1125 : Real-World Evaluation of CXCL9/10 with PD-L1 and TMB as Predictors of Pembrolizumab Benefit in Triple-Negative Breast Cancer (TNBC)

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Background

- Pembrolizumab is approved for TNBC; however, current biomarkers PD-L1 and tumor mutational burden (TMB) have limited predictive accuracy and show weak correlation with clinical benefit.
- We evaluated whether chemokines (CXCL9 and CXCL10) that recruit cytotoxic T cells into the tumor microenvironment (TME) may improve prediction of pembrolizumab benefit beyond PD-L1 and TMB.

Methods

- TNBC tumors (n = 3662) were profiled by next-generation sequencing (592 NextSeq; WES/WTS NovaSeq; Caris Life Sciences, Phoenix, AZ). Chemokine expression was classified as high vs low based on 50th percentile.
- Immune cells were estimated using WTS deconvolution (Quantiseq).
- PD-L1 positivity was defined as ≥10% CPS (PharmDx 22C3). Tumor mutational burden (TMB) totaled somatic mutations per tumor (high>10 mt/MB).
- Real-world median overall survival (mOS) was derived from insurance claims and calculated from pembrolizumab initiation to last contact. Statistical significance was assessed by chi-square and Mann-Whitney U with multiple comparison adjustments (q < 0.05).

Table 1. Distribution of demographic characteristics

		CXCL9		*CXCL10*	
		Low	High	Low	High
Count (N)		1831	1831	1831	1831
Median age [range]		61 (23 - 89)	62 (22 - 89)	62 (23 - 89)	61 (22 - 89)
Race	White	64.94% (902/1389)	65.78% (902/1397)	66.01% (934/1415)	64.7% (887/1371)
	Black	26.57% (369/1389)	25.05% (369/1397)	25.72% (364/1415)	25.89% (355/1371)
	Asian/Pacific Islander	3.38% (47/1389)	4.01% (47/1397)	3.32% (47/1415)	4.08% (56/1371)
	Other	5.11% (71/1389)	5.15% (71/1397)	4.95% (71/1415)	5.32% (73/1371)
Ethnicity	Not Hispanic or Latino	88.43% (1254/1418)	86.77% (1220/1406)	88.6% (1267/1430)	86.59% (1207/1394)
	Hispanic or Latino	11.57% (164/1418)	13.23% (186/1406)	11.4% (163/1430)	13.41% (187/1394)
Tumor site	Primary	45.28% (829/1831)	53.58% (981/1831)	43.75% (801/1831)	55.11% (1009/1831)
	Metastatic	54.72% (1002/1831)	46.42% (850/1831)	56.25% (1030/1831)	44.89% (822/1831)

Race/Ethnicity data is self-reported

Conclusions

- ***In this large real-world study, PD-L1 but not TMB predicted pembrolizumab benefit in TNBC.***
- ***CXCL9/10-high define an immune-active TME and are predictors of pembrolizumab response. When integrated with PD-L1 and TMB, these chemokines help identify additional patients with TNBC who may derive benefit from pembrolizumab, supporting their inclusion as biomarkers in prospective studies.***

Results

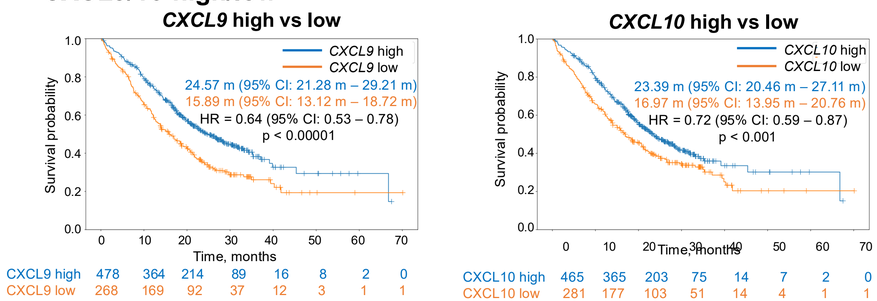
Figure 1. Immune cell infiltration

	CXCL9 high vs low		*CXCL10* high vs low	
	Median %		Median %	
	CXCL9 Low	CXCL9 High	*CXCL10* Low	CXCL10 High
B cell	3.51	4.42	3.61	4.27
DC	2.84	3.1	2.79	3.16
Mϕ M1	2.44	3.75	2.24	3.98
Mϕ M2	2.63	3.37 *	2.81	3.23 *
Neutrophil	4.56	4.07 *	4.39	4.16 *
NK cell	2.89	2.85 *	2.87	2.88 *
CD8+ T cell	0	1.28 *	0	1.11 *
Tregs	1.02	2.55 *	1.17	2.4 *

Low Median% High Median%

CXCL9/10-high expression showed increased fraction of CD8$^+$ T, DC, B cells, M1 Mϕ, M2 Mϕ, Tregs but lower infiltration of neutrophils, ***q<0.05***

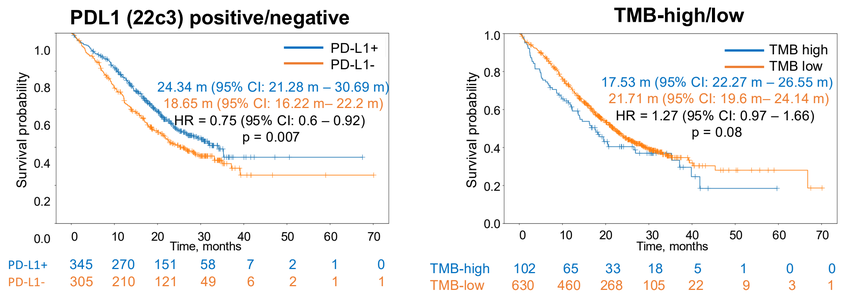
Figure 2. Overall survival on treatment with pembrolizumab by CXCL9/10-high/low



Among patients treated with pembrolizumab, *CXCL9/10*-high expression was associated with improved mOS (*CXCL9-high*: 24.5 months (m) vs 15.8 m; *CXCL10-high*: 23.4 m vs 17 m; all *p < 0.05*) compared to *CXCL9/10*-low.

Results

Figure 3. Overall survival on treatment with pembrolizumab by PDL1+/- and TMB-high/low



PD-L1+ tumors had improved mOS (24.3 m vs 18.6 m, *p = 0.007*) compared with PD-L1-negative; and TMB-low tumors had numerically improved mOS (21.7 m vs 17.5, *p = 0.08*) compared with TMB-high.

Table 2. Patient survival in *CXCL9/10* PDL1+/- and TMB-high/low TNBC

PD-L1	Chemokine	*CXCL9* mOS (95% CI)	p-value	*CXCL10* mOS (95% CI)	p-value
+	High	25.7 m (22.1 - 32.1 m)	<0.01	25.7 m (22.2 - 34.1 m)	<0.01
–	High	26.9 m (17.8 - 39.2 m)		21.7 m (17.5 - 28.2 m)	
+	Low	18.5 m (11.9 m - NR)		20.7 m (13.3 - 30.1 m)	
–	Low	15.8 m (12.2 - 19.2 m)		16.7 m (13.1 - 21.5 m)	
TMB					
Low	High	25.0 m (22.1 - 30.1 m)	<0.01	23.7 m (20.9 - 28.2 m)	<0.01
High	High	20.6 m (17.5 -37.1 m)		19.5 m (16.3 m - NR)	
Low	Low	18.3 m (14.1 - 21.3 m)		18.6 m (15.7 - 22.2 m)	
High	Low	6.6 m (3.6 - 13.7 m)		7.6 m (5.1 - 16.2 m)	

Combining *CXCL9/10* with PD-L1 or TMB identified subgroups with PD-L1-negative or TMB-high expression with better OS with pembrolizumab.

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- For any questions, please contact Shipra Gandhi (Shipra.Gandhi@emory.edu)