ImmunoDriver-2: CD8 T cell and PD-L1 levels associate with first-line (1L) overall survival (OS) in immune checkpoint inhibition (ICI)-treated non-small cell lung cancer (NSCLC)

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INTRODUCTION

- Immunogenome characterization in early (eNSCLC; stage I-III) and metastatic (mNSCLC; stage IV) NSCLC is needed to improve ICI efficacy.
- We evaluated how CD8 T cell (CD8T) and PD-L1 proportions associate with real-world OS (rwOS) and driver alterations (dAlts) in pts with NSCLC treated with first line (1L) ICI ± chemotherapy (CT).

METHODS

De-identified NSCLC adenocarcinoma samples (eNSCLC n=3,159; mNSCLC n=2,184) were sequenced using Tempus xT DNA and xR RNA assays. mNSCLC samples were collected pre-1L therapy.

dAlts were classified as EGFR classic (L858R, exon 19 del), EGFR non-classic (S768I, L861Q, G719X, exon 20 insertion), KRAS G12C/non-G12C, or other (BRAF V600E, ERBB2, NTRK1-3, ALK, ROS1, RET fusions, METex14 skipping).

Immune cell proportions were estimated by quanTIseq from RNA-seq; CD8T [High/Low] assigned by cohort median. PD-L1 assessed by IHC. Analyses stratified by dAlts and stage; significance ($p < 0.05$) by chi-squared or Kruskal-Wallis test.

rwOS defined as time from 1L start to death (2-year follow-up). Median rwOS and hazard ratios estimated via Kaplan-Meier and Cox proportional hazards models.

Table 1. OS cohort characteristics

Characteristic	Overall N = 3,325[1]	Low, <1 N = 266	Low, 1-49 N = 209	Low, 50-100 N = 143	High, <1 N = 597	High, 1-49 N = 239	High, 50-100 N = 251	p-value[2]
Age at treatment start								0.001
Median (Q1, Q3)	67 (61, 74)	65 (59, 72)	68 (62, 75)	65 (61, 71)	66 (60, 74)	68 (62, 75)	68 (62, 76)	
Min, Max	27, 88	27, 86	35, 86	27, 88	29, 87	36, 86	38, 88	
Sex, n (%)								0.058
Male	696 (53%)	145 (55%)	127 (61%)	89 (55%)	93 (47%)	116 (49%)	126 (50%)	
Female	629 (47%)	121 (45%)	82 (39%)	74 (45%)	104 (53%)	123 (51%)	125 (50%)	
Histology within 30 days of sample collection, n (%)								0.037
Adenocarcinoma	1,274 (96%)	251 (94%)	202 (97%)	162 (99%)	187 (95%)	226 (95%)	246 (98%)	
Other adenocarcinoma subtype[3]	51 (3.8%)	15 (5.6%)	7 (3.3%)	1 (0.6%)	10 (5.1%)	13 (5.4%)	5 (2.0%)	
TMB category, n (%)								0.075
Low (<10 mut/Mb)	913 (69%)	183 (69%)	154 (74%)	106 (65%)	147 (75%)	164 (69%)	159 (63%)	
High (>=10 mut/Mb)	412 (31%)	83 (31%)	55 (26%)	57 (35%)	50 (25%)	75 (31%)	92 (37%)	
Treatment category, n (%)								<0.001
Chemo+IO	1,011 (76%)	252 (95%)	177 (85%)	98 (60%)	182 (92%)	201 (84%)	101 (40%)	
IO	314 (24%)	14 (5.3%)	32 (15%)	65 (40%)	15 (7.6%)	38 (16%)	150 (60%)	
Driver mutation status, n (%)								<0.001
Oncogene addicted	742 (56%)	143 (54%)	124 (59%)	112 (69%)	87 (44%)	123 (51%)	153 (61%)	
No driver mutation	583 (44%)	123 (46%)	85 (41%)	51 (31%)	110 (56%)	116 (49%)	98 (39%)	
Smoking status, n (%)								0.6
Ex-smoker	491 (37%)	98 (37%)	75 (36%)	63 (39%)	74 (38%)	77 (32%)	104 (41%)	
Current-smoker	405 (31%)	82 (31%)	60 (29%)	44 (27%)	62 (31%)	83 (35%)	74 (29%)	
Unknown	321 (24%)	62 (23%)	56 (27%)	39 (24%)	41 (21%)	62 (26%)	61 (24%)	
Never-smoker	108 (8.2%)	24 (9.0%)	18 (8.6%)	17 (10%)	20 (10%)	17 (7.1%)	12 (4.8%)	

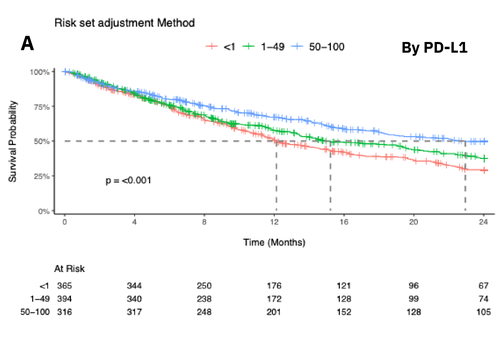
1 n (%)
2 Kruskal-Wallis rank sum test; Pearson's Chi-squared test; Fisher's Exact Test for Count Data with simulated p-value (based on 2000 replicates)
3 Mucinous adenocarcinoma, Acinar cell carcinoma, Papillary adenocarcinoma, Solid carcinoma, Micropapillary adenocarcinoma, Signet-ring cell carcinoma, Adenocarcinoma with neuroendocrine differentiation, Bronchiolo-alveolar adenocarcinoma, Hepatoid adenocarcinoma, Lepidic Predominant Adenocarcinoma

SUMMARY

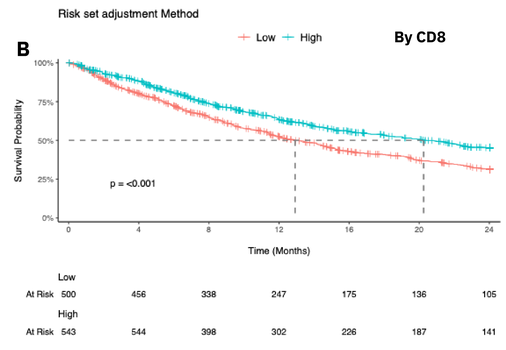
- OS following ICI + CT or ICI alone in mNSCLC was greatest when both CD8T and PD-L1 were high.
- CD8T/PD-L1 immunophenotype analysis indicates these findings may apply across stage and dAlt status.

RESULTS

Figure 1A & B. rwOS in patients treated with 1L ICI ± CT by PDL1 and CD8 alone



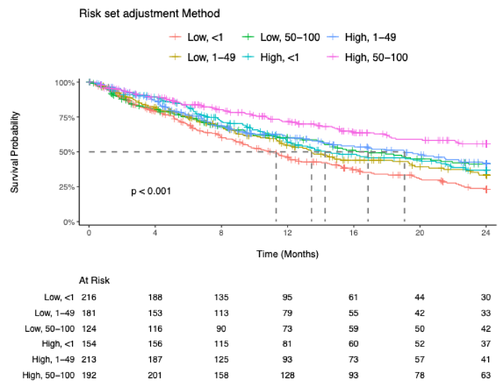
PD-L1 TPS Category	N	50th Percentile (months)	HR	95% CI	p-value
<1	463	12.1 (10.9, 14.4)	-	-	
1-49	448	15.2 (13.2, 19.7)	0.78	0.65, 0.94	0.009
50-100	414	22.9 (18.3, -)	0.59	0.47, 0.73	<0.001



CD8 Category	N	50th Percentile (months)	HR	95% CI	p-value
Low	638	12.9 (11.4, 14.7)	-	-	
High	687	20.2 (17.1, 23.8)	0.65	0.56, 0.77	<0.001

Figure 1. After 1L ICI ± CT, PD-L1 and CD8T were associated with significantly improved mOS in mNSCLC. HRs were adjusted for age at treatment start, sex, driver mutation status, treatment category, TMB category, and smoking status.

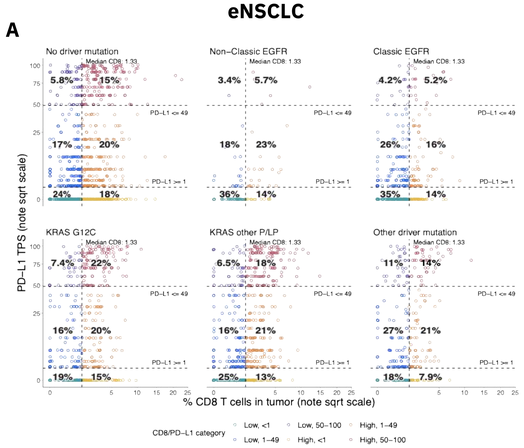
Figure 2. rwOS in patients treated with 1L ICI ± CT in PDL1 subgroups stratified by CD8 status



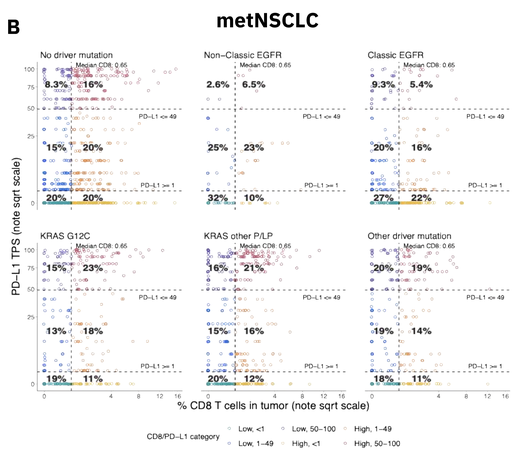
CD8, PDL1 Status	N	50th Percentile (months)	HR	95% CI	p-value
Low, <1	266	11.3 (9.2, 12.5)		Reference	
High, <1	197	14.3 (12.0, 21.3)	0.64	0.50, 0.83	<0.001
Low, 1-49	209	13.4 (11.4, 19.3)		Reference	
High, 1-49	239	19.1 (13.9, 23.8)	0.79	0.60, 1.04	0.093
Low, 50-100	163	16.9 (12.9 22.9)		Reference	
High, 50-100	251	- (22.1, -)	0.58	0.42, 0.80	<0.001

Figure 2. After 1L ICI ± CT, CD8T further stratified OS within PD-L1 groups (<1%, 1-49%, and ≥50%). HRs were adjusted for age at treatment start, sex, driver mutation status, treatment category, TMB category, and smoking status.

Figure 3 A & B. CD8/PDL1 Landscape in early & late-stage NSCLC according to dAlt status and respective cohort characteristics



Characteristic	N = 3,159
Age at diagnosis	
Median (Q1, Q3)	69 (63,75)
Min, Max	25, 90
Unknown	28
Sex, n (%)	
Female	1,831 (58%)
Male	1,328 (42%)
Race, n (%)	
White	1,749 (55%)
Unknown	974 (31%)
Black or African American	231 (7.3%)
Other Race	136 (4.3%)
Asian	69 (2.2%)
Ethnicity, n (%)	
Not Hispanic or Latino	1,457 (95%)
Hispanic or Latino	82 (5.3%)
Unknown	1620
Smoking status, n (%)	
Ex-smoker	1,117 (35%)
Unknown	873 (28%)
Current-smoker	685 (22%)
Never-smoker	484 (15%)



Characteristic	N = 2184
Age at diagnosis	
Median (Q1, Q3)	67 (60,74)
Min, Max	22, 89
Unknown	30
Sex, n (%)	
Female	1,133 (52%)
Male	1,051 (48%)
Race, n (%)	
White	1,346 (62%)
Unknown	396 (18%)
Black or African American	185 (8.5%)
Other Race	173 (7.9%)
Asian	84 (3.8%)
Ethnicity, n (%)	
Not Hispanic or Latino	1,124 (92%)
Hispanic or Latino	103 (8.4%)
Unknown	957
Smoking status, n (%)	
Ex-smoker	704 (32%)
Unknown	533 (24%)
Current-smoker	518 (24%)
Never-smoker	429 (20%)

Figure 3. In eNSCLC and mNSCLC, CD8T and PD-L1 were highest in cases with no dAlts and *KRAS* dAlts, and lowest in the c/n*cEGFR* dAlt cohorts ($p<0.001$). CD8T-H/PD-L1≥1 and CD8T-H/PD-L1≥50 were most frequent in the non-dAlt and *KRAS* groups ($p<0.001$), while CD8T-H/PDL1≥50% was least common and CD8T-L/PD-L1<1 was most frequent in the c/n*cEGFR* dAlt cohort ($p<0.001$).

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