



EP11.12:Association of FOXP3-Positive Tumor-Infiltrating Lymphocytes With the Response to Combined PD-1 and CTLA-4 Blockade in NSCLC



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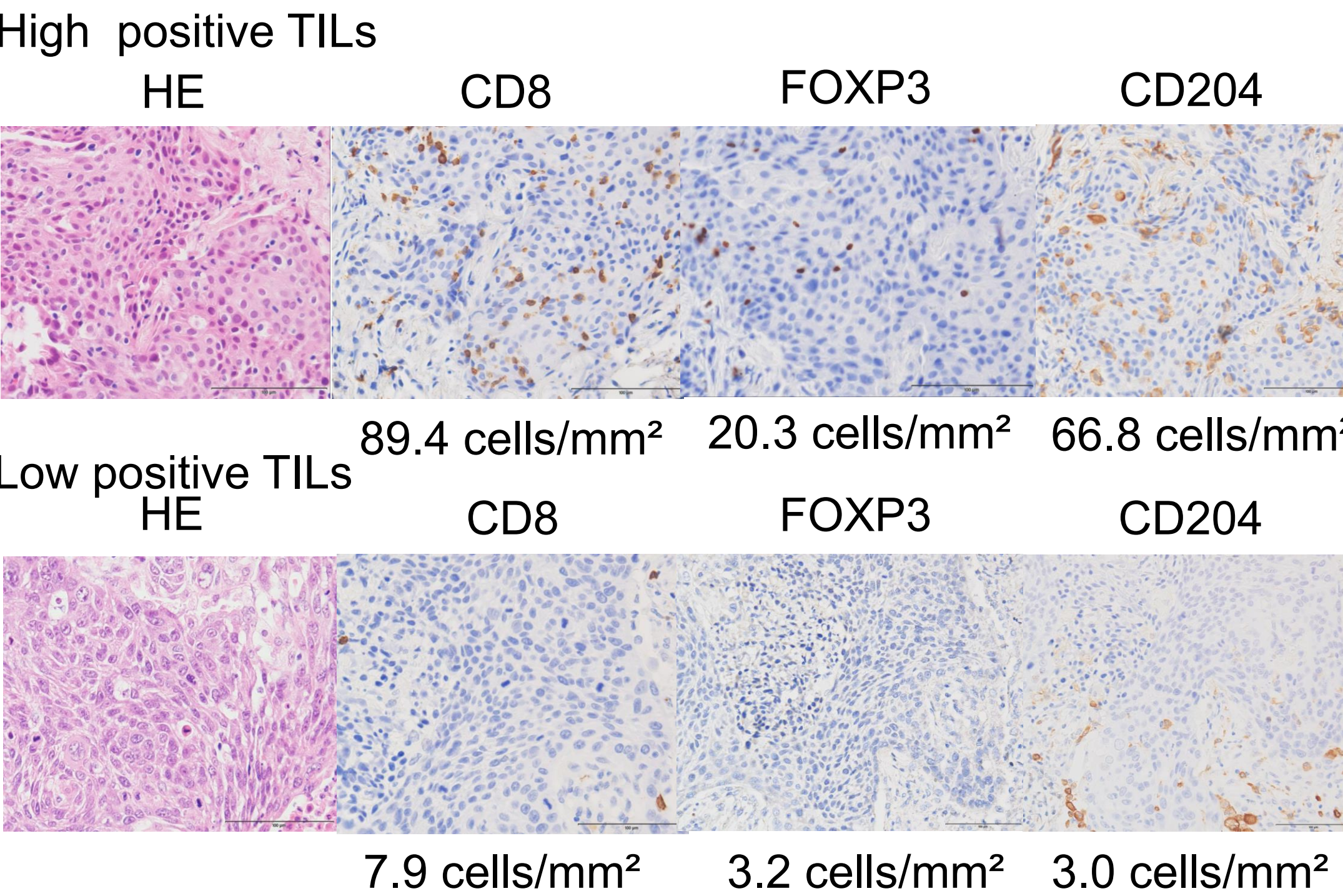
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INTRODUCTION

• Combined anti-PD-1 and anti-CTLA-4 blockade is a standard first-line treatment for patients with advanced NSCLC, but no reliable predictive biomarker has been established(1,2).
• The tumor immune microenvironment (TME) has been reported to be associated with the efficacy of immune checkpoint inhibitors(3-5).
• Anti-CTLA-4 antibodies may act in part through depletion of FOXP3-positive regulatory T cells within the tumor, suggesting that TME composition could be especially relevant to this combination(6-8).
• We therefore evaluated FOXP3-positive, CD8-positive, and CD204-positive tumor-infiltrating cells by immunohistochemistry (IHC) and examined their association with treatment response.

METHODS

• We retrospectively evaluated patients with advanced NSCLC treated with first-line nivolumab plus ipilimumab at Kitasato University Hospital between February 2021 and April 2025.
• We investigated the association between the efficacy of nivolumab plus ipilimumab therapy, and the status of TME based on the density of FOXP3- (clone 236A/E7), CD8- (clone 4B11), and CD204- (clone KT118) positive TILs by IHC.
• The density of positive TILs was calculated as the number of positive cells divided by the examined area (/mm²).
• We defined responders as patients who achieved a partial response (PR) or maintained stable disease (SD) for at least 6 months, whereas non-responders were defined as those with SD lasting less than 6 months or progressive disease (PD).

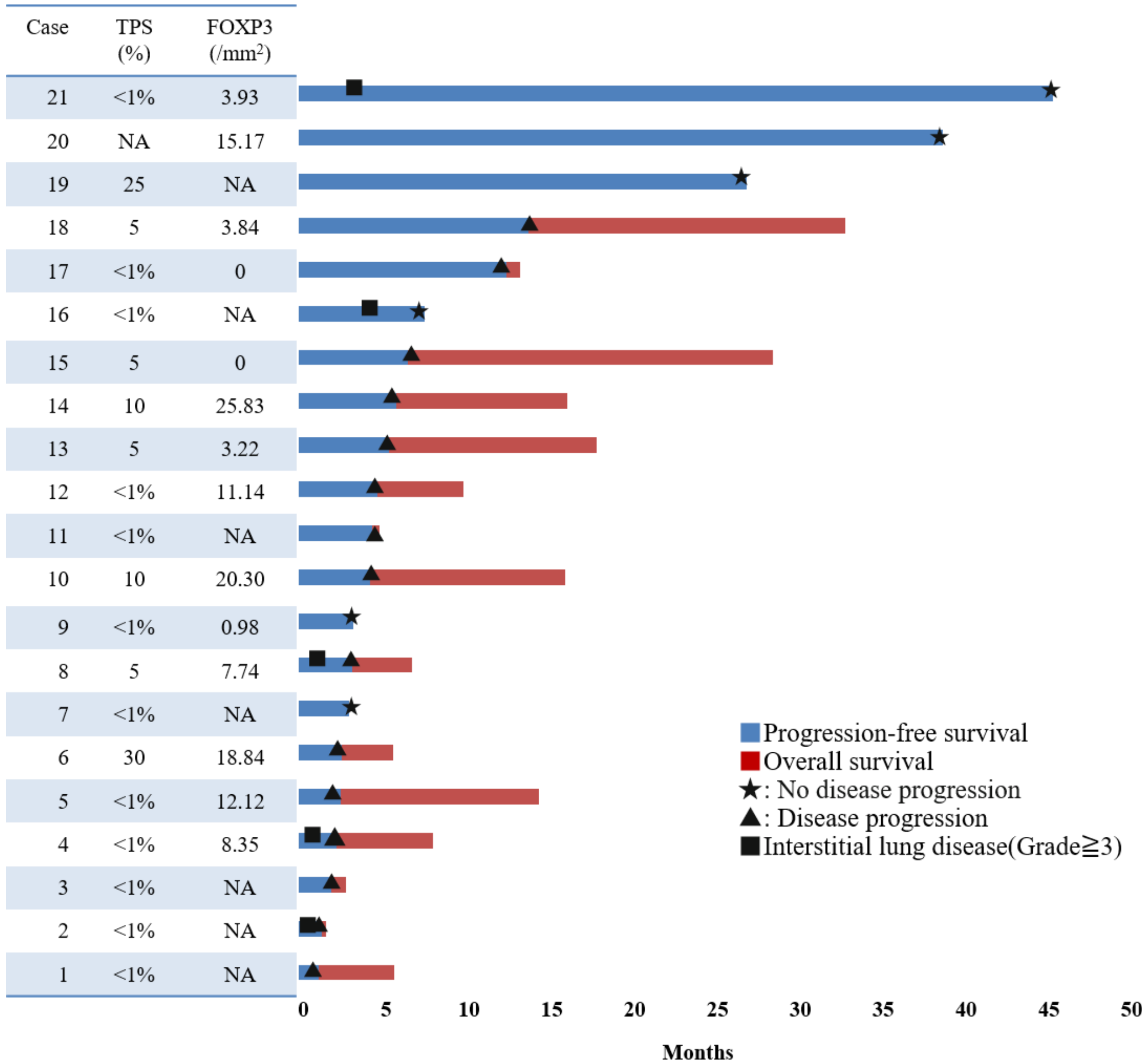


RESULTS

Patient characteristics (N = 21)

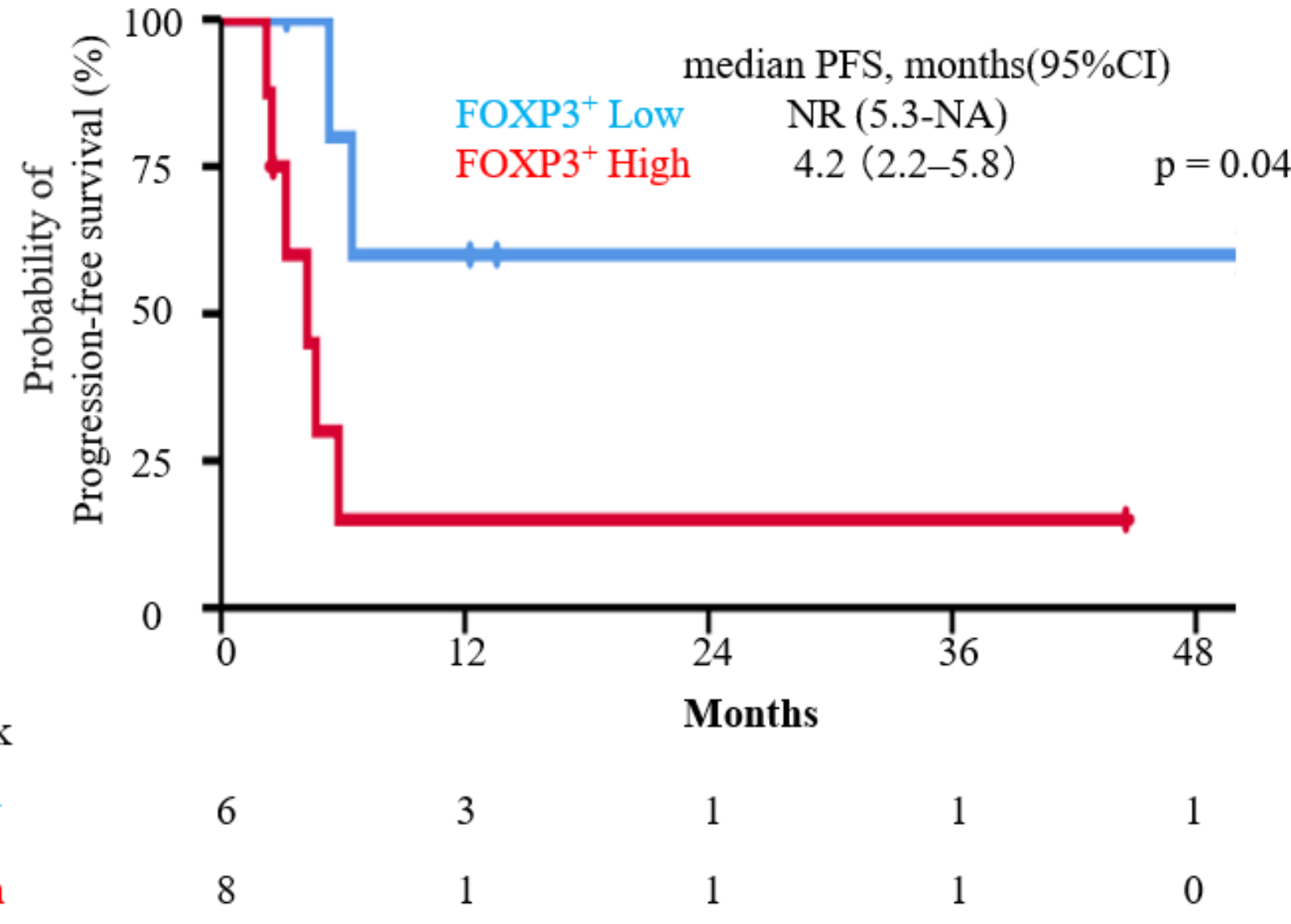
Variable	All patients (N = 21)	Responder (n = 8)	Non-responder (n = 13)	P
Median age (range), years	74 (45–84)	74 (71–80)	72 (45–84)	0.27
Age, n (%)				1.00
<75 y	19 (90.5)	7 (87.5)	12 (92.3)	
≥75 y	2 (9.5)	1 (12.5)	1 (7.7)	
Sex, n (%)				1.00
Male	12 (57.1)	5 (62.5)	7 (53.8)	
Female	9 (42.9)	3 (37.5)	6 (46.2)	
Smoking, n (%)				0.51
Never	2 (9.5)	0 (0)	2 (15.4)	
Former/current	19 (90.5)	8 (100)	11 (84.6)	
ECOG PS, n (%)				1.00
0	5 (23.8)	2 (25.0)	3 (23.1)	
1	16 (76.2)	6 (75.0)	10 (76.9)	
Stage, n (%)				1.00
IIIB	1 (4.8)	0 (0)	1 (7.7)	
IV	6 (28.6)	1 (12.5)	5 (38.5)	
Recurrence	14 (66.7)	7 (87.5)	7 (53.8)	
Histology, n (%)				1.00
Adenocarcinoma	12 (57.1)	4 (50.0)	8 (61.5)	
Squamous	7 (33.3)	3 (37.5)	4 (30.8)	
Others	2 (9.5)	1 (12.5)	1 (7.7)	
PD-L1 expression, n (%)				0.61
<1%	12 (57.1)	4 (50.0)	8 (61.5)	
1–49%	8 (38.1)	3 (37.5)	5 (38.5)	
≥50%	0 (0)	0 (0)	0 (0)	
Unknown	1 (4.8)	1 (12.5)	0 (0)	

Clinical course of patients with first-line nivolumab plus ipilimumab

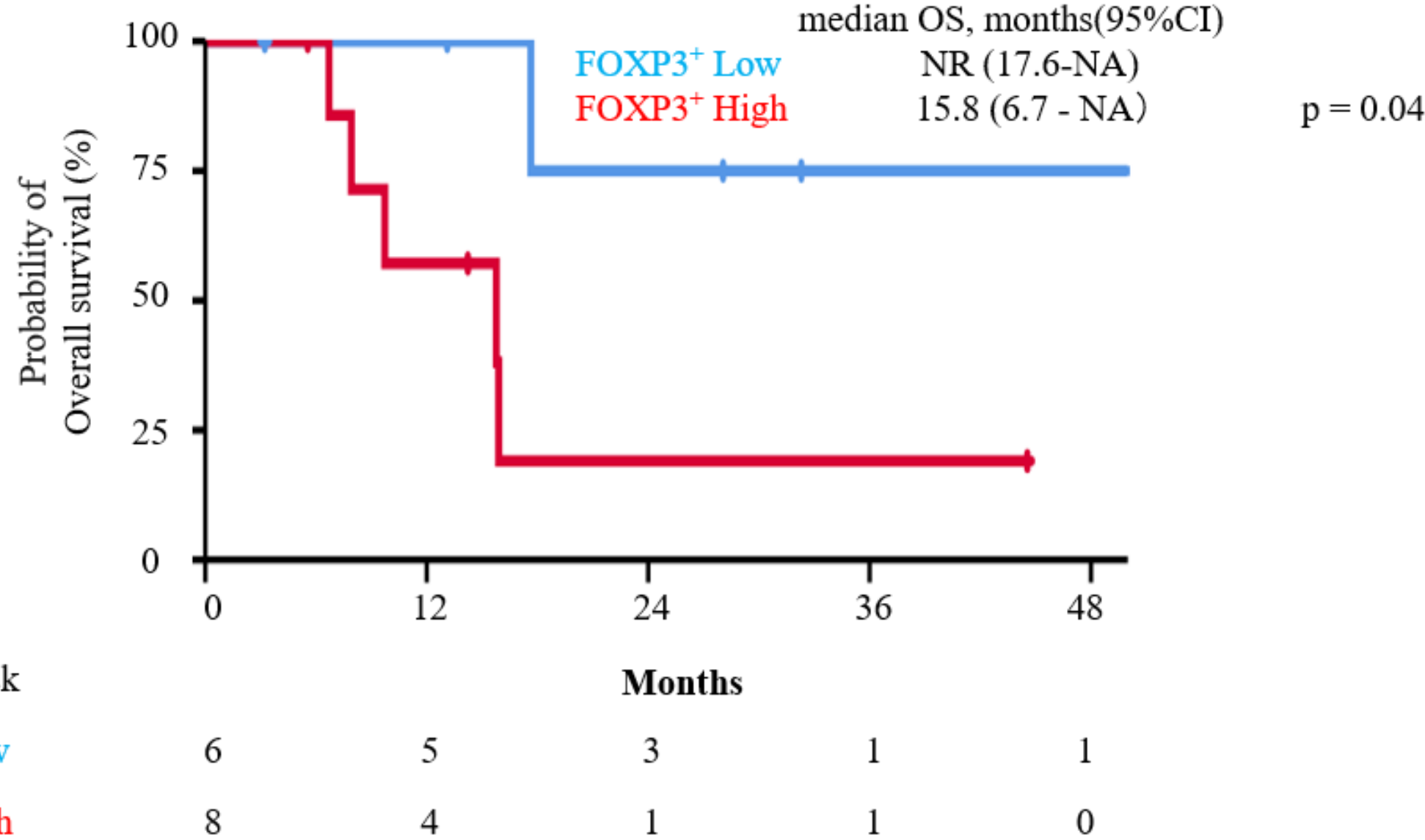


Efficacy of PD-1/PD-L1 blockade according to TME types

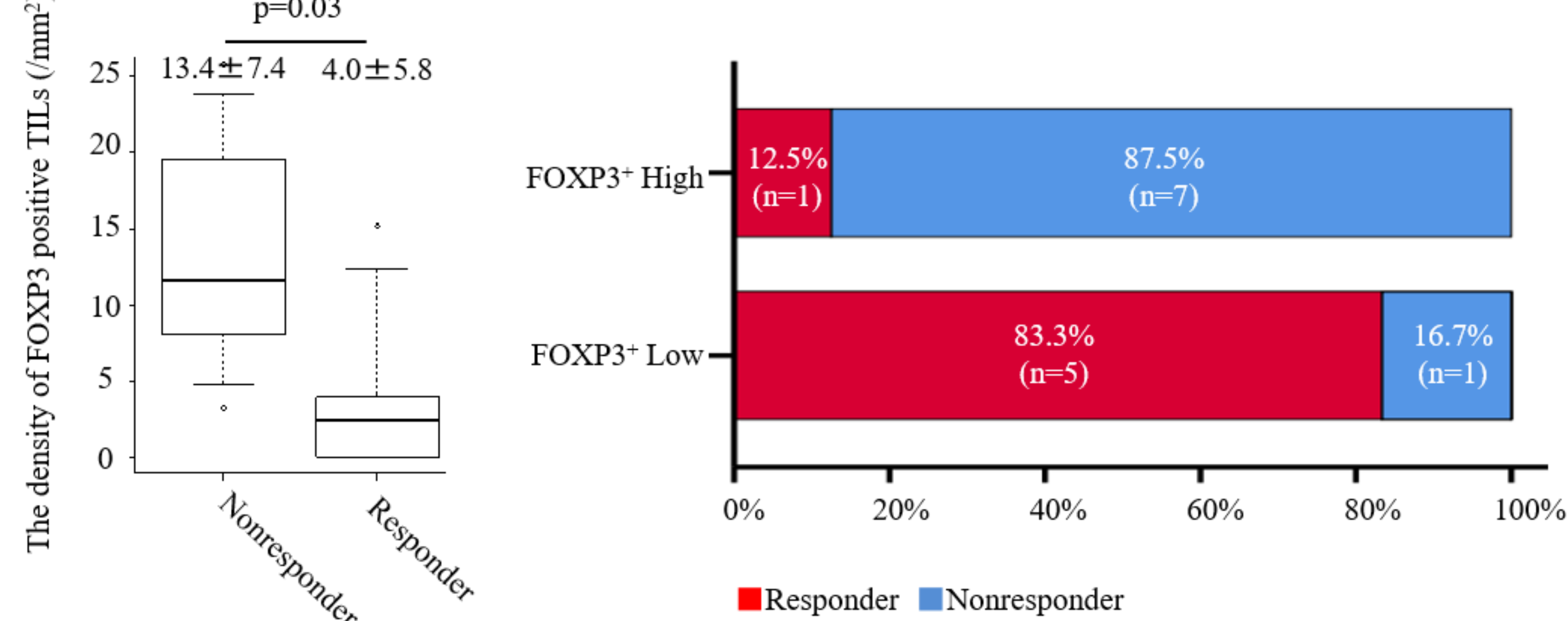
PFS



OS



Association of FOXP3 density with treatment response



Summary of the result

• Intratumoral FOXP3-positive cell density was significantly higher in non-responders than in responders.
• Patients with low FOXP3-positive cell density had significantly longer PFS and OS than those with high FOXP3-positive cell density.
• CD8-positive and CD204-positive cell densities were not significantly associated with treatment outcomes.

DISCUSSION AND CONCLUSION

• CTLA-4 is highly expressed on regulatory T cells (Tregs)(9,10), but ipilimumab does not deplete FOXP3-positive Tregs in human tumors(11). CTLA-4-independent suppression (IL-10, TGF-β) may persist and limit benefit in FOXP3-enriched tumors(12).
• CD8 density correlates with PD-L1 expression(3-5), and no patient had a TPS ≥50% in this study. Anti-CTLA-4 acts at the priming phase, upstream of the PD-1/PD-L1 axis(13), so CD8 density may not identify responders here.
• We measured absolute CD204-positive macrophage density, whereas prior studies assessed the M2 proportion among all macrophages. The M1/M2 balance may matter more than absolute density(14,15).
• In conclusion, low intratumoral FOXP3-positive cell density was associated with better response and longer PFS, suggesting its potential as a biomarker for nivolumab plus ipilimumab in advanced NSCLC.

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