The Genomic, Transcriptomic, and Immunological Landscape of TROP2 in Solid Tumors

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Background

- TROP2 expression is associated with decreased overall survival in colorectal and pancreatic cancers.
- The antibody drug conjugate Sacituzumab delivers a SN38 toxic payload to TROP2-expressing cells and is approved for the treatment of breast cancer and urothelial carcinoma.
- We aimed to explore the genomic and immunological landscape of *TACSTD2* (TROP2-encoding gene) in different solid tumors.

Methods

- Tumors from breast cancer (BC, N=11,246), colorectal carcinoma (CRC, N= 15,425), liver cancer (LC, N=433), pancreatic cancer (PC, N=5,488) and urothelial carcinoma (UC, N=5,488) were assessed at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing of DNA (592-gene or whole exome) and RNA (whole transcriptome).
- PD-L1 (SP142; Positive (+): ≥2+, ≥5%) expression was assessed by IHC. When investigating the genomic landscape, mutation prevalence was calculated for pathogenic SNVs/indels.
- *TACSTD2*-High (H) and -Low (L) expression was defined as top and bottom quartile of *TACSTD2* transcripts per million, respectively.
- A transcriptomic signature predictive of response to immunotherapy was applied (T cell-inflamed [Bao, 2020]).
- χ^2 tests were applied as appropriate, with P-values adjusted for multiple comparisons ($p < .05$).
- Real-world overall survival data was obtained from insurance claims and Kaplan-Meier estimates were calculated for molecularly defined subpopulations of patients.

Results

1. Genomic Landscape segmented by *TACSTD2* expression

(A)

TACSTD2		NGS																							
		APC	ARID1A	BAP1	BCL9	BRAF	CDH1	CDKN1A	CDKN2A	CTNNB1	ELF3	ESR1	FGFR3	GATA3	KDM6A	KMT2D	KRAS	MSH3	NF1	NFE2L2	RB1	SMAD4	STAG2	TERT*	TP53
UC	(Q1-Q4) %	-1.39	**-8.94**	0.02	0.31	0.43	1.39	-4.12	**4.10**	0.02	**-6.46**	0	**-11.10**	0.39	-5.55	9.81	2.16	-0.98	2.16	2.05	0.62	-0.09	-4.91	**-17.54**	**13.39**
CRC	(Q1-Q4) %	**12.35**	**3.51**	0.24	**3.05**	**-3.91**	0.44	0	-0.66	0.57	0	-0.05	0.00	0.13	0.48	**3.63**	**-16.15**	**4.63**	0.85	-0.03	-0.08	**-7.63**	0	-0.62	-4.97
PDAC	(Q1-Q4) %	1.84	-2.12	0.83	0.26	0.29	0.33	0	-2.62	1.95	0	0	0	0	0.09	1.34	**-18.69**	0.97	0.39	0.11	1.57	**-8.46**	0.29	1.32	**-14.75**
Breast	(Q1-Q4) %	0.48	-1.01	0.02	0.16	-0.13	**3.44**	0.00	0.04	0.04	-0.06	**4.25**	-0.07	**6.21**	-0.13	0.88	-0.37	-0.11	1.24	0.02	0.78	-0.45	0.05	1.04	**-11.63**
Liver	(Q1-Q4) %	0.00	9.12	-3.74	0.00	0.00	1.85	0.00	1.87	**25.46**	0.00	0.00	0.00	0.00	0.96	3.76	0.00	1.33	5.06	7.96	7.14	0.00	0.00	-2.39	-19.95

(B)

TACSTD2		CNA									
		ADGRA2	CCND1	EMSY	FGF19	FGF3	FGF4	FGFR1	MDM2	NSD3	ZNF703
UC	(Q1-Q4) %	0.86	2.91	0.31	2.08	1.35	1.30	0.67	-3.49	0.18	0.24
CRC	(Q1-Q4) %	0.19	-0.08	-0.05	-0.48	-0.37	-0.37	-0.31	**-0.25**	-0.30	0.32
PDAC	(Q1-Q4) %	0.54	0.39	0	1.05	0.79	0.74	0.02	0.20	-0.21	0.61
Breast	(Q1-Q4) %	**9.60**	**6.99**	**4.69**	**5.99**	**5.04**	**4.88**	**6.48**	1.27	**7.06**	**9.60**
Liver	(Q1-Q4) %	-4.17	-6.78	0.00	-6.86	-4.90	-3.90	0.98	0.00	3.13	-4.00

Figure 1: Difference in prevalence between *TACSTD2*-High and –Low tumors of **(A)** mutations and **(B)** copy number amplification (CNA). An alteration is included in the heatmap if it has an absolute difference in prevalence of >3% in one of the investigated cancer types. Bolded numbers in heat map indicate statistical significance ($p < 0.05$)

(Q1—Q4)%: 20 / 0.00 / -20.00

2. TACSTD2 expression segmented by site and CMS

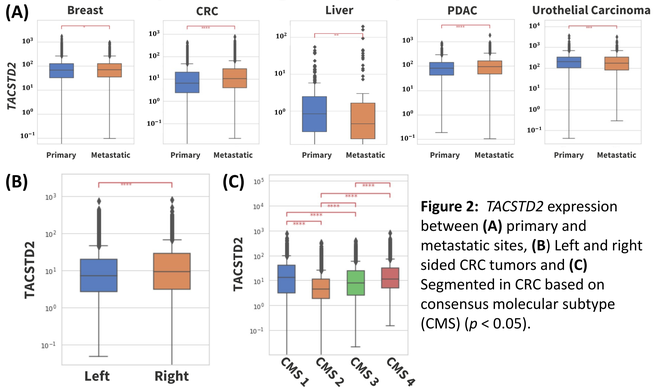

Figure 2: *TACSTD2* expression between **(A)** primary and metastatic sites, **(B)** Left and right sided CRC tumors and **(C)** Segmented in CRC based on consensus molecular subtype (CMS) ($p < 0.05$).

3. Prevalence of ICI biomarkers by TACSTD2 expression

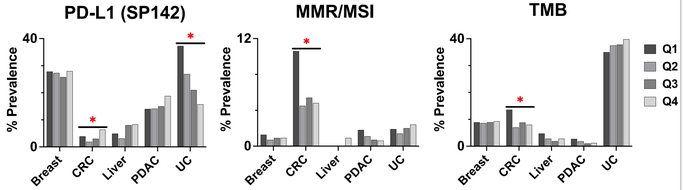

Figure 3: Prevalence of PD-LI positive IHC, MSI-high and TMB-high tumors segmented by *TACSTD2* expression ($p < 0.05$ indicated by asterisk).

4. Immune populations segmented by *TACSTD2* expression

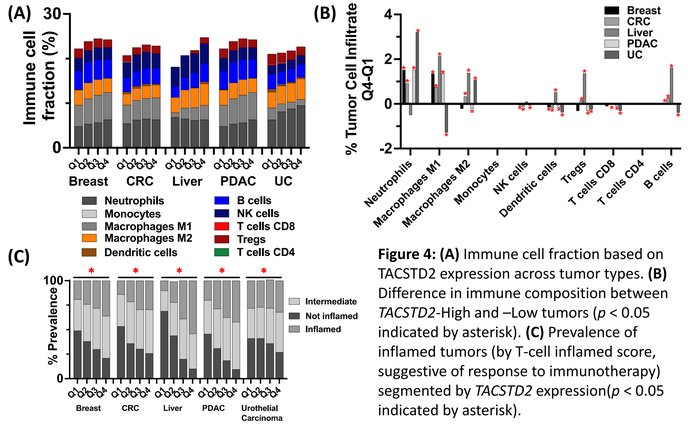

Figure 4: (A) Immune cell fraction based on TACSTD2 expression across tumor types. **(B)** Difference in immune composition between *TACSTD2*-High and –Low tumors ($p < 0.05$ indicated by asterisk). **(C)** Prevalence of inflamed tumors (by T-cell inflamed score, suggestive of response to immunotherapy) segmented by *TACSTD2* expression($p < 0.05$ indicated by asterisk).

5. Overall survival based on TACSTD2 expression

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	HR	Low CI	Upper CI	*p*-value	Q1	Q4
Breast	1.13	1.03	1.23	0.007	2124	2118
CRC	1.33	1.24	1.42	<0.001	3249	3223
Liver	1.14	0.82	1.57	0.441	112	109
PDAC	1.31	1.19	1.44	<0.001	1141	1166
UC	0.98	0.86	1.12	0.754	717	715

Figure 5: Overall survival across tumor types between *TACSTD2*-High and –Low tumors .

Higher hazard / Lower hazard: 2 / 1 / 0 **of death for TACSTD2 high tumors**

Study Highlights

- The genomic landscape of high versus low *TACSTD2* expressors varied widely by cancer type.
- Significant but small difference in *TACSTD2* expression was observed between primary and metastatic sites.
- There was an increased prevalence of T Cell-inflamed tumors in the top quartile of *TACSTD2* expressors across investigated tumor types.
- High expression of *TACSTD2* was associated with worse overall survival in Breast, CRC and PDAC tumors.

Conclusion

- The association of *TACSTD2* expression with *KRAS*, *TP53* and *ARID1A* mutations and T cell-inflamed tumors (ICI responsive) should be considered as possible combination therapies with TROP2 targeting antibody drug conjugates.