Molecular Epidemiology Study of PD-L1 Expression in Patients With *EGFR*-Mutant NSCLC

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Disclosures

- The authors having nothing to disclose
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Background

- The programmed cell death 1 (PD-1) receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control
- We have previously demonstrated that PD-L1 expression, particularly strong positivity, may be associated with decreased survival in patients with non-squamous cell lung cancer (NSCLC), most notably in patients with adenocarcinoma[1]
- However, currently there are limited data on PD-L1 expression in *EGFR*-mutant NSCLC patients who are treated with standard of care[2]

1. Sun J-M et al. *J Clin Oncol.* 2014. 32:5 supplement: Abstract 8066.
2. Shin SJ et al. *Ann Surg Oncol*. 2015. [Epub ahead of print].

Methods

- The relationship between PD-L1 expression and recurrent-free survival (RFS) and overall survival (OS) among *EGFR*-mutant NSCLC patients was evaluated
  - Patients underwent surgery at Samsung Medical Center between April 2006 and January 2014
- PD-L1 expression was measured using an investigational version of the PD-L1 IHC 22C3 pharmDx (Dako North America), an immunohistochemistry (IHC) assay employing the 22C3 antibody
- PD-L1 strong and weak positivity were defined by tumor proportional scores (TPS) of ≥50% and 1–49%, respectively

Statistical Methods

- The prevalence of PD-L1 strong and weak positivity was compared with the use of Chi-square analysis in different subgroups based on age, sex, smoking status, stage, and types of *EGFR* mutations
- OS was defined as time from the date of diagnosis to the date of death or last follow-up
- RFS was defined as time from the date of diagnosis to the date of recurrence, death, or last follow-up
- Kaplan-Meier method, log-rank test, and Cox proportional hazards models were used for survival analysis, with the PD-L1–negative group as the reference group

Statistical Methods (cont)

- Two adjusted Cox proportional hazards models were used
  - Adjusted Cox model 1: adjusted for known prognostic factors age, sex, smoking status, stage, and performance status
  - Adjusted Cox model 2: adjusted for known prognostic factors and chemotherapy, and radiation therapy
- Covariates included in the final models were based on a backward stepwise variable selection process
  - Different types of *EGFR* mutations were also included in the initial models

Patient Characteristics

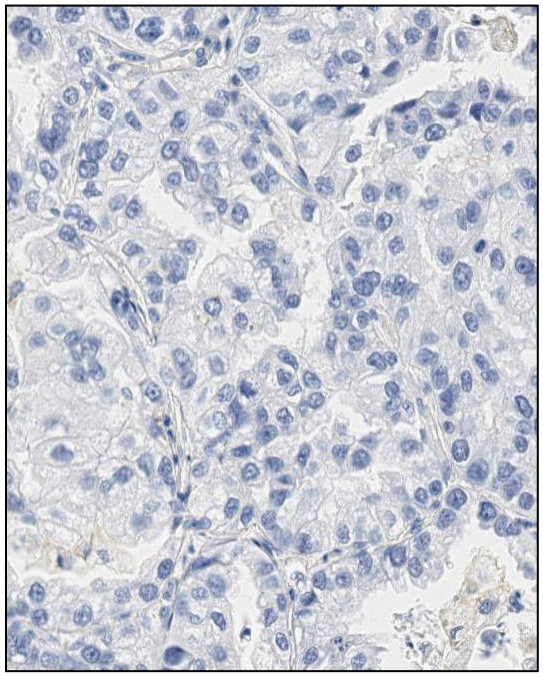
	N = 319*
Age, median (range), y	62.0 (35-84)
Sex, n (%)	
Male	125 (39%)
Female	194 (61%)
Never Smokers	64%
Stage IA Disease	48%
Median Follow-up, y	7
Resection with Curative Intent	94%
Post-surgery Chemotherapy	43%
EGFR-TKI	30%
Radiation	18%

*97% of patients had adenocarcinoma.

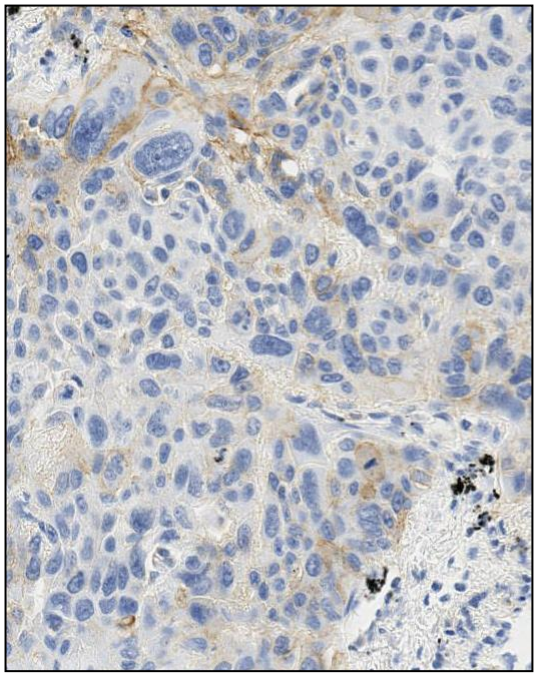
Biomarker Status

- *EGFR* mutation was detected at Samsung Medical Center using direct sequencing or PNA-clamp method of exon 18 through 21 of chromosome 7
  - 171 pts (54%) had mutation in exon 19, including 130 deletion
  - 124 pts (39%) had mutation in exon 21, including 115 L858R mutation
  - 14 pts (4%) had mutation in exon 18
  - 11 pts (3%) had mutation in exon 20
- 305 pts had K-ras tested (exon12/13/61); only 1 had K-ras mutation
- 280 pts had ALK IHC tested, only 2 were ALK (+)
  - 3 pts had ALK FISH tested, all ALK (-)

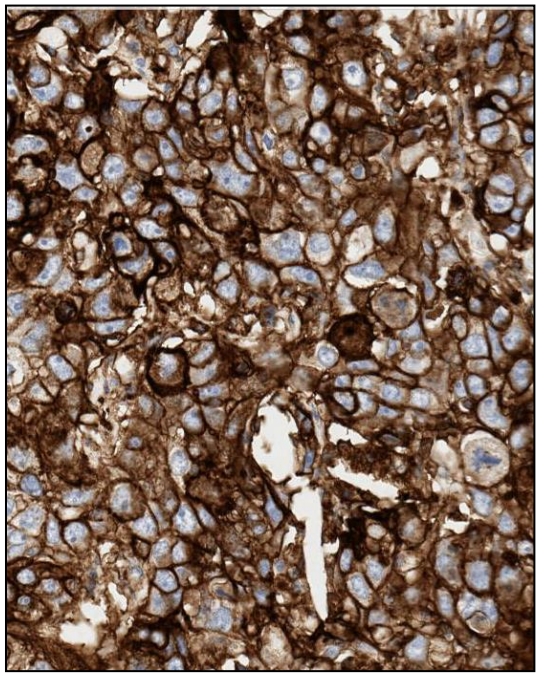
PD-L1 Expression Status



PD-L1 Negative
(TPS = 0)



PD-L1 Weak Positive
(TPS = 15%)



PD-L1 Strong Positive
(TPS = 100%)

All images are at 20x, blue counterstain is hematoxylin, and PD-L1 is identified by brown chromagen.

PD-L1 Status

- A total of 52% of pts were PD-L1 positive, including 8% strong positive and 44% weak positive
- Similar to previous results, higher PD-L1 positivity was observed among male (vs. females), smokers (vs. never smokers), and more advanced pts (stage II/III/IV vs. I)
  - Please note that sample size among stage IV pts is limited

PD-L1 Expression In Patients With EGFR Mutations

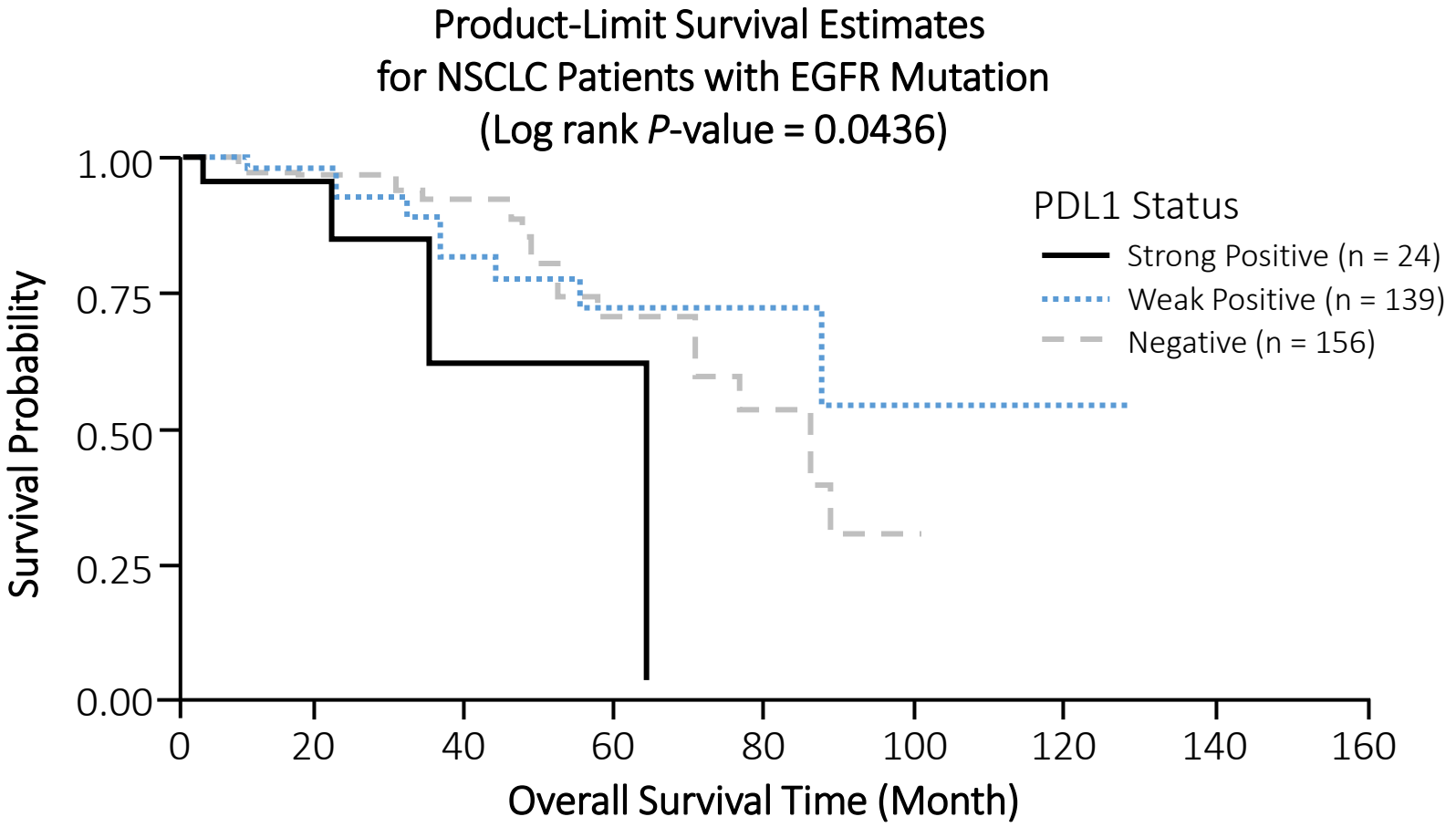
Subgroup	Sample Size	PD-L1 Expression Status			Chi-square
		Strongly Positive	Weakly Positive	Negative	
	N	n (%)	n (%)	n (%)	P-value
Overall	319	24 (7.5)	139 (43.6)	156 (48.9)	
Gender	.				
Male	125	13 (10.4)	64 (51.2)	48 (38.4)	0.008
Female	194	11 (5.7)	75 (38.7)	108 (55.7)	
Smoking Status	.				
Never	205	11 (5.4)	82 (40.0)	112 (54.6)	0.011
Smokers	114	13 (11.4)	57 (50.0)	44 (38.6)	
ECOG	.				
0	202	12 (5.9)	88 (43.6)	102 (50.5)	0.345
1/2/3/4	116	12 (10.3)	50 (43.1)	54 (46.6)	
Stage	.				
IA	154	6 (3.9)	61 (39.6)	87 (56.5)	0.004
IB	47	1 (2.1)	20 (42.6)	26 (55.3)	
II	40	7 (17.5)	20 (50.0)	13 (32.5)	
III	59	9 (15.3)	28 (47.5)	22 (37.3)	
IV	16	1 (6.3)	9 (56.3)	6 (37.5)	

PD-L1 Positivity is Lower in Patients With Exon 19 Deletion and Exon 21 L858R Mutation Compared with Other Mutations*

	PD-L1 Expression Status, n (%)			
EGFR Mutation Types	Strong Positive	Weak Positive	Negative	Total
Exon 19 Deletion	7 (5.4)	60 (46.2)	63 (48.4)	130
Exon 21 L858R	8 (7.0)	37 (32.2)	70 (60.9)	115
Other†	9 (12.2)	42 (56.8)	23 (31.1)	74

**P* = 0.001 by chi-square test.
†Exon 19, non-deletion (n = 41); exon 21, non-L858R mutation (n = 9); exon 18 (n = 14); exon 20 (n = 11); 1 patient had mutations in both exons 18 and 20.

Overall Survival among *EGFR*-Mutant NSCLC Patients

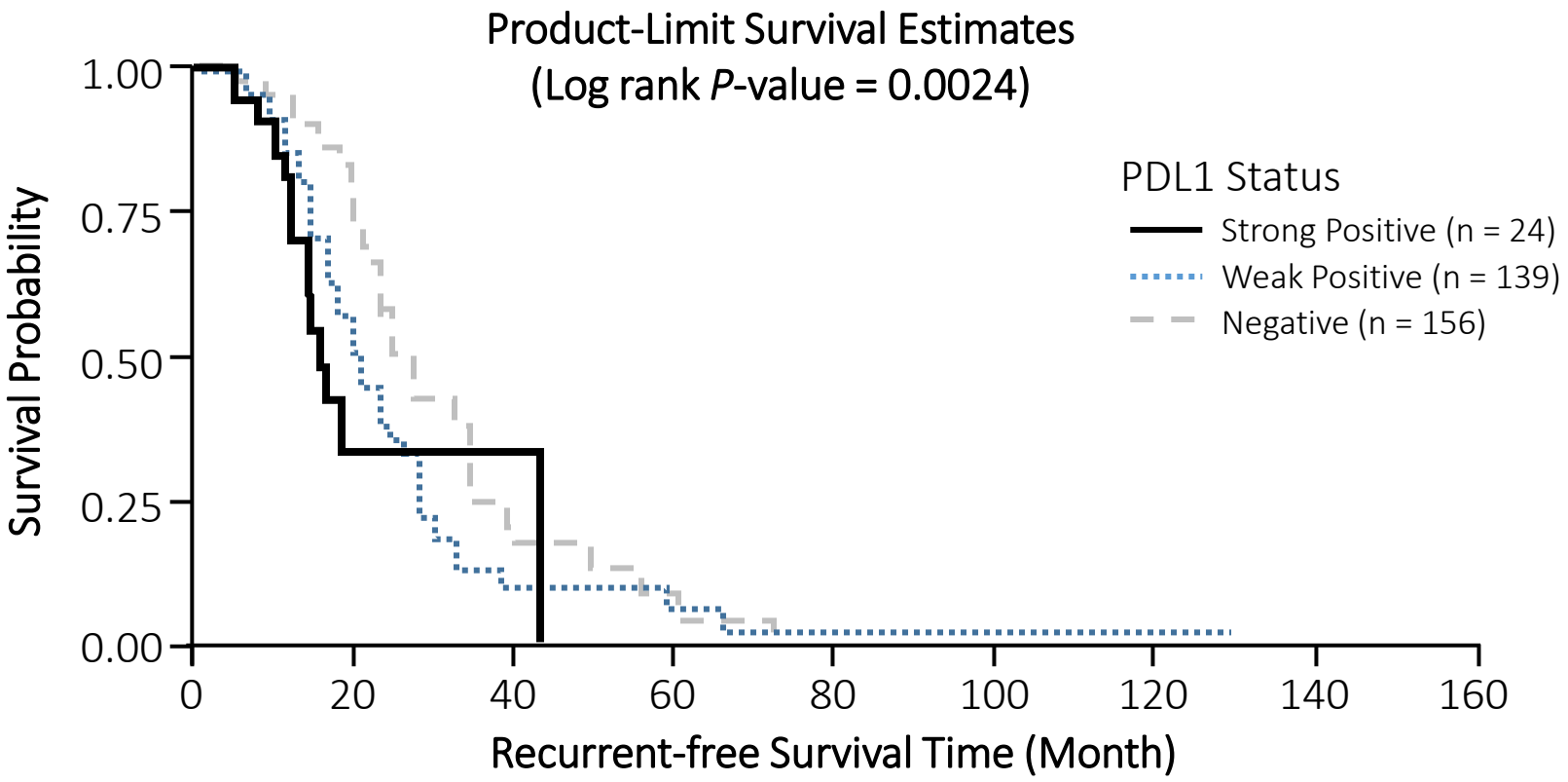


Cox Proportional Hazard Model for OS*

- Crude HR
  - PD-L1 strong positive: 3.46; 95%CI, 1.11-10.69
  - PD-L1 weak positive: 0.89; 95%CI, 0.40-1.96
- Adjusted HR (adjusted model #1, adjusting for baseline prognostic factors)
  - PD-L1 strong positive: 1.08; 95%CI, 0.28-4.23
  - PD-L1 weak positive: 0.84; 95%CI, 0.35-2.00
- Adjusted HR (adjusted model #2, adjusting for baseline prognostic factors and treatment)
  - PD-L1 strong positive: 1.15; 95%CI, 0.28-4.79
  - PD-L1 weak positive: 0.81; 95%CI, 0.33-2.02
- Different type of *EGFR* mutation is not associated with OS

* PD-L1 negative was used as reference.

RFS In Patients with *EGFR*-Mutant NSCLC



Cox Proportional Hazard Model for RFS*

- Crude HR
  - PD-L1 strong positive: 2.38; 95%CI, 1.28-4.42
  - PD-L1 weak positive: 1.78; 95%CI, 1.20-2.64
- Adjusted HR (adjusted model #1)
  - PD-L1 strong positive: 1.57; 95%CI, 0.80-3.06
  - PD-L1 weak positive: 1.54; 95%CI, 1.02-2.31
  - Combined PD-L1 strong and weak positive: 1.54; 95%CI, 1.04-2.29
- Adjusted HR (adjusted model #2)
  - PD-L1 strong positive: 1.70; 95%CI, 0.83-3.47
  - PD-L1 weak positive: 1.68; 95%CI, 1.11-2.56
  - Combined PD-L1 strong and weak positive: 1.69; 95%CI, 1.12-2.54
- Different type of *EGFR* mutation is not associated with PFS

* PD-L1 negative was used as reference.

Summary and Conclusion

- A total of 52% of pts were PD-L1 positive among these predominantly early-stage *EGFR*-mutant NSCLC patients
- Consistent with the previous study, higher prevalence of PD-L1 positivity is observed among males, smokers, and patients with advanced disease
- PD-L1 expression status may be associated with specific *EGFR* mutations
    - The prevalence of PD-L1 positivity is lower in patients with exon 19 deletion and exon 21 L858R mutation compared with other mutations
- Consistent with the previous study, PD-L1 positivity might be associated with less favorable RFS among *EGFR*-mutant NSCLC patients

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