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Original Research

PD-L1 score as a prognostic biomarker in asian early-stage epidermal growth factor receptor-mutated lung cancer☆

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Abstract ***Aim:*** To determine the prognostic value of programmed death-ligand 1 (PD-L1) score in early-stage epidermal growth factor receptor (*EGFR*)-mutated non-small cell lung cancer (NSCLC), contrasted against *EGFR*-wildtype NSCLC.
Methods: Consecutive patients with Stage IA-IIIA NSCLC diagnosed 1st January 2010–31st December 2019 at National Cancer Centre Singapore with evaluable EGFR and PD-L1 status were included. Co-primary end-points were 2-year disease-free survival (DFS) and 5-year overall survival (OS) by Kaplan–Meier method.

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Results: 455 patients were included (267 EGFR-mutated, EGFR-M+; 188 EGFR-wildtype, wt). Median age at diagnosis was 65 years, 52.3% (238/455) of patients were males, 62.9% (286/455) of patients were never-smokers and 92.5% (421/455) of patients had R0 resection. Stage IA comprised 42.4% (193/455) of patients, Stage IB comprised 23.1% (105/455) of patients, Stage IIA comprised 10.8% of patients (49/455), Stage IIB comprised 5.1% of patients (23/455) and Stage IIIA comprised 18.7% (85/455) of patients. Among EGFR-M+, 45.3% (121/267) were Ex19del and 41.9% (112/267) were L858R. PD-L1 $\geq$1% among EGFR-M+ and EGFR-wt was 45.3% (121/267) and 54.8% (103/188) respectively (p = 0.047).

At median follow-up of 47 months, 178 patients had relapsed. Among EGFR-M+, 2-year DFS comparing PD-L1 <1% and PD-L1 $\geq$1% was 78.1% and 67.6% (p = 0.007) while 5-year OS was 59.5% and 42.8% (p = 0.001), respectively. Controlling for age, gender, lymphovascular invasion, adjuvant therapy and resection margin status, PD-L1 $\geq$1% (hazard ratio, HR 2.18, 95% CI 1.04–4.54, p = 0.038), stage IIB (HR 7.78, 95% CI 1.72–35.27, p = 0.008) and stage IIIA (HR 4.45, 95% CI 1.44–13.80, p = 0.01) emerged as independent predictors of inferior OS on multivariable analysis.

In exploratory analysis, genomic analysis of 81 EGFR-M+ tumours was performed. PD-L1 $\geq$1% tumours had significantly higher rates of *TP53* mutations (36.1% versus 15.6%, p = 0.04), with predominantly missense mutations.

Conclusion: PD-L1 $\geq$1% is an independent predictor of worse OS among early-stage EGFR-mutated NSCLC and is associated with inferior DFS regardless of *EGFR* status. PD-L1 score as a risk stratification factor should be evaluated in prospective adjuvant studies among EGFR-mutated NSCLC.

1. Introduction

The adjuvant therapy landscape in early-stage resected epidermal growth factor receptor (*EGFR*)-mutated non-small cell lung cancer (NSCLC) has seen significant developments following the landmark approvals of adjuvant osimertinib and atezolizumab, both notably based on disease-free survival (DFS) benefit alone in the absence of mature overall survival (OS) data [1,2]. Additional trials involving other immune checkpoint inhibitors (ICI) are anticipated, such as adjuvant pembrolizumab in PEARLS/KEYNOTE-091 (3). Although atezolizumab has been granted broad approval in PD-L1 positive stage II-IIIA NSCLC (including *EGFR*-mutated NSCLC), DFS benefit was mainly driven by PD-L1 $\geq$50% subgroup [2]. Notably among the *EGFR*-mutated subgroup in IMpower010, no DFS benefit was observed with atezolizumab when PD-L1 0% patients were included in the analysis [2]. On the other hand, preliminary subgroup analysis from PEARLS/KEYNOTE-091 suggests that *EGFR*-mutated patients may benefit from adjuvant pembrolizumab, although data by PD-L1 status have not been reported [3].

We previously demonstrated that 37% of patients with Stage IB–IIIA *EGFR*-mutated NSCLC remain disease-free at 5 years without adjuvant osimertinib [4], highlighting the importance of risk stratification. Multiple studies have shown that PD-L1 positivity is associated with inferior survival in advanced NSCLC, albeit this is less established in early-stage disease [5–7]. A meta-analysis comprising 40 studies found PD-L1 expression to be associated with worse OS in early-stage NSCLC but outcomes specific to *EGFR*-mutated NSCLC and association with DFS were unknown [8]. A smaller meta-analysis of 13 studies found increased PD-L1 expression to be an unfavourable prognostic factor for Asian populations but not for non-Asian populations [9]. Considering that none of the patients in IMpower010 or PEARLS/KEYNOTE-091 would have received adjuvant osimertinib, the clinical implications of PD-L1 status among *EGFR*-mutated NSCLC, especially in a post-ADAURA era remain undefined [1].

We sought to determine the prognostic value of PD-L1 score in a cohort of patients with early-stage resected *EGFR*-mutated NSCLC (*EGFR*-M+) with mature follow-up data predating adjuvant osimertinib, using patients with *EGFR*-wildtype NSCLC (*EGFR*-wt) as a comparator cohort. In exploratory analysis, we examined genomic and transcriptomic features associated with PD-L1 score among patients with *EGFR*-mutated NSCLC.

2. Material and methods

2.1. Data collection

This cohort study was conducted under the approval of SingHealth Centralised Institutional Review Board. All participants provided written informed consent. Clinicopathological information, treatment data and survival outcomes were collated through manual electronic database review managed by the Lung Cancer Consortium Singapore.

2.2. Study population

Consecutive patients with AJCC7 Stage IA-IIIA NSCLC diagnosed between 1st January 2010 and 31st December 2019 at National Cancer Centre Singapore, a multidisciplinary tertiary cancer centre, who underwent curative-intent surgery with evaluable EGFR and PD-L1 status were included. *EGFR* mutations were prospectively detected by Cobas, Sanger sequencing and/or next generation sequencing. *Ex19del*, *L858R* and other uncommon *EGFR* mutations were included. Patients with either *Ex19del* or *L858R* mutation in combination with another *EGFR* co-mutation were classified as *Ex19del* or *L858R* accordingly [1]. PD-L1 tumour proportion score was evaluated using SP263 immunohistochemistry as per institutional practice. Exclusion criteria included metastatic disease at diagnosis, mixed small cell lung carcinoma histology and unknown *EGFR* or PD-L1 status.

Patients were followed up from diagnosis until death or date of last follow-up. The cut-off for data analysis was 4th February 2022.

2.3. Outcomes

Co-primary end-points for this study were 2-year DFS and 5-year OS. DFS was defined as time from diagnosis until disease recurrence or death (whichever occurred first); surviving patients without recurrence were censored at their date of last follow-up. OS was defined as the time from initial diagnosis to date of death, with surviving patients censored at their date of last follow-up.

2.4. Genomic and transcriptomic analyses

Whole-exome and RNA-sequencing were performed on a subset of patients with available tissue. Fresh frozen tumour and healthy tissue samples or paired blood samples were subject to whole-exome sequencing at approximately 100x-400x coverage and 100x coverage, respectively, with the mean number of paired-end reads for RNA-sequencing at approximately 30 million. Driver gene alterations that correlate with PD-L1 status were identified, with methods as described elsewhere [10]. Somatic focal copy number alterations (CNA) were identified using GISTIC2.0 and only high level amplifications and homozygous deletions [11] were included in analysis. To minimise batch effect due to variations in sequencing depth, only lung adenocarcinoma driver genes were analysed [12]. For patients with multi-region sequencing data, only clonal mutations or CNA detected in every sequenced sector were used for analysis on a per patient basis. For genes that were mutated in at least 4 patients, mutation frequencies between PD-L1 $\geq$1% and PD-L1 <1% groups were compared using Fisher exact test. T cell–inflamed gene expression profile (GEP) scores were computed for samples that had RNA-seq data. GEP scores were categorised as high or low using the median as cut-off. Comparisons of PD-L1 tumour proportion score, GEP score [13] and tumour mutational burden were conducted using Wilcoxon rank-sum test [14].

2.5. Statistical analysis

Categorical variables were summarised as frequency and percentage, and continuous variables were summarised using median with range or mean with standard deviation and range. We performed $\chi 2$ tests or Fisher exact test for categorical variables and Mann–Whitney U test for continuous variables to assess the association between patient characteristics and PD-L1 status. Multivariable logistic regression analysis was performed to assess the association of clinical features and PD-L1 score (≥1%). Survival curves were estimated using Kaplan–Meier method. Differences in survival curves were assessed using log-rank test. Univariable and multivariable Cox regression analyses were performed to assess the association between OS/DFS with clinicopathologic and treatment characteristics. Variable selection for multivariable Cox regression analyses was performed using the backward elimination method, by optimising Akaike information criterion and Harrell's C index. The proportional hazards assumption for the Cox regression models was checked using statistical tests based on the scaled Schoenfeld residuals. A two-sided $P < 0.05$ was considered statistically significant. All analyses were performed in R software (version 4.2.0) and STATA version 16.0.

3. Results

3.1. Characteristics of EGFR-mutated versus EGFR-wildtype

A total of 1490 patients were screened, of which 455 patients met the inclusion criteria for analysis (267 EGFR-M+ and 188 EGFR-wt). Patient characteristics of all patients are summarised in Table S1. Approximately 83.5% (380/455) of patients had staging positron emission tomography-computed tomography at diagnosis. Median age at diagnosis was 65 years (range 33–86) and distribution by stage was similar between *EGFR*-M+ and *EGFR*-wt. Stage IA comprised 42.4% (193/455) of patients, Stage IB 23.1% (105/455) of patients, Stage IIA 10.8% (49/455) of patients, Stage IIB 5.1% (23/455) of patients and Stage IIIA 18.7% (85/455) of patients. There were significantly more males (69.1% versus 40.4%, $p < 0.001$), non-Chinese ethnicity (18.1% versus 9.7%, $p = 0.049$) and current or former smokers (60.6% versus 20.6%, $p < 0.001$) among *EGFR*-wt than *EGFR*-M+. For histological features, *EGFR*-wt was significantly associated with higher incidence of

squamous cell carcinomas (12.8% versus 0.7%, $p < 0.001$), non-acinar adenocarcinoma subtype (66.5% versus 28.8%, $p < 0.001$) and poorly differentiated tumours (27.1% versus 11.6%, $p < 0.001$). There was a significantly higher representation of PD-L1 ≥1% among EGFR-wt than EGFR-M+ (54.8% versus 45.3%, $p = 0.047$), particularly for PD-L1 ≥50% (22.3% versus 6.0%, $p < 0.001$). There was no significant difference in the methods used to detect *EGFR* mutation among adenocarcinomas between EGFR-wt and EGFR-M+ ($p = 0.613$).

3.2. Patient characteristics of EGFR-mutated cohort by PD-L1 score

As there were only 16 patients with PD-L1 ≥50% among EGFR-M+ (Table S1), we classified patients into PD-L1 <1% versus ≥1% for subsequent analysis. Patient characteristics of EGFR-M+ distributed by PD-L1 score are summarised in Table 1. There were 4 patients with compound *EGFR* mutations, of which 3 patients had *L858R* (2 with *T790M*, 1 with *I759M*). The remaining 1 patient had *G719A* with *S768I*, which was classified as Others.

There was no significant association between PD-L1 score and age at diagnosis, ethnicity, smoking status, stage or *EGFR* mutation subtype. However, PD-L1 ≥1% was significantly associated with male gender ($p = 0.006$), higher histological grade ($p = 0.024$), non-acinar adenocarcinoma subtype ($p = 0.035$) and lymphovascular invasion (LVI) ($p = 0.021$).

Multivariable analysis was performed to evaluate the association between clinical features and PD-L1 status (Table S2), which found that only male gender remained significantly associated with PD-L1 ≥1% in the multivariable model comprising of age, ethnicity, smoking status, stage, LVI, grade, adenocarcinoma subtype and EGFR mutation.

3.3. DFS and OS by PD-L1 score

At median follow-up of 47 months (range 0–126), 178/455 (39.1%) patients had relapsed. These represented 42.7% (114/267) of EGFR-M+ and 34.0% (64/188) of EGFR-wt cohort. Among EGFR-M+ cohort, 2-year DFS comparing PD-L1 <1% and PD-L1 ≥1% was 78.1% and 67.6% (hazard ratio [HR] 1.67; $p = 0.007$) while 5-year OS was 59.5% and 42.8% (HR 2.90; $p = 0.001$), respectively. A similar trend was observed among EGFR-wt cohort, although the difference in 5-year OS did not reach statistical significance (Table 2). DFS and OS by PD-L1 and EGFR mutation status are shown in Fig. 1, showing significantly inferior outcomes of PD-L1 ≥1% except for OS among EGFR-wt cohort. In exploratory analysis, DFS and OS by PD-L1 tertile were analysed (Figure S1), demonstrating consistently worse outcomes with higher PD-L1 score for both EGFR-M+ and EGFR-wt.

3.4. Clinicopathological features associated with recurrence among EGFR-mutated cohort

After demonstrating that PD-L1 ≥1% was significantly associated with both inferior DFS and OS among EGFR-M+, we sought to identify clinicopathological features associated with recurrence.

Univariable and multivariable analysis was performed to identify clinicopathological features associated with DFS and OS. While PD-L1 ≥1%, age ≥65 at diagnosis, smoking status, higher stage at diagnosis, higher histological grade, LVI, solid/micropapillary adenocarcinoma subtype, receiving adjuvant platinum doublet chemotherapy and R1/R2 resection margins were associated with DFS on univariable analysis, only stage IIB (HR 3.67, 95% CI 1.45–9.32, $p = 0.006$), stage IIIA (HR 2.83, 95% CI 1.41–5.67, $p = 0.003$) and LVI (HR 1.82, 95% CI 1.13–2.94, $p = 0.014$) remained significantly associated with inferior DFS on multivariable analysis (Table 3). After controlling for age, gender, LVI, adjuvant therapy and resection margin status, PD-L1 ≥1% (HR 2.18, 95% CI 1.04–4.54, $p = 0.038$), stage IIB (HR 7.78, 95% CI 1.72–35.27, $p = 0.008$) and stage IIIA (HR 4.45, 95% CI 1.44–13.80, $p = 0.01$) were found to be independent predictors of inferior OS on multivariable analysis (Table 4).

3.5. Molecular features among EGFR-mutated cohort by PD-L1 score

In exploratory analysis, genomic and transcriptomic data of 81 patients from EGFR-M+ cohort were analysed to interrogate the relationship between PD-L1 status and molecular correlates. As there were only 2 patients with PD-L1 ≥50%, patients were segregated into PD-L1 <1% (n = 45) and PD-L1 ≥1% (n = 36). We sought to examine differences in lung adenocarcinoma-specific driver genes [12] as shown in Fig. 2.

TP53, *RBM10* and *CTNNB1* were the most frequently mutated genes seen in 24.7% (20/81), 17.3% (14/81) and 6.2% (5/81), respectively. PD-L1 ≥1% tumours had significantly higher rates of *TP53* mutations than PD-L1 <1% tumours at 36.1% (13/36) versus 15.6% (7/45) ($p = 0.04$), whereas PD-L1 <1% tumours had higher rates of *RBM10* mutations than PD-L1 ≥1% tumours at 24.4% (11/45) versus 8.3% (3/36) ($p = 0.08$). Accordingly, PD-L1 scores were significantly higher among tumours with *TP53* mutations than *TP53*-wild-type ($p = 0.016$) while *RBM10*-wild type tumours had a non-significant trend towards higher PD-L1 scores ($p = 0.11$) as shown in Figure S2.

To further explore the *TP53* pathway, we evaluated CNA of MDM2 and MDM4, both key regulators of

Table 1
Patient characteristics of EGFR-M+ by PD-L1 score.

	PD-L1 score, Number (%)			
	Total (N = 267)	<1% n = 146 (54.7)	≥1% n = 121 (45.3)	p-value
Age				0.526#
Mean (SD)	64.5 (9.29)	64.7 (9.49)	64.2 (9.07)	
Range	36.0–86.0	36.0–86.0	39.0–85.0	
Age at diagnosis				0.219
<65 years old	128 (47.9)	65 (44.5)	63 (52.1)	
≥65 years old	139 (52.1)	81 (55.5)	58 (47.9)	
Gender				**0.006**
Female	159 (59.6)	98 (67.1)	61 (50.4)	
Male	108 (40.4)	48 (32.9)	60 (49.6)	
Ethnicity				0.542^
Chinese	241 (90.3)	131 (89.7)	110 (90.9)	
Malay	12 (4.5)	5 (3.4)	7 (5.8)	
Indian	4 (1.5)	3 (2.1)	1 (0.8)	
Others	10 (3.7)	7 (4.8)	3 (2.5)	
Smoking status				0.065
Never smoker	212 (79.4)	122 (83.6)	90 (74.4)	
Current or former	55 (20.6)	24 (16.4)	31 (25.6)	
Histo type				0.284
Adenocarcinoma	264 (98.9)	143 (97.9)	121 (100.0)	
Squamous	2 (0.7)	2 (1.4)	0 (0.0)	
Others	1 (0.4)	1 (0.7)	0 (0.0)	
Adenocarcinoma subtype (n = 264)				**0.035**^
Acinar	190 (72.0)	103 (72.0)	87 (71.9)	
Pleomorphic/sarcomatoid	2 (0.8)	1 (0.7)	1 (0.8)	
NOS/mixed/unknown	23 (8.7)	16 (11.2)	7 (5.8)	
Lepidic	11 (4.2)	8 (5.6)	3 (2.5)	
Micropapillary	6 (2.3)	2 (1.4)	4 (3.3)	
Minimally invasive	2 (0.8)	2 (1.4)	0 (0.0)	
Papillary	12 (4.5)	7 (4.9)	5 (4.1)	
Solid	18 (6.8)	4 (2.8)	14 (11.6)	
Grade				**0.024 (0.011)**
Well	18 (6.7)	13 (8.9)	5 (4.1)	
Moderate	201 (75.3)	115 (78.8)	86 (71.1)	
Poor	31 (11.6)	10 (6.8)	21 (17.4)	
Unknown	17 (6.4)	8 (5.5)	9 (7.4)	
Staging (AJCC7)				0.110
IA	104 (39.0)	65 (44.5)	39 (32.2)	
IB	71 (26.6)	38 (26.0)	33 (27.3)	
IIA	29 (10.9)	14 (9.6)	15 (12.4)	
IIB	12 (4.5)	8 (5.5)	4 (3.3)	
IIIA	51 (19.1)	21 (14.4)	30 (24.8)	
Lymphovascular invasion				**0.021 (0.006)**
No	156 (58.4)	95 (65.1)	61 (50.4)	
Yes	89 (33.3)	38 (26.0)	51 (42.1)	
Unknown	22 (8.2)	13 (8.9)	9 (7.4)	
EGFR mutation				0.906
Ex19del	121 (45.3)	65 (44.5)	56 (46.3)	
L858R	112 (41.9)	63 (43.2)	49 (40.5)	
Others	34 (12.7)	18 (12.3)	16 (13.2)	

P-value estimated using chi-squared test unless otherwise stated.
P-value within parenthesis excludes the category 'Unknown/NA'.
#P-value estimated using Mann–Whitney U test.
^P-value estimated using Fisher's exact test.

Table 2
2-year DFS and 5-year OS by PD-L1 score for *EGFR*-M+ and *EGFR*-wt.

		2-year DFS (95% CI)	HR (95% CI)	p value	5-year OS (95% CI)	HR (95% CI)	p value
EGFR-M+	PD-L1 <1% (n = 146)	78.1% (70.3%–84.1%)	1		59.5% (48.7%–68.7%)	1	
	PD-L1 ≥1% (n = 121)	67.6% (58.4%–75.1%)	1.67 (1.15–2.41)	**0.007**	42.8% (32.8%–52.4%)	2.90 (1.52–5.54)	**0.001**
EGFR-wt	PD-L1 <1% (n = 146)	77.2% (66.6%–84.8%)	1		76.3% (62.8%–85.5%)	1	
	PD-L1 ≥1% (n = 121)	58.2% (47.8%–67.2%)	1.80 (1.15–2.79)	**0.009**	60.4% (47.4%–71.2%)	1.36 (0.79–2.36)	0.269

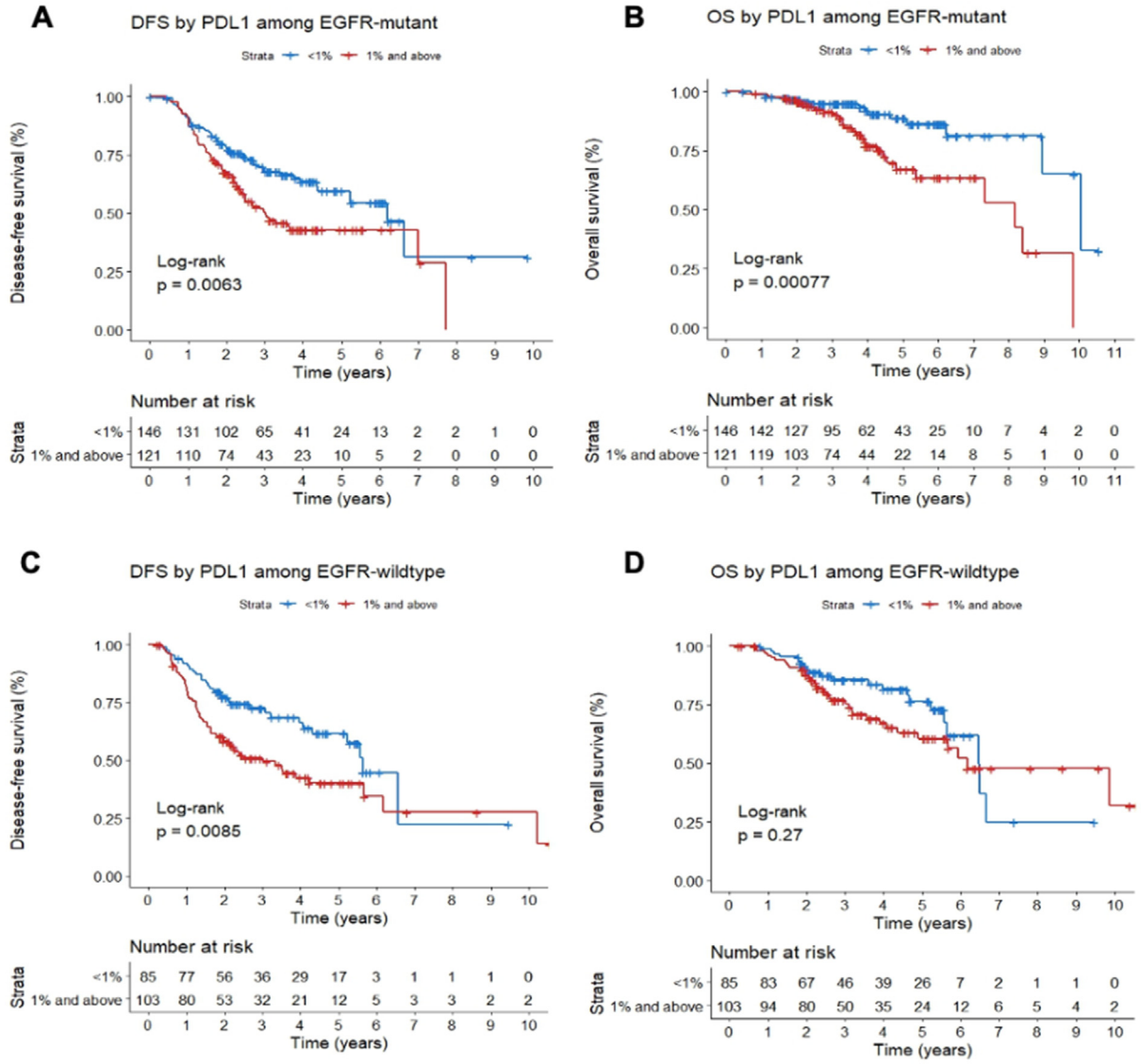

Fig. 1. DFS and OS by PD-L1 score and EGFR status. DFS, disease-free survival; EGFR, epidermal growth factor receptor.

p53 activity, in relation to PD-L1 status. We observed mutual exclusivity between *TP53* mutation and *MDM2* or *MDM4* amplification (Fig. 2). *TP53* mutations were associated with a trend towards higher incidence of disease relapse than *TP53*-wildtype at 45.0% (9/20) versus 32.8% (20/61), although the difference was not statistically significant ($p = 0.42$). We then examined the impact of various *TP53* mutation subtypes, classified into missense, nonsense and frameshift deletion mutations. TP53 missense mutations were more common among PD-L1 $\geq$1% tumours than PD-L1 <1% tumours at 27.8% (10/36) versus 11.1% (5/45) ($p = 0.08$), as shown in Fig. 2.

Tumour mutational burden, defined as total clonal non-synonymous mutations per megabase of genome sequenced, and GEP scores were also computed, showing no significant difference between PD-L1 <1% and PD-L1 $\geq$1% (Fig. S3).

4. Discussion

Our findings confirm that PD-L1 $\geq$1% is an independent predictor of worse OS among early-stage EGFR-mutated NSCLC, consistent with what has been reported [8,9]. A smaller Japanese study of 280 patients found PD-L1 $\geq$50% was associated with a significantly higher risk of post-operative recurrence and was more common among *EGFR*-wildtype and Stage II-IIIA [15], in keeping with our findings. The differential impact of PD-L1 score on long-term outcomes for resected *EGFR*-mutated NSCLC contrasted against *EGFR*-wildtype NSCLC has not been well described previously. We demonstrated that higher PD-L1 score is associated with inferior outcomes among resected NSCLC regardless of EGFR status, although this did not reach statistical significance for OS among *EGFR*-wildtype and the small number of PD-L1 $\geq$50% *EGFR*-mutated NSCLC limits

Table 3
Univariable and multivariable analysis of DFS for *EGFR*-M+.

DFS (Events/Pts = 112/264)	Univariable		Multivariable	
	HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
PD-L1 TPS				
<1%	1		1	
≥1%	1.72 (1.18–2.50)	0.005	1.24 (0.81–1.90)	0.328
Age at diagnosis				
<65 years old	1		1	
≥65 years old	0.60 (0.41–0.88)	0.008	0.70 (0.47–1.06)	0.096
Smoking Status				
Never smoker	1		1	
Current or former smoker	1.83 (1.22–2.77)	0.004	1.33 (0.85–2.10)	0.213
Staging (AJCC7)				
IA	1		1	
IB	1.46 (0.84–2.54)	0.176	1.15 (0.64–2.07)	0.646
IIA	2.56 (1.38–4.77)	0.003	1.28 (0.56–2.91)	0.553
IIB	3.37 (1.47–7.75)	0.004	3.67 (1.45–9.32)	**0.006**
IIIA	4.86 (2.94–8.01)	<0.001	2.83 (1.41–5.67)	**0.003**
Lymphovascular invasion				
No	1		1	
Yes	2.69 (1.80–4.02)	<0.001	1.82 (1.13–2.94)	**0.014**
Unknown	3.02 (1.65–5.52)	<0.001	3.92 (1.68–9.11)	0.002
Grade				
Well/Moderate	1		1	
Poor	2.48 (1.50–4.10)	<0.001	1.29 (0.55–3.08)	0.558
Unknown	2.33 (1.27–4.29)	0.007	1.97 (0.95–4.12)	0.07
Adenocarcinoma Subtype				
Minimally invasive/lepidic	1		1	
Acinar/papillary	1.49 (0.55–4.08)	0.436	0.87 (0.30–2.55)	0.797
Solid/micropapillary	3.83 (1.28–11.41)	0.016	1.11 (0.27–4.50)	0.881
Others	2.68 (0.88–8.19)	0.084	1.18 (0.33–4.24)	0.8
Adjuvant therapy				
No	1		1	
Gefitinib	1.78 (0.85–3.75)	0.127	0.89 (0.39–2.04)	0.777
Platinum doublet chemotherapy	2.54 (1.71–3.79)	<0.001	0.84 (0.47–1.48)	0.541
Single agent chemotherapy	8.71 (1.19–63.92)	0.033	1.19 (0.13–11.40)	0.878
Resection margins				
R0	1		1	
R1/R2	2.40 (1.12–5.18)	0.025	2.08 (0.85–5.12)	0.109
Unknown	1.10 (0.48–2.54)	0.821	0.23 (0.07–0.75)	0.015

interpretation. PD-L1 ≥1% was significantly associated with inferior DFS among both EGFR-mutated and EGFR-wildtype NSCLC on univariable analysis, but strikingly emerged as the only feature apart from higher stage that was associated with inferior OS in *EGFR*-mutated NSCLC on multivariable analysis.

The clinical significance of PD-L1 score among oncogene-driven NSCLC remains poorly defined. ICI have limited efficacy in the metastatic setting for *EGFR*-mutated NSCLC regardless of PD-L1 score [16,17]. In the setting of resectable NSCLC, subset analysis from IMpower010 and PEARLS/KEYNOTE-091 suggest that patients with *EGFR* mutations could potentially benefit from adjuvant ICI, particularly for PD-L1 ≥1% [2,3]. While these results should be interpreted with caution given the relatively small patient numbers, our data supports evaluating PD-L1 score as risk stratification factor in prospective adjuvant studies among resected EGFR-mutated NSCLC.

High PD-L1 expression has been shown to predict for poor response and de novo resistance to EGFR tyrosine kinase inhibitors (TKI) including osimertinib in the metastatic setting [18–20]. Proposed mechanisms include activation of the JAK-STAT pathway as well as high *MUC16* mutation frequency observed among PD-L1 ≥50% tumours [21]. In addition, CD8 and PD-L1 dual positivity were detected in 46.7% (7/15) *EGFR*-mutated tumours with *de novo* TKI resistance, suggesting that the tumour microenvironment could be influenced by PD-L1 expression and consequently affect TKI sensitivity [18]. In view of these considerations, mature survival data from ADAURA analysed by PD-L1 status will be highly relevant [1]. If high PD-L1 expression is found to predict for worse survival outcomes with adjuvant osimertinib, future trials could explore the role of novel therapeutic strategies in this subgroup.

PD-L1 expression has been reported to be associated with *TP53* mutations in NSCLC [22,23]. *TP53*

Table 4
Univariable and multivariable analysis of OS for *EGFR*-M+.

OS (Events/Pts = 43/267)	Univariable		Multivariable	
	HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
PDL1 TPS				
<1%	1		1	
≥1%	2.90 (1.52–5.54)	0.001	2.18 (1.04–4.54)	**0.038**
Age at diagnosis				
<65 years old	1		1	
≥65 years old	1.17 (0.62–2.20)	0.625	1.78 (0.85–3.73)	0.126
Gender				
Female	1		1	
Male	1.91 (1.04–3.51)	0.038	1.70 (0.87–3.31)	0.121
Staging (AJCC7)				
IA	1		1	
IB	1.61 (0.60–4.31)	0.339	1.42 (0.51–3.92)	0.501
IIA	2.64 (0.95–7.32)	0.062	3.02 (0.92–9.92)	0.069
IIB	4.24 (1.12–16.05)	0.033	7.78 (1.72–35.27)	**0.008**
IIIA	3.82 (1.64–8.94)	0.002	4.45 (1.44–13.80)	**0.01**
Lymphovascular invasion				
No	1		1	
Yes	2.81 (1.43–5.49)	0.003	1.78 (0.83–3.84)	0.14
Unknown	2.48 (0.94–6.55)	0.066	2.60 (0.80–8.46)	0.113
Adjuvant therapy				
No	1		1	
Gefitinib	1.10 (0.26–4.75)	0.895	0.57 (0.12–2.79)	0.489
Platinum doublet chemotherapy	1.50 (0.78–2.89)	0.226	0.49 (0.20–1.17)	0.109
Single agent chemotherapy	5.95 (0.80–44.38)	0.082	4.24 (0.20–88.28)	0.351
Resection margins				
R0	1		1	
R1/R2	1.09 (0.26–4.53)	0.908	0.44 (0.05–3.62)	0.448
Unknown	0.94 (0.22–3.92)	0.929	0.63 (0.11–3.66)	0.61

mutations are a known poor prognostic marker in NSCLC but the significance of the various subtypes is less established. *TP53* missense mutations were found to be associated with increased PD-L1 expression and predictive of benefit with ICI, whereas nonsense mutations were more similar to *TP53*-wildtype tumours [24]. Our findings support *TP53* mutations as being associated with increased relapse risk and missense subtype mutations as being positively correlated with PD-L1 expression. In addition, we observed higher rates of *RBM10* mutations among PD-L1 <1% tumours, with majority non-overlapping with *TP53* mutations.

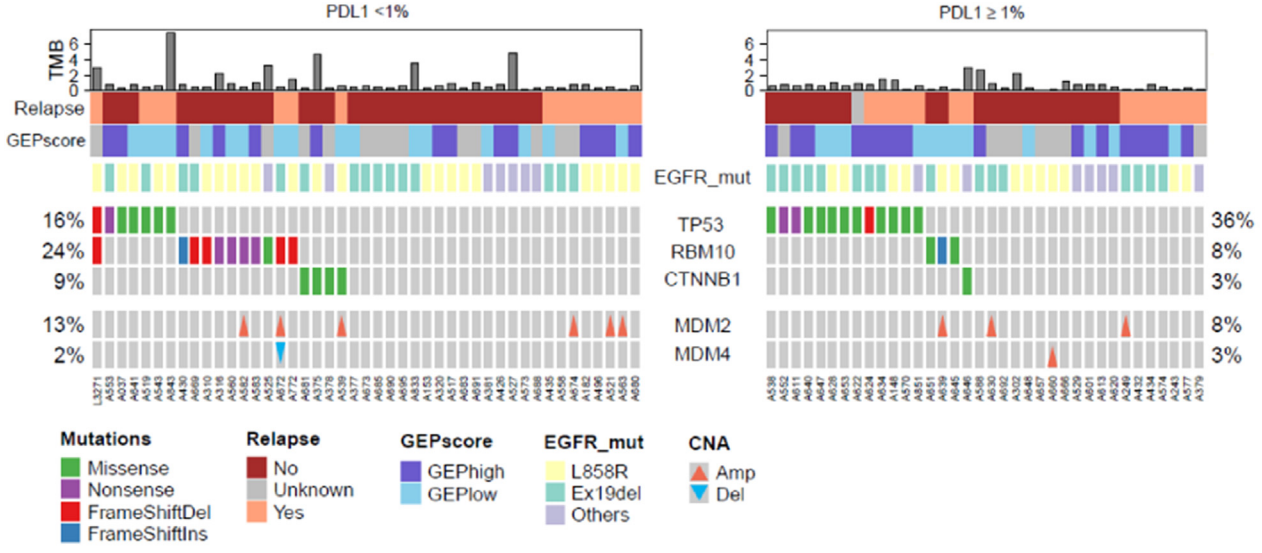

Fig. 2. Oncoprint of mutations and copy number alterations comparing PD-L1 <1% and ≥1% among *EGFR*-M+. EGFR, epidermal growth factor receptor.

RBM10 regulates the p53-MDM2-pathway by reducing degradation of p53 via MDM2 binding [25] and the association between *RBM10* mutations with lower PD-L1 scores among *EGFR*-mutated NSCLC has been previously reported [26]. One possible explanation for this observation could be *RBM10* mutations prevent inactivation of p53, which consequently reduces PD-L1 expression, although functional studies are needed to confirm this.

Our study had several limitations. A single-centre study comprising predominantly Asian patients could limit the generalisability of the data. Being retrospective in nature, the sample size was also limited as PD-L1 and *EGFR* were not routinely tested in early-stage tumours until recent years. The heterogeneous assays used for *EGFR* testing could have also affected the sensitivity of detecting uncommon and compound mutations. Genomic and transcriptomic data were only available for a small subset of patients, although our findings highlight the potential for molecular risk stratification to complement clinical practice.

5. Conclusion

In conclusion, our study confirms PD-L1 score $\geq$1% as an independent predictor of worse OS among early-stage EGFR-mutated NSCLC. Our findings underscore the importance of personalised risk-stratified adjuvant strategies, which can be enhanced with the integration of molecular features. This is especially relevant given the increasing availability of novel adjuvant therapies with uncertain risk-benefit ratios for each patient subgroup in the absence of long-term survival data. Lastly, the clinical significance of PD-L1 score in resectable *EGFR*-mutated NSCLC warrants further study and PD-L1 score as a risk stratification factor should be evaluated in prospective adjuvant studies among EGFR-mutated NSCLC.

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Author contributions section

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Anders J. Skanderup: Formal analysis; Funding acquisition; Visualisation; Writing − review & editing.

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Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Dr. Saw reported receiving personal fees from Pfizer, Bayer, AstraZeneca and MSD outside the submitted work. Dr A. Tan reported receiving personal fees from Amgen and Pfizer outside the submitted work. Dr Lai reported receiving personal fees from Amgen and grants from Merck, Astra Zeneca, Pfizer, Bristol Myers Squibb, and Roche outside the submitted work. Dr D.W.T. Lim reported receiving grants from Bristol Myers Squibb and Boehringer-Ingelheim and personal fees from Merck, Roche, Pfizer, Taiho, and

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Appendix A. Supplementary data

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