Clovis Oncology; received research support from Novartis, Genentech/Roche, and Ariad/Takeda; and received institutional research support from Bristol-Myers Squibb, Tesaro, Moderna, Blueprint, Jounce, Array Biopharma, Merck, Adaptimmune, Novartis, and Alexo. SD performs consulting for AstraZeneca. JVH has participated in scientific advisory boards for Genentech, BMS, Lilly, AstraZeneca, Merck, Boehringer, GSK, Spectrum; received research support from AstraZeneca, Spectrum; and received royalties from licensing from Spectrum. MN is a consultant to Toshiba Medical Systems, WorldCare Clinical, Daiichi Sankyo; and received research grant from Merck, Canon Medical Systems, AstraZeneca; Honorarium from Bayer and Roche. SD provided independent image analysis through hospital for clinical research trial program sponsored by Merck, Pfizer, Bristol Mayer Squibb, Novartis, Roche, Polaris, Cascadian, Abbvie, Gradalis, Clinical Bay, Zai laboratories; and received honorarium from Siemens Medical Services. KA is a consultant or received honoraria from AstraZeneca and The Jackson Laboratory. MDH received research funding from Bristol-Myers Squibb. Consultant to Merck, Bristol-Myers Squibb, AstraZeneca, Genentech/Roche, Janssen, Nektar, Syndax, Mirati, and Shattuck Labs; received travel support/honoraria from AztraZeneca and BMS. A patent has been filed by MSK related to the use of tumor mutation burden to predict response to immunotherapy (PCT/US2015/062208), which has received licensing fees from PGDx. All remaining authors have declared no conflicts of interest.

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