PD-L1 Prevalence in Advanced Urothelial Carcinoma By Demographic and Clinical Characteristics

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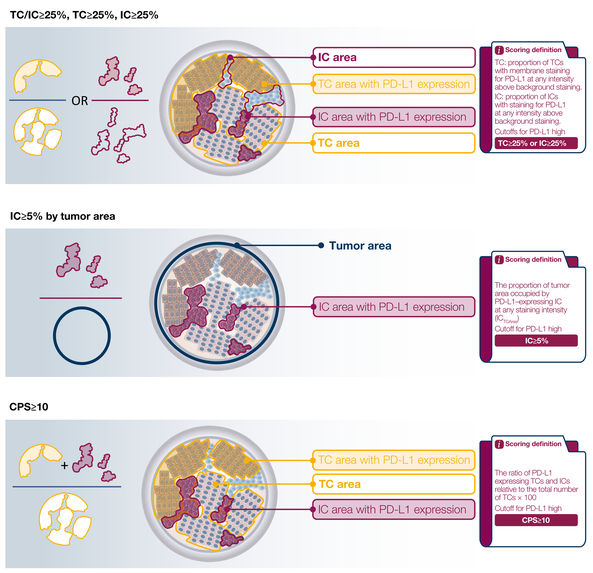
Introduction

- High programmed cell death ligand-1 (PD-L1) expression in tumor cells (TCs) and/or immune cells (ICs) has been linked to the efficacy of PD-1/PD-L1 inhibitors in urothelial carcinoma (UC).[1]
- However, PD-L1 expression in tumor-infiltrating ICs has also been linked to improved prognosis in UC, which may confound analysis of its value as a predictive biomarker for immunotherapy.[1]
- To better understand the prognostic role of PD-L1 in UC, we investigated the association of PD-L1 expression with clinical and demographic characteristics.

Methods

- PD-L1 expression of tumor biopsy samples from 2 studies of patients with metastatic UC, who had previously been treated, were assessed (CD-ON-MEDI4736-1108 [NCT01693562] and D4910C00010 [NCT02261220]).
- Tumor biopsy samples were stained using the VENTANA PD-L1 (SP263) Assay.
  - Specimens were scored at TC≥25%, IC≥25%, TC or IC≥25%. IC score was the proportion of ICs with PD-L1 staining at any intensity.
  - The clinically relevant cutoffs of combined positive score ≥10 (CPS≥10) and IC≥5% (as percentage of tumor area) were also derived using raw scores provided by the pathologist.
- Scoring methods for determining PD-L1 expression using the different algorithms are summarized in **Figure 1**.
- Prevalence was reported for various characteristics and statistical associations were calculated using Fisher's exact test, adjusted for multiple testing using the Benjamini-Hochberg (FDR) method.

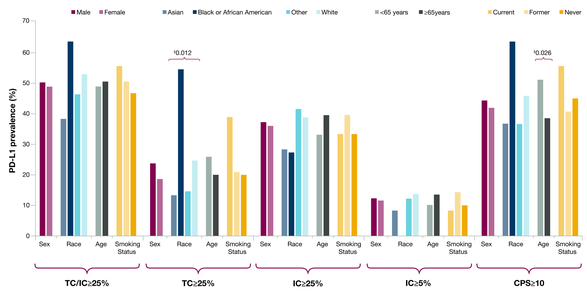
Figure 1: Summary of scoring methods



Results

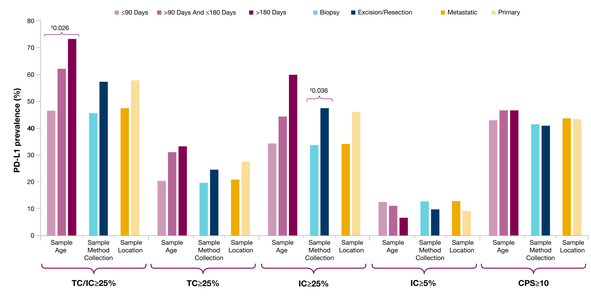
- A total of 339 tumor biopsy samples were evaluated, the majority (97.2%) from Stage IV tumors.
- PD-L1 expression by demographic characteristics for each cutoff are shown in **Figure 2** and **Supplemental Table 1** (via QR code).
- PD-L1 expression by sample characteristics for each cutoff are shown in **Figure 3** and **Supplemental Table 2** (via QR code).
- PD-L1 expression by clinical characteristics for each cutoff are shown in **Table 1**.
- The impact of prior treatment (chemotherapy, radiotherapy, surgery, or immunotherapy) on PD-L1 expression was assessed. No significant associations were observed.
- PD-L1 expression as defined by IC≥5% was associated with the highest number of positive prognostic factors (following adjustment for multiple testing), including Eastern Cooperative Oncology Group (ECOG) performance status, Bellmunt scores, absence of visceral metastases at baseline, lower tumor burden, and lymph node-only involvement (**Figure 4**).
- IC≥25% was independently associated with the absence of visceral metastases, lymph node-only involvement, and favorable Bellmunt score, but TC≥25% alone was not (**Figure 4**).
- Inclusion of a TC component into the algorithm abrogated the prognostic effect.

Figure 2: PD-L1 expression by demographic characteristics



‡*P*-value calculated using Fisher's exact test.

Figure 3: PD-L1 expression by sample characteristics



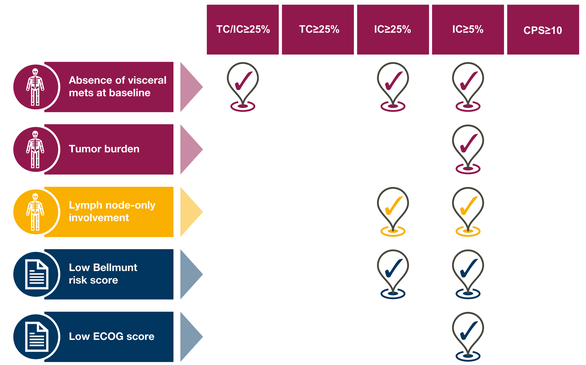
‡*P*-value calculated using Fisher's Exact test.

Table 1: PD-L1 expression by clinical characteristics

Characteristic	Category	n	TC/IC≥25%			TC≥25%			IC≥25%			IC≥5%			CPS≥10		
			% PD-L1 high	‡*P*-value	*Adj *P*-value	% PD-L1 high	‡*P*-value	*Adj *P*-value	% PD-L1 high	‡*P*-value	*Adj *P*-value	% PD-L1 high	‡*P*-value	*Adj *P*-value	% PD-L1 high	‡*P*-value	*Adj *P*-value
Hemoglobin[a]	<10 g/dL	68	51.5	0.787	0.924	33.8	0.015	0.204	29.4	0.205	0.485	8.8	0.142	0.758	48.5	0.412	0.714
	≥10 g/dL	270	49.3			19.6			38.5			13.0			42.2		
Creatinine clearance[a]	<60 mL/min	145	45.5	0.187	0.405	17.9	0.087	0.294	37.9	0.732	0.854	10.3	0.498	0.761	37.2	0.059	0.246
	≥60 mL/min	189	52.9			25.9			36.0			13.2			47.6		
ECOG score	0	114	54.4	0.275	0.496	19.3	0.486	0.660	46.5	0.014	0.079	21.9	**<0.001**	**0.002**	45.6	0.800	0.953
	1	224	47.8			24.1			32.1			7.1			42.9		
	2	1	0.0			0.0			0.0			0.0			0.0		
Tumor burden	<median	163	51.5	0.586	0.902	20.2	0.364	0.590	41.7	0.071	0.221	17.2	**0.007**	**0.038**	43.6	1.000	1.000
	≥median	175	48.0			24.6			32.0			7.4			43.4		
Liver mets[a]	N	221	52.9	0.110	0.323	22.2	0.891	0.963	41.6	**0.013**	0.079	14.9	0.035	0.152	48.0	**0.028**	0.184
	Y	117	43.6			23.1			27.4			6.8			35.0		
Lymph node only[a]	N	287	46.3	**0.004**	0.051	22.6	1.000	1.000	33.1	**0.002**	**0.015**	9.1	**<0.001**	**0.002**	40.4	**0.009**	0.115
	Y	51	68.6			21.6			56.9			29.4			60.8		
Visceral mets[a]	N	94	67.0	**<0.001**	**0.003**	23.4	0.884	0.963	53.2	**<0.001**	**0.004**	24.5	**<0.001**	**0.001**	56.4	**0.003**	0.087
	Y	244	43.0			22.1			30.3			7.4			38.5		
Stage[b]	I	2	0.0	0.673	0.902	0.0	0.857	0.963	0.0	0.518	0.647	0.0	1.000	1.000	0.0	0.387	0.714
	II	3	66.7			0.0			66.7			0.0			0.0		
	III	3	33.3			33.3			33.3			0.0			33.3		
	IV	287	48.1			21.6			35.2			12.2			43.6		
Bellmunt score	0	74	52.7	0.101	0.323	20.3	0.066	0.260	43.2	0.001	**0.015**	23.0	**0.005**	**0.030**	54.1	0.066	0.246
	1	136	53.7			18.4			45.6			12.5			37.5		
	2	105	40.0			24.8			23.8			5.7			41.0		
	3	23	60.9			43.5			21.7			4.3			56.5		

*Adj *P*-value: adjusted for multiple testing with Benjamini-Hochberg (FDR) method. ‡*P*-value calculated using Fisher's exact test.
[a]At baseline; [b]At sample collection; Mets, metastases.

Figure 4: Summary of significant associations by cutoff (after adjustment for multiple testing [FDR])



✓ = significant association

Conclusions

- Higher PD-L1 expression in ICs is associated with clinically favorable characteristics in UC.
- IC-driven PD-L1 algorithms such as IC≥5% are more strongly associated with known favorable prognostic indicators than those incorporating TCs.
- These findings may have implications for clinical studies in urothelial carcinoma where PD-L1 expression is utilized as a selective biomarker.

Reference

1. Powles T, et al. *Cancer Treat Rev*. 2020;82:101925. Epub 2019 Nov 11.

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