

Determining molecular and genomic characteristics of TROP2-high non-small cell lung cancer (NSCLC)

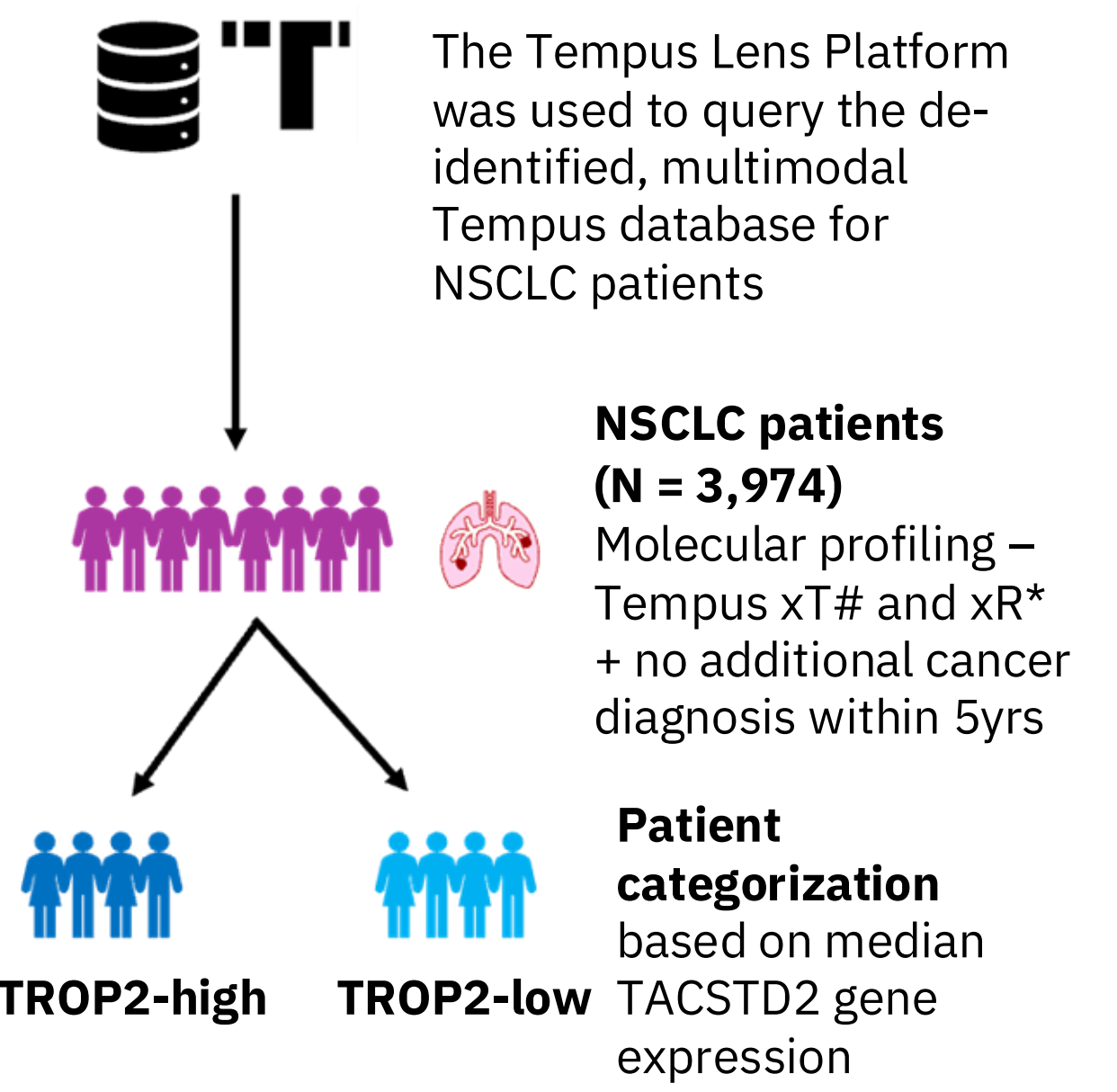
Kathleen Kennedy, MD¹; Yingying Yu, MSc²; Stamatina Fragkogianni, PhD²; Kayla Viets Layng, PhD²; Nan Sethakorn, MD, PhD¹

¹Loyola University Chicago Stritch School of Medicine, Maywood, IL; ²Tempus AI, Inc., Chicago, IL

INTRODUCTION

TROP2 is the protein target for several antibody-drug conjugates (ADCs), and its expression is correlated with poor prognosis and immunosuppressive features in non-small cell lung cancer (NSCLC). Understanding TROP2 biology and RNA expression patterns may inform development of combination therapies and potential biomarkers of response to TROP2 ADCs. We examined patterns of TACSTD2 (the gene encoding TROP2) expression using a large database of NSCLC genomic and transcriptomic data.

METHODS



*DNA-seq of 595-648 genes at 500x coverage; Whole-exome capture RNA-seq

*Whole-transcriptome NGS assay that quantifies transcript- and gene-level expression and identifies fusion RNA species

RNA-seq data were normalized, quantified as transcripts per million (TPM), and reported as log₂(TPM+1). Patient demographics, clinical characteristics, and actionable genomic alterations (AGAs) were compared using Fisher's exact test, Pearson's Chi-squared test, or a Wilcoxon rank sum test, as appropriate.

The tumor immune microenvironment was estimated using quanTiseq. Real-world overall survival (rwOS) and progression-free survival (rwPFS) were defined as the time from treatment initiation to death or loss to follow up (FU) and as the time from treatment initiation to first progression, death, or loss to FU, respectively. Median OS and PFS were estimated by Kaplan-Meier and compared using log-rank tests.

ACKNOWLEDGMENTS

We thank Amrita A. Iyer, Ph.D, from the Tempus Science Communications team for poster development.

SUMMARY

- Patients harboring any actionable genomic alteration were more likely to have low TACSTD2 expression.
- PD-L1-negative tumors were more likely to have low TACSTD2 expression.
- TACSTD2 expression correlated with features of an immunosuppressed tumor immune microenvironment.
- TACSTD2 expression did not correlate with real-world PFS or real-world OS in patients treated with any therapy.
- TACSTD2-high NSCLC had numerically higher real-world OS in a small cohort of patients treated with ADCs, although the difference was not statistically significant, and the treatments were not limited to TROP2-targeting ADCs.
- Limitations of this study include retrospective analysis and heterogeneity in factors such as line of therapy and specific therapeutic modalities.
- Future studies could employ analysis of TROP2 protein localization, and prospective analyses focused on specific NSCLC molecular subtypes.

RESULTS

Table 1. Demographics of TACSTD2-high and low NSCLC

Characteristic	Overall N = 3,974	Stratified by TACSTD2 status		p-value
		Low, N = 1987 (50%)	High, N = 1987 (50%)	
Stage at sample collection				0.012
Stage IV	2,260 (62%)	1,176 (65%)	1,084 (60%)	
Stage III	929 (26%)	436 (24%)	493 (27%)	
Stage II	307 (8.5%)	137 (7.6%)	170 (9.4%)	
Stage I	124 (3.4%)	64 (3.5%)	60 (3.3%)	
Unknown	354	174	180	
Biopsy site				<0.001
Trachea, Bronchus, and Lungs	2,241 (56%)	1,086 (55%)	1,155 (58%)	
Lymph Nodes	624 (16%)	330 (17%)	294 (15%)	
Thymus, Heart, Mediastinum, and Pleura	271 (6.8%)	114 (5.7%)	157 (7.9%)	
Eye, Brain, and Other CNS	225 (5.7%)	118 (5.9%)	107 (5.4%)	
Liver and Intrahepatic Bile Ducts	153 (3.9%)	84 (4.2%)	69 (3.5%)	
Bones, Joints, and Cartilage	122 (3.1%)	78 (3.9%)	44 (2.2%)	
Others	111 (2.8%)	55 (2.8%)	56 (2.8%)	
Soft Tissues	74 (1.9%)	40 (2.0%)	34 (1.7%)	
Unknown	59 (1.5%)	26 (1.3%)	33 (1.7%)	
Thyroid and Other Endocrine Glands	48 (1.2%)	33 (1.7%)	15 (0.8%)	
Respiratory System and Intrathoracic Organs, NOS	46 (1.2%)	23 (1.2%)	23 (1.2%)	
Smoking history				0.13
Ex-smoker	1,042 (53%)	515 (53%)	527 (52%)	
Current smoker	553 (28%)	251 (26%)	302 (30%)	
Never smoker	389 (20%)	201 (21%)	188 (18%)	
Unknown	1,990	1,020	970	
Line of therapy number				0.7
1	1,897 (65%)	973 (65%)	924 (65%)	
2	633 (22%)	330 (22%)	303 (21%)	
3 or higher	399 (14%)	198 (13%)	201 (14%)	
Unknown	1,045	486	559	
Histology				<0.001
Adenocarcinoma	2,305 (58%)	1,273 (64%)	1,032 (52%)	
Squamous cell carcinoma	1,197 (30%)	421 (21%)	776 (39%)	
Other	472 (12%)	293 (15%)	179 (9.0%)	
TMB level				0.5
Low	2,825 (72%)	1,421 (72%)	1,404 (71%)	
High	1,105 (28%)	543 (28%)	562 (29%)	
Unknown	44	23	21	
PD-L1 (22c3)				0.002
<1%	1,066 (38%)	571 (42%)	495 (35%)	
1-49%	1,064 (38%)	499 (36%)	565 (40%)	
50-100%	649 (23%)	302 (22%)	347 (25%)	
Unknown	1,195	615	580	
AGA status				<0.001
KRAS P/LP status	923 (23%)	523 (26%)	400 (20%)	<0.001
EGFR status	527 (13%)	271 (14%)	256 (13%)	0.5
RET/ROS1/NRG1/NTRK status	88 (2.2%)	52 (2.6%)	36 (1.8%)	0.085
BRAF V600E status	41 (1.0%)	20 (1.0%)	21 (1.1%)	0.9
ERBB2 P/LP status	60 (1.5%)	28 (1.4%)	32 (1.6%)	0.6
ALK fusion status	123 (3.1%)	67 (3.4%)	56 (2.8%)	0.3
MET exon 14 skipping status	75 (1.9%)	37 (1.9%)	38 (1.9%)	>0.9

Table 1: TACSTD2-low NSCLC was more enriched in PD-L1-negative tumors (42% vs. 35%, p = 0.002). Patients harboring any AGA were more likely to be TACSTD2-low (49% vs. 42%, p < 0.001), and KRAS alterations were enriched in TACSTD2-low pts (26% vs. 20%, p < 0.001). P-values calculated using Wilcoxon rank-sum test, Pearson's Chi-squared test, and Fisher's exact test.

TACSTD2-high NSCLC is associated with lower infiltration of immune subsets

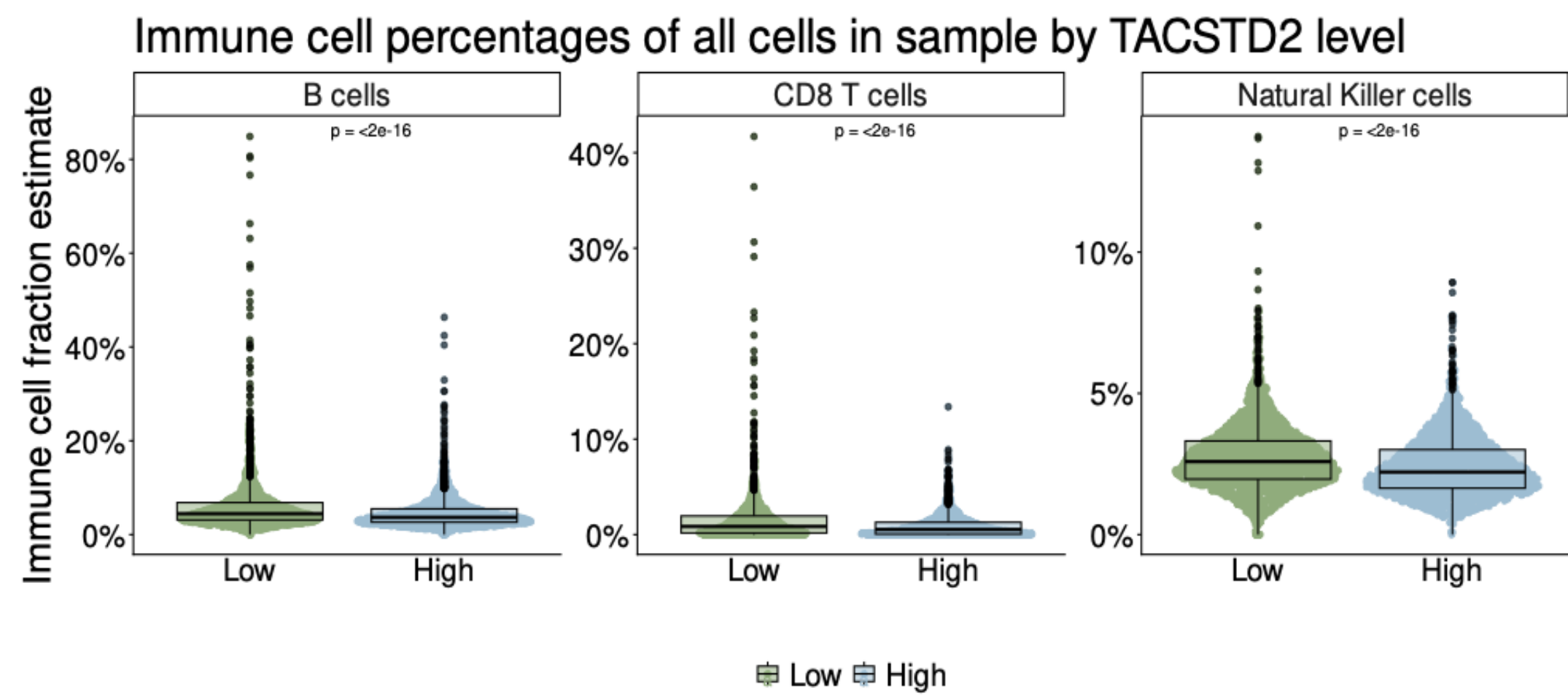


Figure 1. High TACSTD2 expression is associated with lower infiltration of B cells, CD8+ T cells, and Natural Killer cells. These results suggest that high TACSTD2 is associated with an immunosuppressive immune microenvironment. P values calculated using Wilcoxon rank sum test.

TACSTD2-high NSCLC demonstrated a trend towards improved rwOS in patients treated with ADCs

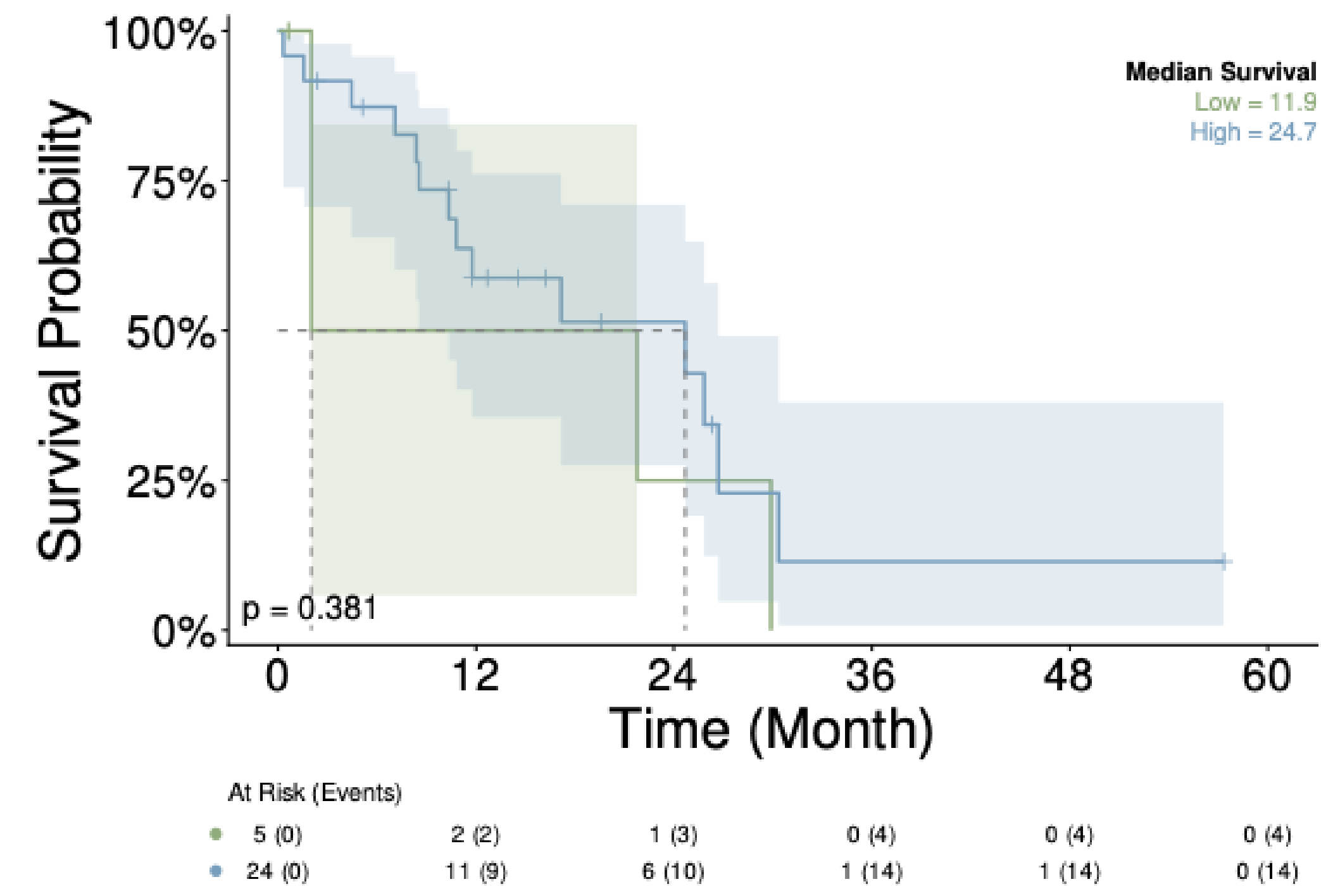


Figure 3. Patients with high TACSTD2 expression treated with any ADC showed a median rwOS of 24.7 months, whereas patients with low TACSTD2 expression had a median rwOS of 11.9 months, although this did not reach statistical significance. Drugs considered as ADC: trastuzumab deruxtecan, datopotamab deruxtecan, telisotuzumab vedotin, ado-trastuzumab emtansine, enfortumab vedotin, sacituzumab govitecan, and tisotumab vedotin. P value calculated using log-rank test.

TACSTD2 expression does not associate with rwOS

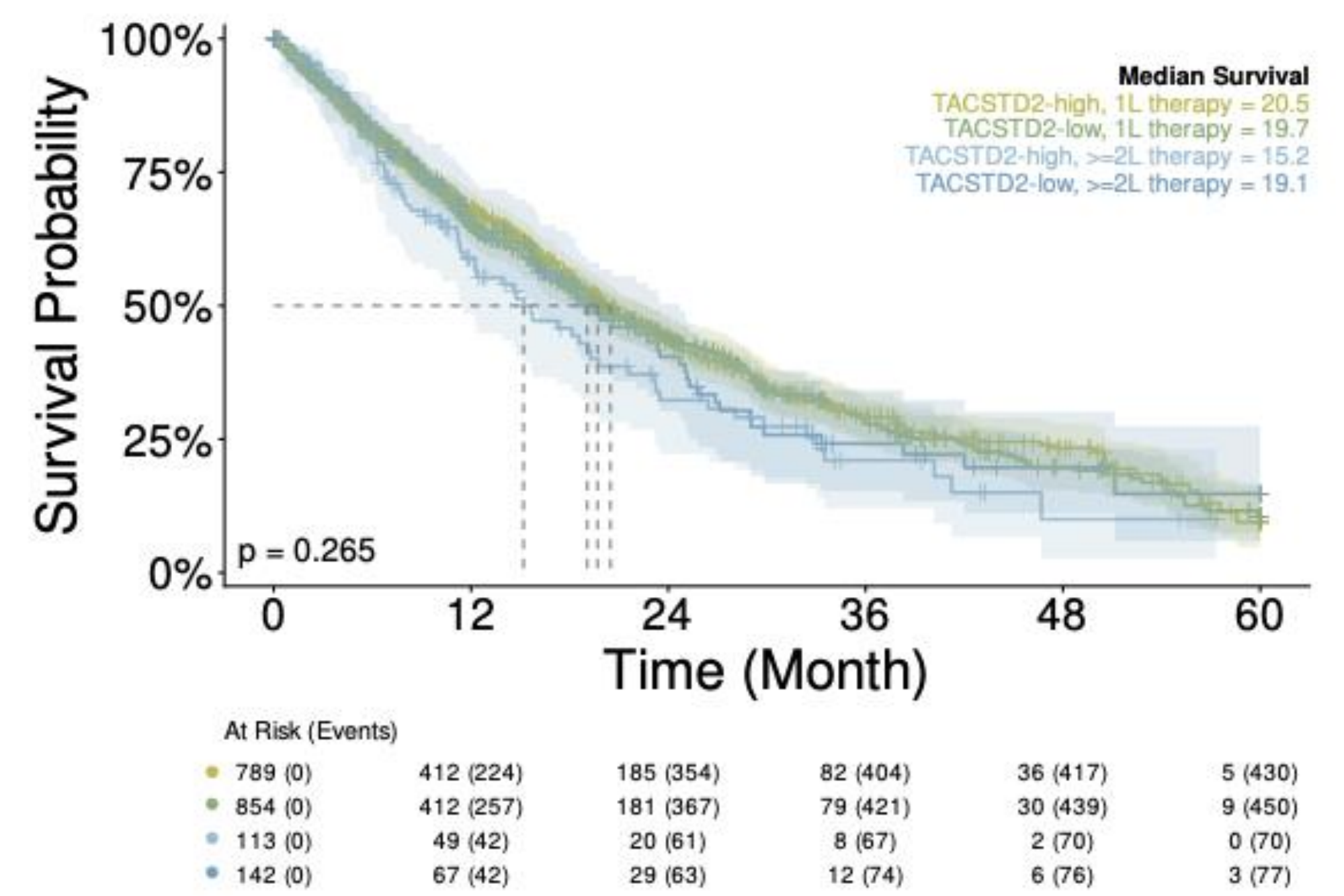


Figure 2. Patients were stratified into TACSTD2-high or -low expression and first-line (1L) or second-line (2L) and beyond therapy, and rwOS was calculated. In this retrospective analysis, there were no statistically significant differences in rwOS between TACSTD2-high and -low groups. P value calculated using log-rank test.

TACSTD2 expression does not associate with rwOS in patients treated with ICIs

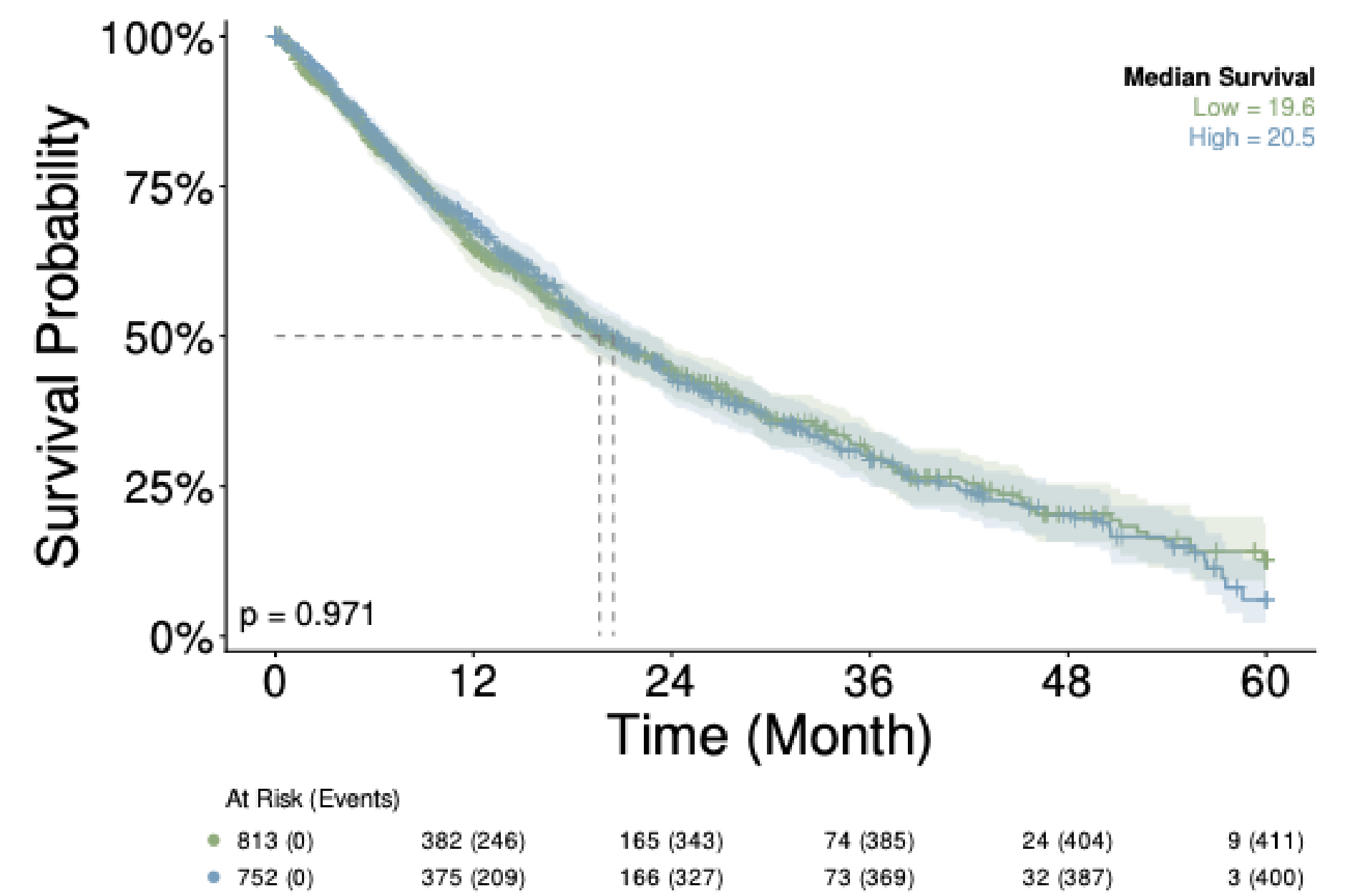


Figure 4. Patients treated with ICI did not demonstrate differences in median rwOS based on TACSTD2 expression. ICI treatment included ICI + chemo, ICI single agent therapy, and ICI combination regimens.