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Very High PD-L1 Expression as a Prognostic Indicator of Overall Survival among Patients with Advanced Non-Small Cell Lung Cancer receiving Anti PD-(L)1 Monotherapies in Routine Practice

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Abstract

Purpose: Programmed death or ligand-1 (PD-(L)1) pathway inhibitors confer improved survival as first-line treatment for advanced non-small cell lung cancer (aNSCLC) in patients with PD-L1 expression (PD-L1+e ≥50%) compared to platinum-doublet chemotherapy and have become a standard therapy. Some recent evidence suggests that among aNSCLC patients with PD-L1+e of ≥50% receiving pembrolizumab monotherapy, very high levels of PD-L1+e (≥90%) may be associated with better outcomes. We sought to assess whether very high PD-L1+e (≥90%) compared to high PD-L1+e (≥50–89%) is associated with an overall survival benefit in aNSCLC patients receiving anti PD-(L)1 monotherapies.

Methods: We conducted a single-site retrospective cohort study of aNSCLC patients who initiated PD-(L)1 inhibitor monotherapy as first-line treatment from October 24, 2016, to August 25, 2021, and had a PD-L1+e ≥50%. The primary outcome was overall survival, measured from the start of first-line PD-(L)1 inhibitor monotherapy (index date) to date of death or last confirmed activity prior to the cohort exit date. Propensity score-based inverse probability weighting (IPW) was used to control for confounding in Kaplan-Meier curves and Cox proportional hazard regression analysis.

Results: 166 patients with aNSCLC receiving PD-(L)1 inhibitor monotherapy met inclusion criteria. Fifty four percent were female, 90% received pembrolizumab, median age was 68 years, 70% had non-squamous cell carcinoma, 94% had a history of smoking, 29% had a KRAS mutation, and 37% had very high PD-L1+e. Unweighted covariates at cohort entry were

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Contributors

Study concept and design: Shah, Hennessy

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similar between groups (absolute standardized mean differences (SMDs) <0.1) except for race (SMD=0.2); age at therapy initiation (SMD=0.13); smoking status (SMD=0.13), and BRAF mutation status (SMD=0.11). After weighting, baseline covariates were well balanced (all absolute SMDs <0.1). In the weighted analysis, having a very high PD-L1+e was associated with lower mortality (weighted hazard ratio 0.57, 95% CI 0.36–0.90) and longer median survival: 3.85 vs 1.49 years.

Conclusions: Very high PD-L1+e (≥90%) was associated with an overall survival benefit over high PD-L1+e (50–89%) in patients receiving first-line PD-(L)1 inhibitor monotherapy in a model controlling for potential confounders. These findings should be confirmed in a larger real-world data set.

Background

Lung cancer is the second most common cancer, and accounts for a quarter of all cancer deaths in the US.[1] Non-small cell lung cancer accounts for approximately 85–90% of all lung cancer cases, with most patients presenting in advanced stages, where systemic treatment is required, and complete surgical resection is no longer an option.[2] First-line treatment for advanced non-small cell lung cancer (aNSCLC) with programmed death ligand-1 (PD-(L)1) pathway inhibitors, a type of immunotherapy, confers improved survival compared to platinum-doublet chemotherapy, and has become a standard therapy in patients with high tumor expression of programmed death or ligand-1 (PD-L1+e).[3]

Factors affecting treatment decisions in aNSCLC patients include tumor histology, disease burden, symptoms, and tumor PD-L1+e. [4] Tumor PD-L1+e is a clinical biomarker, expressed as a percentage of tumor cells that exhibit membranous staining at any intensity. PD-L1+e ≥50% (which is present in 30% of NSCLC cases[2]) predicts a high likelihood of disease response and a longer overall survival in patients treated with first-line immunotherapy compared to lower PD-L1+e.[3] As a result, newly diagnosed NSCLC patients are now routinely tested for PD-L1+e. There is some evidence that among aNSCLC patients with PD-L1+e ≥50% receiving pembrolizumab monotherapy first line, very high PD-L1+e (≥90%) is associated with improved survival.[5] However, this previous study had limited follow up time during which median overall survival was not reached in the very high PD-L1+e group, and adjusted only for Eastern Cooperative Oncology Group (ECOG) performance status (PS). We hypothesized that compared with PD-L1+e of 50–89%, very high PD-L1+e (≥90%) is associated with prolonged overall survival, confirming the prior observation in a dataset with longer follow up time and the ability to control for more potentially important confounders.

Methods

This study was approved by the University of Pennsylvania IRB and was conducted in accordance with all applicable University of Pennsylvania human subjects research requirements and federal regulations. We identified patients treated within the University of Pennsylvania Health System (UPHS) who 1) were 18 years of age or older, 2) had been diagnosed with advanced stage or metastatic stage IV or recurrent NSCLC (ICD-9 codes 162.x or ICD-10 codes C34.x or C39.9) according to the 2009 American Joint

Committee on Cancer classification criteria – between October 24, 2016 (based on FDA approval of first- line pembrolizumab in those with PDL1 expression of at least 50%),[6] and August 25, 2021 (the date of data abstraction), 3) had at least two clinical visits on or after October 24, 2016 4) initiated first line treatment with an anti PD-(L)1 monotherapy (i.e., pembrolizumab, durvalumab or atezolizumab) after diagnosis of advanced stage or metastasis, and 5) had a recorded value of percentage PD-L1 expression of at least 50% of tumor cells 6) had a recorded value of ECOG PS in the 100 days leading up to and including the index date. Patients with incomplete immunotherapy treatment data, those receiving first line immunotherapy as a part of clinical trial, those receiving chemo-immunotherapy combination, or patients harboring sensitizing alterations in EGFR, ALK or ROS1 genes were excluded because of harms associated with immunotherapy in patients with such alterations.[7] We also excluded patients with a gap >90 days between diagnosis and first visit or medication order.

All prior baseline data up to and including the index date were used to ascertain baseline covariates. Baseline data and covariates were derived from prior literature,[5, 8] and included (a) demographic factors age, sex, and race/ethnicity (b) pathological cancer diagnosis, date of diagnosis, and clinical and pathological stage of malignancy (c) smoking status; and (d) genetic mutation status e.g., KRAS, BRAF.

The prognostic variable of interest was very high PD-L1+e, which we defined as ≥90%. The cut off (≥ 90%) was formulated by Aguilar et al, where they performed a recursive partitioning algorithm to investigate an optimal grouping of PDL1+e with respect to overall survival among aNSCLC patients receiving immunotherapy.[5]

PD-L1+e is reported as a percentage of tumor cells with membranous staining using a variety of immunohistochemical antibodies and platforms but primarily assessed using the Dako PD-L1 22C3 assay (~70% of the cohort).[9] The outcome of interest was overall survival measured from the initiation of first-line anti-PD1 monotherapy, [10] which was considered the index date. Patients were followed until death, last structured electronic health record (EHR) activity (including visit or medication administration), or August 25, 2021.

Statistical Analysis

Baseline covariates were compared between the very high PD-L1+e and high PD-L1+e groups using absolute standardized mean differences to identify imbalances in continuous variables, and absolute standardized differences in proportion to assess imbalance for categorical variables, using a threshold of >0.1 to suggest factors with potentially meaningful imbalance between groups.[11]

To control for confounding, we used inverse probability weighting (IPW) by a function of the propensity score, which we defined as the probability of a patient having very high PD-L1+e conditional on baseline variables. The propensity score model was estimated using logistic regression and included all baseline covariates listed above. Patients with very high PD-L1+e were weighted by the inverse of the propensity score, and patients with high PD-L1+e were weighted by the inverse of the complement of the propensity

score. The positivity assumption was assessed by examining overlap of propensity score distributions between the groups based on density plots. Absolute standardized differences were computed after weighting to assess whether any imbalances remained. Inverse probability weighted Kaplan-Meier curves comparing overall survival in the groups were plotted. Cox proportional hazards regression analysis with IPW, using a robust variance estimator, was used to estimate weighted hazard ratios (HRs), and 95% confidence intervals (CIs). We assessed the proportional hazards assumption using Schoenfeld residuals.[12] Statistical analyses were performed using STATA V16.0/IC (College station, TX).

Results

We identified 196 aNSCLC patients who received anti PD-(L)1 monotherapy, of whom 166 met inclusion criteria. The median (IQR) age was 68 (61–75) years; 116 (70%) were White, and 89 (54%) were female. A total of 117 patients (70%) had non squamous cell carcinoma and 156 (94%) had a history of smoking. In the cohort, 150 patients (90%) received pembrolizumab monotherapy, 48 (29%) had a KRAS mutation, and 62 (37%) patients had very high PDL1+e. Unweighted baseline characteristics were generally similar between exposure groups (absolute standardized mean differences (SMDs) <0.1) except for race (SMD=0.2); age at therapy initiation (SMD=0.13); smoking status (SMD=0.13), and BRAF mutation status (SMD=0.11). After IPW, baseline covariates were well balanced between groups (all absolute standardized differences<0.1) (Table 1). Thirty five percent of patients went on to receive a second-line therapy (n=19 (31%) in the ≥90% group and n=40 (38%) in the 50–89% group). Median time on first line treatment was higher for the time PD-L1+e (≥90%) group [median 229.5 days IQR 75–518] versus PD-L1+e (50–89%) group [median 139 days IQR 41.5–448.5].

Overall survival

Median follow-up time from initiation of first-line anti PD-(L)1 monotherapy for the entire cohort in the unweighted sample was 1.20 years (interquartile range 0.40–2.36). During follow-up, there were 87 deaths, 25 (40%) in the very high PD-L1+e and 62 (60%) in the high PD-L1+e group. Inverse probability weighted Kaplan-Meier curves are presented in Figure 1. In the weighted analysis, PD-L1+e ≥90% was associated with lower mortality compared to PD-L1+e of 50–89% (weighted HR 0.57, 95% CI 0.36–0.90, Table 2). Median overall survival from the index date in the inverse probability weighted sample was 3.85 years in patients with PD-L1+e ≥90% and 1.49 years in patients with PD-L1+e of 50–89% (p=0.01).

Discussion

We found that among aNSCLC patients with PD-L1+e ≥50%, treated first-line with anti PD-(L)1 inhibitors, 37% had PDL1+e ≥90%, and that having a PDL1+e ≥90% was associated with better overall survival [weighted HR 0.57 (0.36–0.90)], and longer median survival (3.85 vs. 1.49 years).

Tumor PD-L1 expression has been used to predict immunotherapy benefit compared to conventional chemotherapy and is routinely used in clinical practice to select first-line

therapy among aNSCLC patients. Our finding that, among patients with PD-L1+e ≥50%, 37% have PDL1+e ≥90% is similar to analogous findings in Japan (34%)[13] and the US (44%).[5] As PD-L1+e ≥50% is found in nearly one third of all real-world non-small cell lung cancer patients,[2] this implies that very high PD-L1+e is present in 10–13% of real-world aNSCLC cases.

Our study builds on this prior work by including longer follow up, and accounting for a wider range of potential confounders. Our finding that PD-L1+e ≥90% was associated with a lower mortality after IPW is in line with a previous study of very high PD-L1+e in patients treated with pembrolizumab monotherapy [median overall survival not reached for the very high PD-L1+e group vs 1.32 years, HR 0.39 (0.21–0.70)].[5]

This study's strengths include a clearly defined cohort, and similar distributions of most baseline covariates even before weighting. Potential limitations include its modest sample size, potentially limited generalizability, and the potential for confounding from unmeasured baseline factors such as site of metastasis and body mass index.

In addition to the prognostic information provided by this study, its findings have potential implications in design of future clinical trials. Ongoing aNSCLC clinical trials collectively group baseline PD-L1+e ≥50% and report their outcomes in aggregate. This leads to patients with very high PD-L1+e and high PD-L1+e being placed in the same group (PD-L1+e ≥50%), and treatment arms that, especially for small trials, may not be evenly balanced on PD-L1+e, which could lead to treatment effect estimates that may not be reliable and valid. Building on recommendations by Kernan et al, [14] we believe that anti PD-(L)1 immunotherapy trials with fewer than 100 patients per treatment arm should consider utilizing PD-L1+e stratified randomization (50–89% and ≥90%), and report outcomes accordingly. This would ensure that randomized groups are evenly balanced with respect to prognostic indicators like very high PD-L1+e levels. For larger anti PD-(L)1 monotherapy clinical trials (>200 patients per treatment arm), post-randomization stratification based on a 50–89% and ≥90% scale may be equivalent to stratified randomization.[14]

Conclusions

Among aNSCLC patients treated with anti PD-(L)1 monotherapies and PD-L1+e levels of ≥50%, having very high PD-L1+e is associated with improved survival. Future studies are needed to confirm these findings in larger real world data sets.

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Figure abbreviations

IP	Inverse Probability

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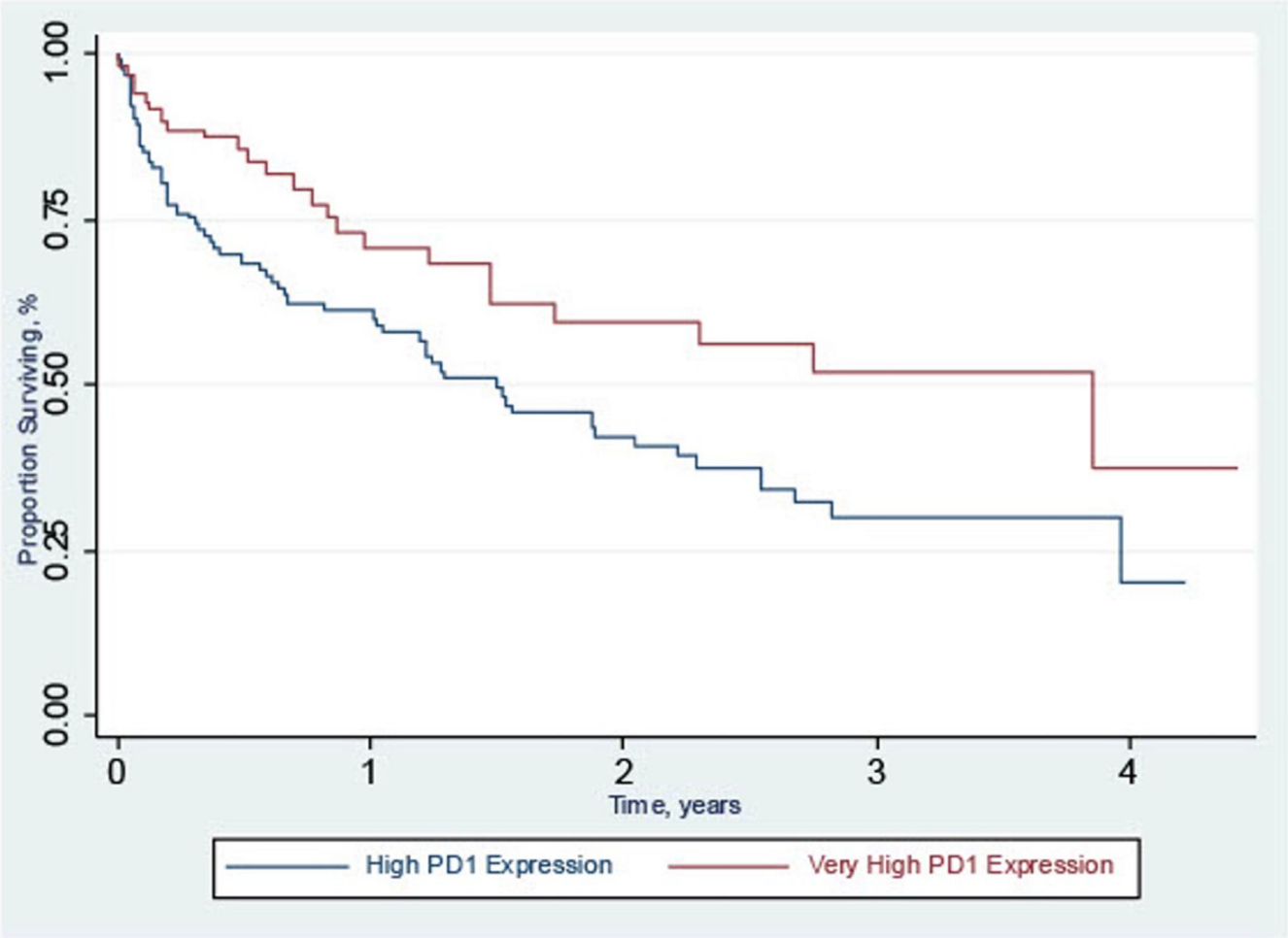
Key points

- Programmed death or ligand-1 (PD-(L)1) pathway inhibitors confer improved survival as first-line treatment for advanced non-small cell lung cancer (aNSCLC) in patients with PD-L1 expression (PD-L1+e ≥50%) compared to platinum-doublet chemotherapy and have become a standard therapy. Some recent evidence suggests that among aNSCLC patients with PD-L1+e of ≥50% receiving pembrolizumab monotherapy, very high levels of PD-L1+e (≥90%) may be associated with better outcomes.
- We hypothesized that compared with PD-L1+e of 50–89%, very high PD-L1+e (≥90%) is associated with prolonged overall survival, confirming the prior observation in a dataset with longer follow up time and the ability to control for more potentially important confounders.
- We observed among aNSCLC patients with PD-L1+e ≥50% treated first-line with anti PD-(L)1 inhibitors in routine practice, 37% had PD-L1+e ≥90%.
- Having a PD-L1+e ≥90% was associated with better overall survival [inverse probability weighted HR 0.57 (0.36–0.90)], and longer median survival (3.85 vs. 1.49 years).
- In addition to the prognostic information provided by this study, its findings have potential implications in design of future clinical trials.



	Time, years	0	1	2	3	4
Very High PD1 Expression		166	94	47	25	8
High PD1 Expression		166	87	48	23	3

Weighted number of patients in the pseudopopulation remaining at risk at each point in each group

Figure 1.
Inverse Probability Weighted Kaplan Meier Curves of Overall Survival by PD-L1 Expression

Table 1.

Unweighted and weighted baseline Characteristics of the Cohort by PD-L1 Expression

	Unweighted population			Weighted population (scaled)		
	Very High PDL1+e	**High PDL1+e**	**Absolute Standardized Difference Before IPW**	**Very High PDL1+e**	**High PDL1+e**	**Absolute Weighted Standardized Difference**
N	N=62	N=104		N=166	N=166	
Age at therapy initiation, median (IQR)	68(62–75)	67(61–76)	0.13	68 (60–74)	68 (61–76)	0.01
Gender n (%)			0.06			0.02
Female	32(52)	57(55)		91 (55)	89 (54)	
Male	30(48)	47(45)		75 (45)	77 (46)	
Race n (%)			0.2			0.02
White	47(76)	69(66)		116 (70)	116 (70)	
Non-White	15(24)	35(34)		50 (30)	50 (30)	
Smoking Status n (%)			0.13			<0.01
Current/Former	57(92)	99(95)		156 (94)	156 (94)	
Never	5(8)	5(5)		10(6)	10(6)	
ECOG PS n (%)			0.01			0.01
0–1	45(73)	75(72)		121(72)	120(72)	
≥2	17(27)	29(28)		45(27)	46(28)	
Tumor histology n (%)			0.07			<0.01
Non squamous cell carcinoma	45(73)	72(69)		117 (70)	117(70)	
Squamous cell carcinoma	13(21)	21(20)		38(23)	31(19)	
NSCLC NOS	4(6)	11(11)		11 (7)	18(11)	
KRAS mutation n (%)			0.05			<0.01
Yes	17(27)	31(30)		48 (29)	48 (29)	
No	45(73)	73(70)		118 (71)	118 (71)	
BRAF mutation n (%)			0.11			<0.01
Yes	4(6)	4(4)		7 (4)	8 (5)	
No	58(94)	100(96)		159 (96)	158 (95)	

IQR, Interquartile range

ECOG, Eastern Cooperative Oncology Group

NSCLC NOS, non-small cell lung cancer not otherwise specified

IPW, inverse probability weighting

Table 2:

Overall Survival in patients with Very High PD-L1 expression

Study groups	No. of subjects	Median duration of follow up, years [IQR]	No. of deaths in the follow up period	Weighted median survival, years [IQR]	Weighted Hazard Ratio [95% CI]	P-value*
Very high PD-L1 expression (90–100%)	**62**	1.38 [0.60–2.37]	25	3.85 [0.86-NR]	0.57 [0.36–0.90]	0.01
High PD-L1 expression (50–89%)	**104**	1.03 [0.32–2.32]	62	1.49 [0.31–3.96]	1.00 [Reference]	

IQR, interquartile range; NR, Not reached;

*Based on test for two survival curves using cox proportional hazards regression analysis adjusted with IPW