

Impact of TLS Status on Outcomes in Patients with High TMB or MSI-High Status Treated with Immune Checkpoint Inhibitors



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Background

Tertiary Lymphoid Structures (TLS) are critical components of the tumor microenvironment and may influence the efficacy of immune checkpoint inhibitors (ICIs)^{1,2}. High tumor mutational burden (TMB) and microsatellite instability-high (MSI-High) are now established biomarkers approved to guide treatment with ICIs such as pembrolizumab. This study explores the impact of TLS status on the outcomes of patients with these biomarker-positive profiles undergoing pembrolizumab treatment.

Methods

Retrospective review of DNA (592-gene or whole exome) and RNA-seq (whole transcriptome) data real-world patient tumor samples with high TMB (>10 mut/Mb; N=12,674) or MSI-High status (N=1,915), representing >40 tumor types. PD-L1 expression was assessed by IHC (22c3, 28-8, SP142 tumor cell only, or SP142 immune cell only). TLS signature analysis included specific gene sets indicative of B cell infiltration/TLS presence (Messina et al., 2012; Goc et al., 2014; Cabrita et al., 2020; Meylan et al., 2022), with a specific focus on the highest quartile (Q4) of expression. Survival outcomes and duration of pembrolizumab treatment were compared across patients stratified by TLS gene signature score quartiles.

Results

Patients with high TLS expression (Q4) demonstrated significantly improved survival outcomes and prolonged treatment duration compared to those with lower TLS levels, across both TMB high and MSI-High groups. Multivariate analysis, adjusting for gender, age, tumor type, and PD-L1 expression status confirmed the independent predictive value of high TLS status for better clinical outcomes in this patient cohort.

Conclusion

High TLS gene expression signatures, particularly in the highest quartile, are associated with favorable outcomes in patients with high TMB or MSI-High status treated with pembrolizumab. These findings suggest that TLS status could serve as a potent biomarker to stratify patients more likely to benefit from ICI therapy, advocating for its integration into routine clinical assessments prior to ICI treatment in these specific group of patients.

References

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- Vanhersecke L, et al. Mature tertiary lymphoid structures predict immune checkpoint inhibitor efficacy in solid tumors independently of PD-L1 expression. *Nat Cancer.* 2021 Aug;2(8):794-802. doi: 10.1038/s43018-021-00232-6. Epub 2021 Aug 12. PMID: 35118423; PMCID: PMC8809887.

Table 1: Patient demographics/characteristics among TMB-High and MSI-High populations

TMB-High			MSI-High		
Age	Median	Range	Age	Median	Range
Years, at time of biopsy collection	68	4-90+	Years, at time of biopsy collection	67	12-90+
Sex	N	%	Sex	N	%
Male	6645	52.43%	Male	623	32.53%
Female	6029	47.57%	Female	1292	67.47%
Cancer Type	N	%	Cancer Type	N	%
Non-small Cell Lung Cancer	5397	42.58%	Endometrial Carcinoma	617	32.22%
Melanoma	1576	12.43%	Colorectal Adenocarcinoma	503	26.27%
Bladder Cancer	1093	8.62%	Gastric Adenocarcinoma	109	5.69%
Colorectal Adenocarcinoma	733	5.78%	Non-small Cell Lung Cancer	80	4.18%
Endometrial Carcinoma	720	5.68%	Cancer of Unknown Primary	65	3.39%
Cancer of Unknown Primary	439	3.46%	Prostatic Adenocarcinoma	63	3.29%
Head and Neck Cancers	365	2.88%	Bladder Cancer	52	2.72%
Breast Carcinoma	293	2.31%	Esophageal/Esophagogastric Junction Carcinoma	52	2.72%
Small Cell Cancer	285	2.25%	Cholangiocarcinoma	41	2.14%
Esophageal/Esophagogastric Junction Carcinoma	223	1.76%	Pancreatic Adenocarcinoma	40	2.09%
Other	1550	12.23%	Other	293	15.30%
PD-L1 (22c3) IHC	N	%	PD-L1 (22c3) IHC	N	%
0%	2350	31.79%	0%	65	22.57%
1-49%	2911	39.38%	1-49%	174	60.42%
≥50%	2132	28.84%	≥50%	49	17.01%
Not tested/indeterminate	5281	NA	Not tested/indeterminate	1627	NA
PD-L1 (28-8) IHC	N	%	PD-L1 (28-8) IHC	N	%
0%	1542	39.82%	0%	36	26.28%
1-49%	1219	31.48%	1-49%	83	60.58%
≥50%	1111	28.69%	≥50%	18	13.14%
Not tested/indeterminate	8802	NA	Not tested/indeterminate	1778	NA
PD-L1 (SP142) IHC	N	%	PD-L1 (SP142) IHC	N	%
0%	2444	57.60%	0%	1038	71.73%
1-49%	1358	32.01%	1-49%	340	23.50%
≥50%	441	10.39%	≥50%	69	4.77%
Not tested/indeterminate	8431	NA	Not tested/indeterminate	468	NA
Treatment	N	%	Treatment	N	%
Pembrolizumab	8718	68.79%	Pembrolizumab	8718	68.79%
Nivolumab (any)	2586	20.40%	Nivolumab (any)	2586	20.40%
Ipilimumab (any)	1400	11.05%	Ipilimumab (any)	1400	11.05%
Nivolumab+Ipilimumab	1324	10.45%	Nivolumab+Ipilimumab	1324	10.45%
Durvalumab	1171	9.24%	Durvalumab	1171	9.24%
Atezolizumab	884	6.97%	Atezolizumab	884	6.97%
avelumab	179	1.41%	avelumab	179	1.41%

Figure 2: Real-world Immunotherapy TOT and OS by TLS score among patients with TMB-high or MSI-high tumors.

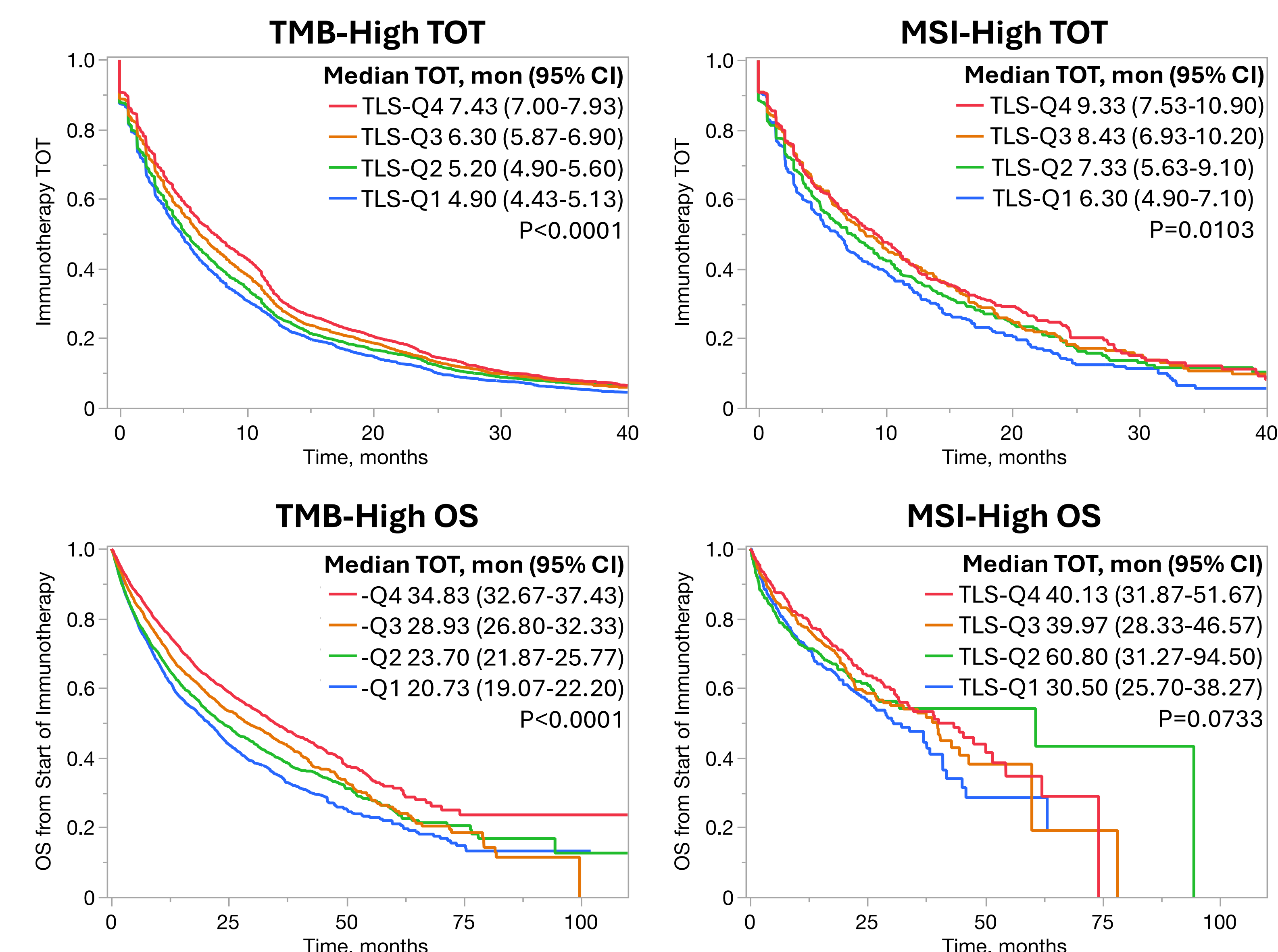


Table 2: Multivariate analysis of Immunotherapy TOT and OS by TLS score among patients with TMB-high or MSI-high tumors.

TMB-High TOT										MSI-High TOT									
Variable	Subgroup	Median TOT	Lower 95%	Upper 95%	Multivariate Model				P-value	Variable	Subgroup	Median TOT	Lower 95%	Upper 95%	Multivariate Model				P-value
					Multi HR	Lower 95%	Upper 95%	Multi HR							Lower 95%	Upper 95%			
Cancer Type	NSCLC	6.07	5.80	6.37	1.08	1.04	1.13	0.0002	Cancer Type	Endometrial	7.83	6.33	9.10	0.89	0.77	1.03	0.1173		
	Other	5.80	5.60	6.07	Ref	----	----	----											
	Other	7.70	6.87	9.07	Ref	----	----	----											
Sex	Male	6.07	5.70	6.30	0.99	0.95	1.03	0.7372	Sex	Male	7.33	6.07	9.40	0.95	0.83	1.09	0.5089		
	Female	5.83	5.60	6.10	Ref	----	----	----											
Age at Biopsy	Above	5.57	5.13	5.63	1.09	1.05	1.14	<0.0001	Age at Biopsy	Above	7.70	6.53	8.93	1.01	0.91	1.14	0.812		
	Below	6.33	6.10	6.73	Ref	----	----	----											
PD-L1 expression	≥50%	7.60	7.00	8.13	0.86	0.81	0.91	<0.0001	PD-L1 expression	≥50%	7.93	5.20	10.73	1.01	0.79	1.30	0.9069		
	1-49%	5.93	5.63	6.30	0.96	0.91	1.00	0.0516											
	0%	5.17	4.93	5.60	Ref	----	----	----											
TLS Score Quartiles	TLS-Q4	7.43	7.00	7.93	0.84	0.79	0.89	<0.0001	TLS Score Quartiles	TLS-Q4	9.33	7.53	10.90	0.75	0.63	0.89	0.0009		
	TLS-Q3	6.30	5.87	6.90	0.88	0.83	0.94	<0.0001											
	TLS-Q2	5.20	4.90	5.60	0.96	0.90	1.01	0.1259											
	TLS-Q1	4.90	4.43	5.13	Ref	----	----	----											