

Integrated Tumor-Resident Memory T Cells and PD-L1 Define Distinct Immune Phenotypes and Prognosis in Resected Non-Small Cell Lung Cancer

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PD-L1

Widely used as a predictive biomarker for immune checkpoint inhibitors, but its prognostic value after resection remains inconsistent.



TRM cells

CD103-positive tumor-resident memory T cells represent tissue-resident, tumor-reactive effector T cells and may reflect active anti-tumor immunity.

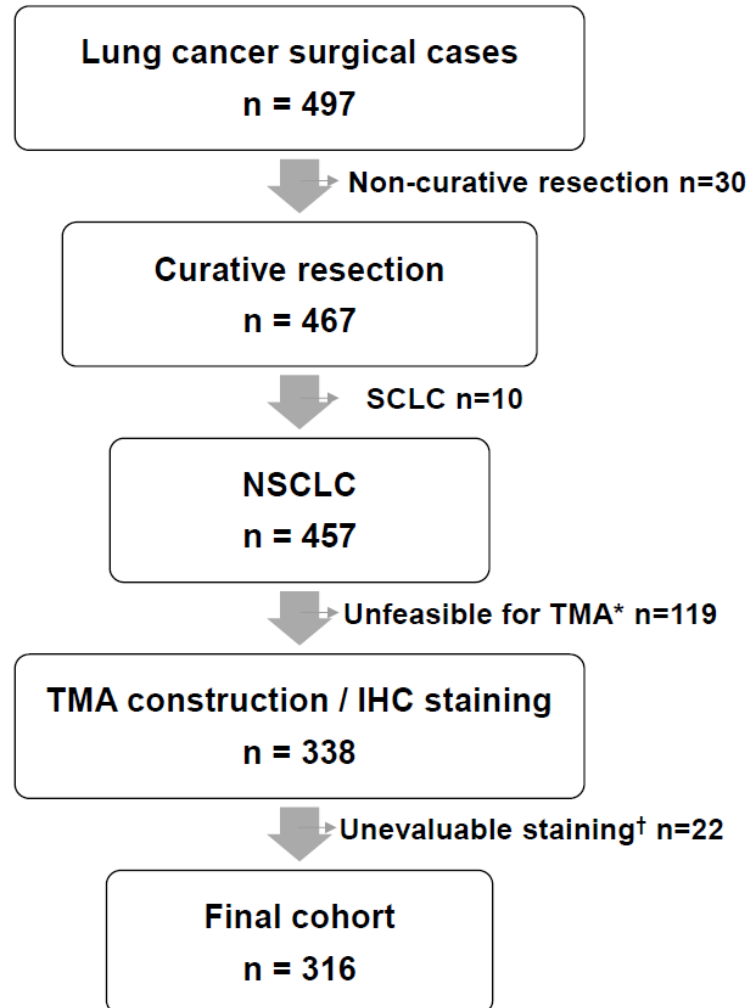


Integrated phenotype

We hypothesized that combining TRM infiltration with PD-L1 expression would better characterize the tumor immune microenvironment and prognosis.

Study question: Does the combination of TRM density and PD-L1 status improve prognostic stratification after curative resection of NSCLC?

Fig. 1: Patient selection



- Curative NSCLC resection: March 2017–February 2020
- CD103 immunohistochemistry on tissue microarrays
- Digital quantification using QuPath (cells/mm²)
- PD-L1 assessed using the 22C3 assay
- Recurrence: Gray's test / competing-risk analysis
- RFS and OS: Kaplan–Meier and Cox models

Median follow-up: 62.5 months

Table 1: Patient characteristics

Variables (n = 316)	n
Age: median (range)	72 (33 - 90)
Sex (Male / Female)	193 / 123
Smoking history (Never / Ever)	69 / 247
ECOG PS (0 / 1 / 2 / 3)	237 / 67 / 10 / 2
Histology (Ad / Sq / Others)	187 / 109 / 20
pStage ^{a)} (0 / I / II / IIIA / IIIB)	5 / 195 / 58 / 48
EGFR mutation ^{b)} (Wild type / Mutant)	106 / 75
PD-L1 expression ^{c)} (<1 / 1-49 / 50-100)	114 / 121 / 67

ECOG, eastern cooperative oncology group; PS, performance status; Ad, Adenocarcinoma; Sq, Squamous cell carcinoma; pStage, pathological stage; EGFR, epidermal growth factor receptor; PD-L1, programmed cell death ligand-1

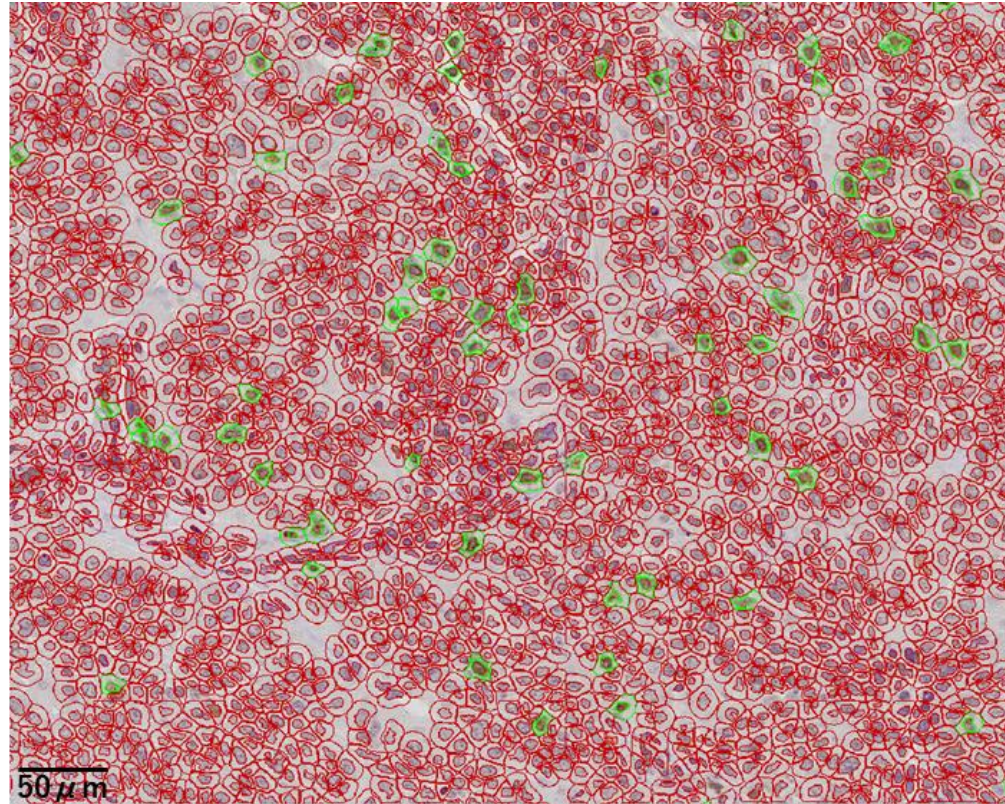
^{a)}, according to the UICC TNM Classification, 8th edition.

^{b)}, EGFR mutation was analyzed exclusively in AD. EGFR mutation was not assessed in 6 patients.

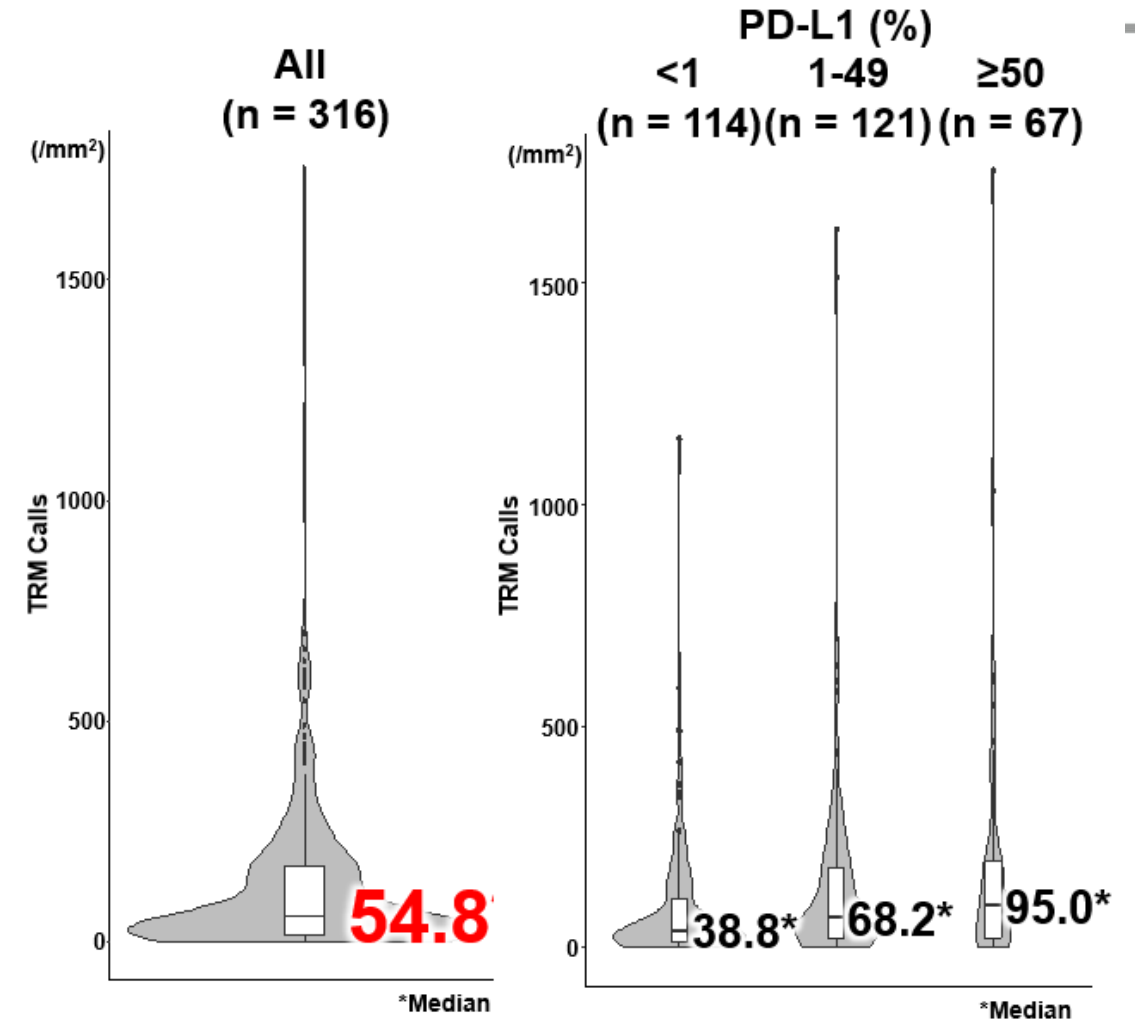
^{c)}, PD-L1 status was not assessed in 14 patients.

Digital Quantification of TRM Cells

Density of TRM cell



CD103-positive cells were digitally detected with QuPath.



Median TRM density = 54.8 cells/mm²
TRM-low <54.8 | TRM-high ≥54.8

Correlation between characteristics and levels of TRM and PD-L1

Variables (n = 316)	TRM-low (n = 158)	TRM-high (n = 158)	p	PD-L1<1% (n = 114)	PD-L1≥1% (n = 188)	p
Age (≤72 / >72)	82 / 76	71 / 87	0.26	61 / 53	89 / 99	0.3
Sex (Male / Female)	92 / 66	101 / 57	0.36	58 / 56	127 / 61	0.0050
Smoking history (Never / Ever)	38 / 120	31 / 127	0.41	29 / 85	38 / 150	0.32
ECOG performance status (0 / 1-3)	112 / 46	125 / 33	0.12	93 / 21	132 / 56	0.030
Histology (Ad / Non-Ad)	103 / 55	84 / 74	0.039	87 / 27	94 / 94	<0.001
pStage (0-I / II-III)	93 / 65	107 / 51	0.13	81 / 33	108 / 80	0.020
EGFR mutation (Wild type / Mutant)	57 / 44	49 / 31	0.55	43 / 43	61 / 32	0.048
PD-L1 expression (<1 / ≥1)	72 / 80	42 / 108	<0.001	-	-	-

TRM-high was associated with non-adenocarcinoma and PD-L1 ≥1%.

PD-L1 ≥1% was associated with male, poorer PS, non-adenocarcinoma, pstage II–III, and EGFR wild-type status.

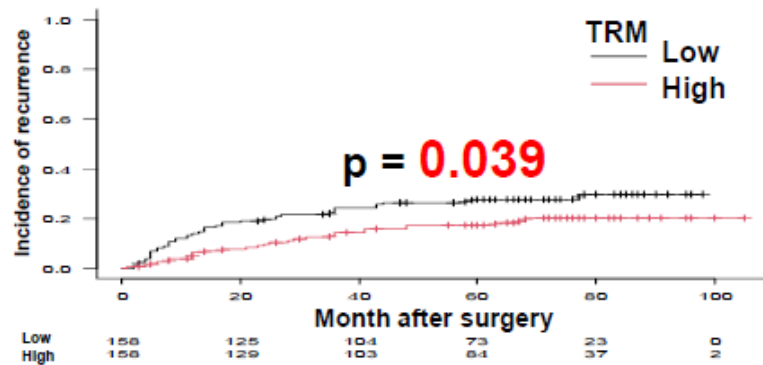
Clinicopathologic associations

TRM-high tumors were significantly associated with: Non-adenocarcinoma histology and PD-L1 ≥1%

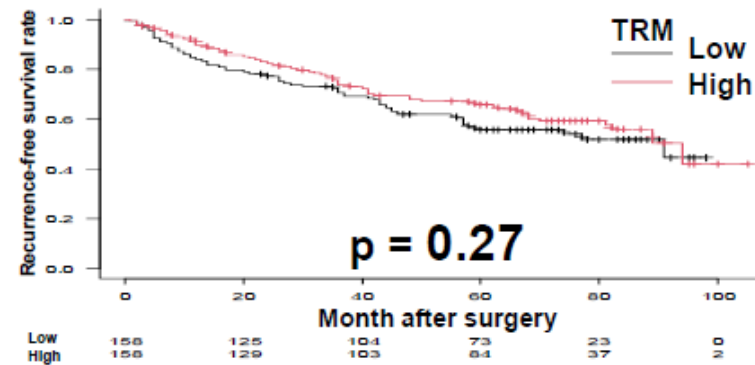
PD-L1 ≥1% was associated with male sex, poorer performance status, non-adenocarcinoma, pathological stage II–III, and EGFR wild-type status.

Prognostic Impact of TRM Alone

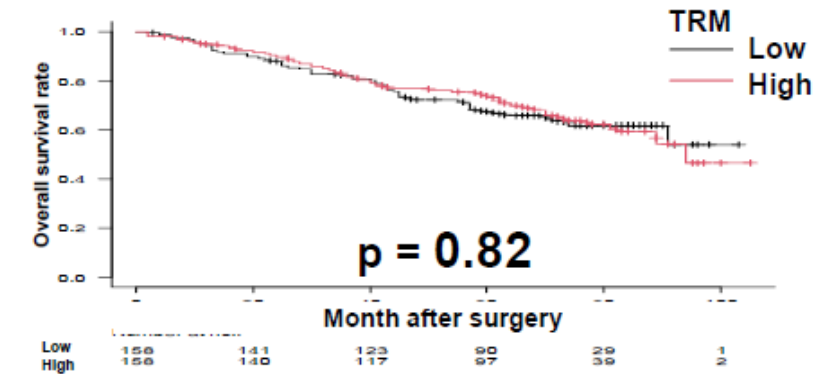
Recurrence



RFS



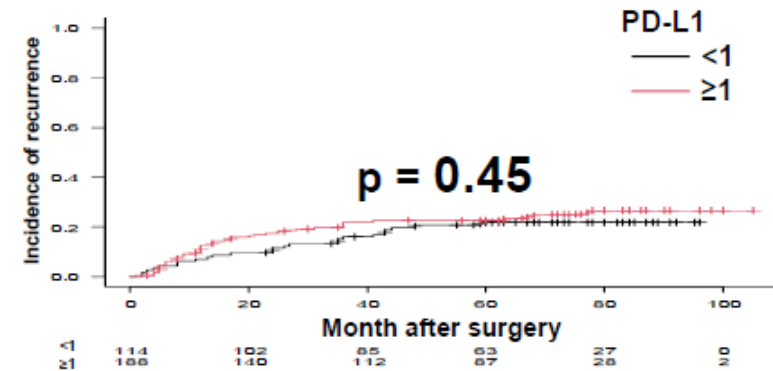
OS



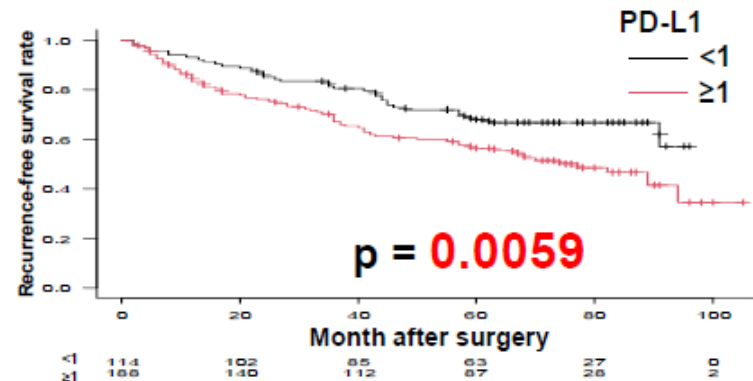
TRM-high was associated with significantly lower recurrence, but not with significant improvement in RFS or OS.

Prognostic Impact of PD-L1 Alone

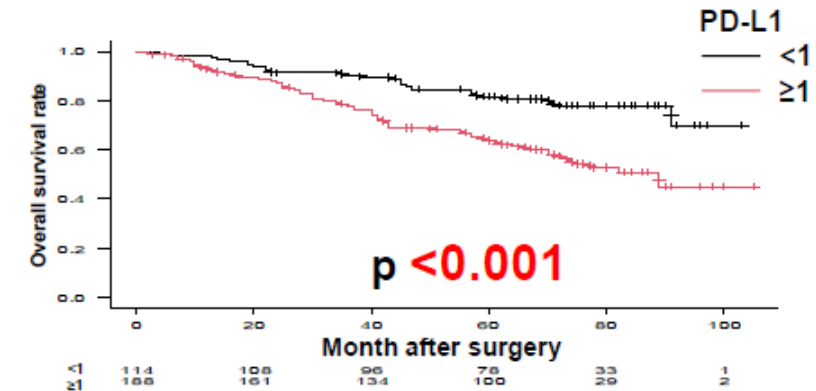
Recurrence



RFS



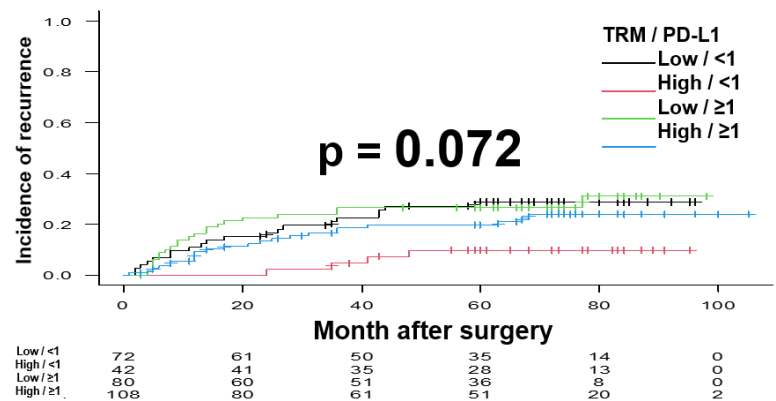
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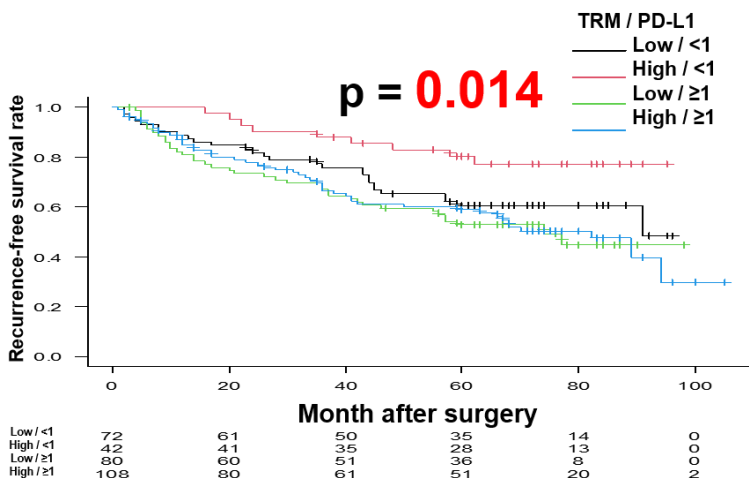
PD-L1 ≥1% was associated with significantly worse RFS and OS, but recurrence did not differ significantly.

Four Immune Phenotypes Defined by TRM and PD-L1

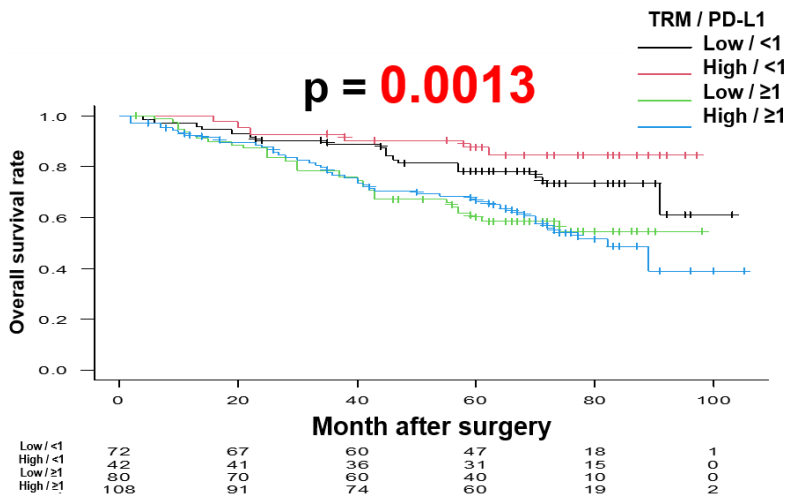
Recurrence



RFS

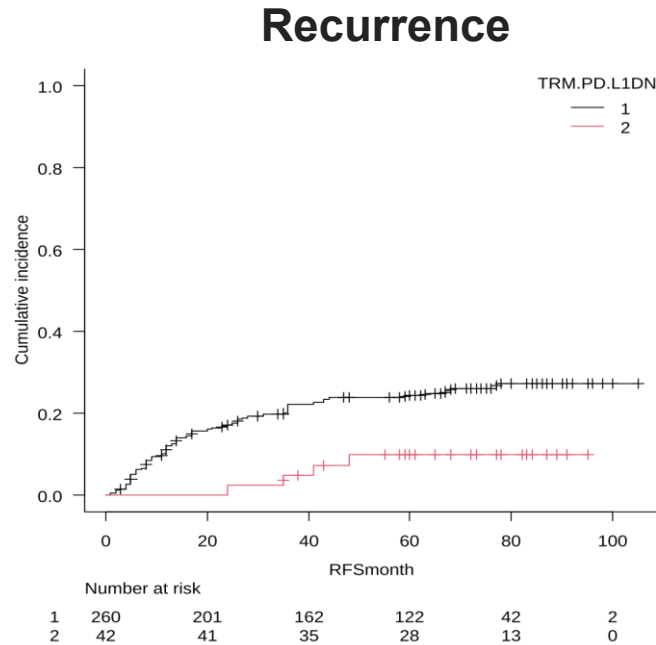


OS



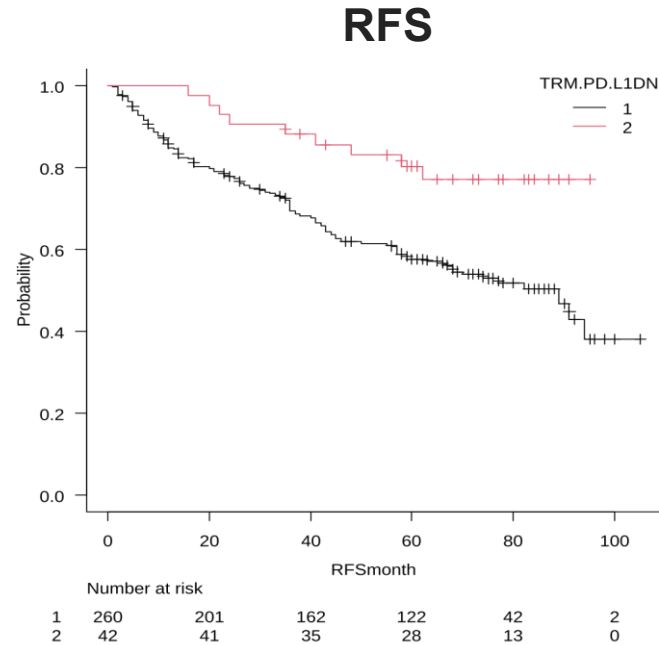
TRM-high / PD-L1 <1% consistently showed the most favorable outcomes.

TRM-High / PD-L1 <1% Identifies a Favorable Prognostic Subgroup



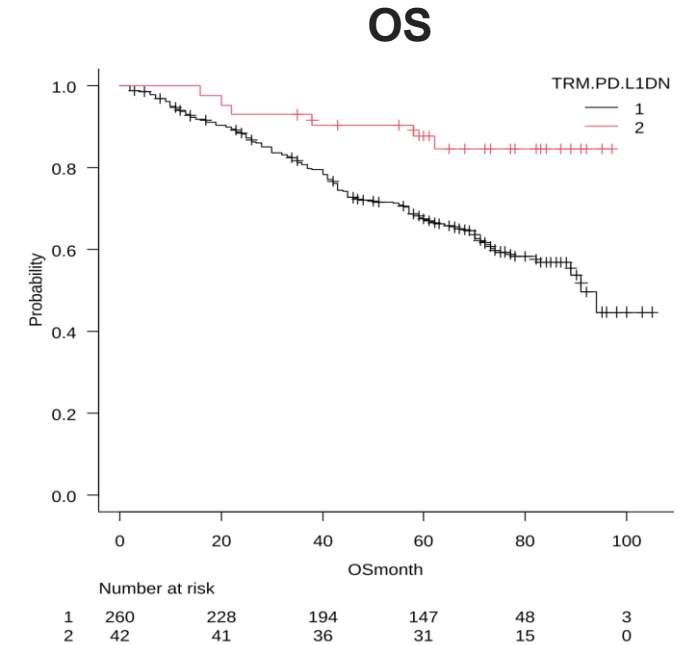
p = 0.017

Adjusted HR 0.36 (95% CI 0.14–0.93), p=0.034



p = 0.0035

Adjusted HR 0.47 (95% CI 0.24–0.93), p=0.031



p = 0.0031

Adjusted HR 0.46 (95% CI 0.20–1.08), p=0.074

Independent association with reduced recurrence and improved RFS after multivariable adjustment.

Univariable and Multivariable analyses about incidence of recurrence

Variables	Incidence of recurrence					
	Univariable			Multivariable ^{a)}		
	HR	95%CI	p	HR	95%CI	p
Age (>72 vs ≤72)	1.41	0.89-2.24	0.15	1.41	0.88-2.28	0.16
Sex (Female vs Male)	1.03	0.65-1.63	0.9			
Smoking history (Ever vs Never)	0.76	0.46-1.26	0.29	0.49	0.30-0.82	0.007
ECOG performance status (1-3 vs 0)	1.56	0.95-2.56	0.08			
Histology (Non-Ad vs Ad)	1.08	0.68-1.72	0.74			
pStage (II-III vs 0-I)	2.72	1.73-4.30	<0.001	3.36	2.06-5.49	<0.001
TRM cell / PD-L1 (High & <1% vs Other)	0.32	0.12-0.87	0.025	0.36	0.14-0.93	0.034

Univariable and Multivariable analyses about RFS

Variables	RFS					
	Univariable			Multivariable ^{a)}		
	HR	95%CI	p	HR	95%CI	p
Age (>72 vs ≤72)	1.97	1.38-2.81	<0.001	1.87	1.30-2.69	<0.001
Sex (Female vs Male)	0.69	0.48-0.99	0.043			
Smoking history (Ever vs Never)	1.60	1.01-2.53	0.044			
ECOG performance status (1-3 vs 0)	1.83	1.27-2.63	0.0013	1.56	1.07-2.27	0.021
Histology (Non-Ad vs Ad)	1.8	1.28-2.53	<0.001			
pStage (II-III vs 0-I)	2.13	1.51-2.99	<0.001	2.05	1.44-2.92	<0.001
TRM cell / PD-L1 (High & <1% vs Other)	0.38	0.19-0.75	0.0051	0.47	0.24-0.93	0.031

Univariable and Multivariable analyses about OS

Variables	OS					
	Univariable			Multivariable ^{a)}		
	HR	95%CI	p	HR	95%CI	p
Age (>72 vs ≤72)	2.40	1.61-3.58	<0.001	2.21	1.47- 3.33	<0.001
Sex (Female vs Male)	0.47	0.30-0.71	<0.001	0.69	0.44-1.09	0.11
Smoking history (Ever vs Never)	2.26	1.29-3.97	0.0043			
ECOG performance status (1-3 vs 0)	2.39	1.62-3.54	<0.001	1.91	1.26-2.88	0.0023
Histology (Non-Ad vs Ad)	2.51	1.72-3.68	<0.001	1.63	1.07-2.48	0.022
pStage (II-III vs 0-I)	1.98	1.36-2.89	<0.001	1.65	1.12-2.45	0.012
TRM cell / PD-L1 (High & <1% vs Other)	0.31	0.14-0.71	0.0053	0.46	0.20-1.08	0.074

TRM and PD-L1 provide complementary prognostic information in resected NSCLC.

- 1** High TRM infiltration was associated with reduced recurrence.
- 2** PD-L1 $\geq 1\%$ was associated with worse RFS and OS.
- 3** TRM-high / PD-L1 $< 1\%$ showed the lowest recurrence and most favorable survival.
- 4** Combined assessment may improve postoperative risk stratification and may have implications for perioperative immunotherapy.

No potential conflicts of interest were disclosed.