Comparative analysis of the tumor immune microenvironment (TIME) and primary and metastatic tissue in HR+/HER2- and triple-negative breast cancer (TNBC)

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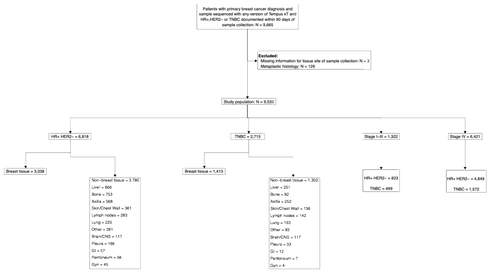
BACKGROUND

- Immune checkpoint inhibitor (ICI)-based regimens are standard-of-care for patients with early-stage and PD-L1+ metastatic TNBC.
- Clinical trials are investigating ICI in HR+/HER2- breast cancer in both the early and metastatic setting and have shown encouraging results in a subset of patients.[1-4]
- The tumor immune microenvironment (TIME) plays a critical role in ICI response and can differ significantly by metastatic site.[5]
- Given the rapidly expanding integration of ICIs in HR+/HER2- breast cancer trials, we examined the TIME across sites of metastatic disease to identify which subset of patients with HR+/HER2- breast cancer benefit from ICI using TNBC for comparison.

METHODS



- We used Tempus Lens (Tempus AI, Inc., Chicago, IL) to retrospectively analyze de-identified next-generation sequencing data from patients with HR+/HER2- breast cancer (n=6,818) and TNBC (n=2,715) in the Tempus Database who underwent testing with xT (DNA) and xR (RNA) assays. Metaplastic histology was excluded.
- TMB, MSI, PD-L1 (CPS, clone 22c3), proportions of B, T (CD4+, CD8+), NK cells, and macrophages of immune cells via quanTIseq deconvolution, and immune profile score (IPS) were compared across metastatic sites in HR+/HER2- breast cancer and compared to TNBC.
- IPS-high was defined as an IPS score of 48-100.
- Chi-squared/Fisher's exact or Kruskal-Wallis tests were used to assess statistical significance.

RESULTS

Table 1. Demographics of patients with HR+/HER2 and TNBC.

	Overall N = 9,533[1]	HR+/HER2- N = 6,818[1]	TNBC N = 2,715[1]	p-value[2]
Age at diagnosis	58 (48, 67)	58 (48, 67)	57 (47, 67)	0.4
Unknown	238	179	59	
Race				<0.001
White	4,605 (48%)	3,426 (50%)	1,179 (43%)	
Unknown	3,195 (34%)	2,251 (33%)	944 (35%)	
Black or African American	935 (9.8%)	548 (8.0%)	387 (14%)	
Other Race	517 (5.4%)	378 (5.5%)	139 (5.1%)	
Asian	281 (2.9%)	215 (3.2%)	66 (2.4%)	
Ethnicity				0.025
Unknown	4,872 (51%)	3,431 (50%)	1,441 (53%)	
Not Hispanic or Latino	4,020 (42%)	2,934 (43%)	1,086 (40%)	
Hispanic or Latino	641 (6.7%)	453 (6.6%)	188 (6.9%)	
Stage				<0.001
Stage 4	6,421 (67%)	4,849 (71%)	1,572 (58%)	
Unknown	1,790 (19%)	1,146 (17%)	644 (24%)	
Stage 3	604 (6.3%)	324 (4.8%)	280 (10%)	
Stage 2	498 (5.2%)	322 (4.7%)	176 (6.5%)	
Stage 1	220 (2.3%)	177 (2.6%)	43 (1.6%)	

[1] Median (Q1, Q3); n (%)
[2] Wilcoxon rank sum test; Pearson's Chi-squared test

Figure 1. a) Percent of TMB high (>=10 mut/mB) and **b)** PD-L1 positive (>=10% CPS) pts in HR+/HER2- and TNBC by tissue site of biopsy. Bone and brain were more commonly TMB high, while breast and lymph nodes (LN) were more more commonly PD-L1+ in HR+/HER2- and TNBC.

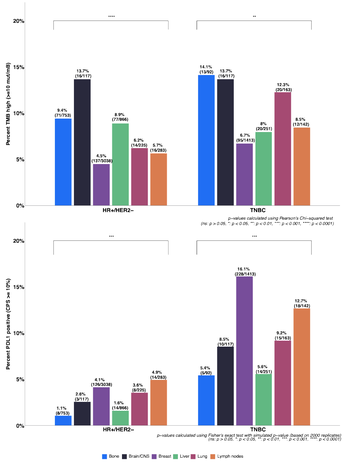
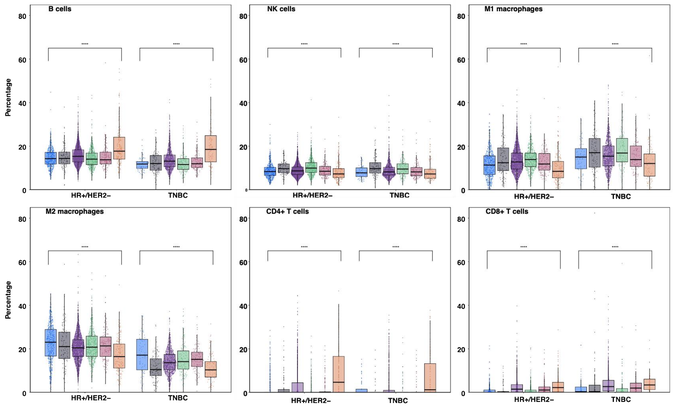


Figure 2. Percentage of infiltrating immune cells in HR+/HER2- and TNBC, subset to population of patients with RNAseq. Compared to TNBC, HR+/HER2- breast cancer had different proportions for all immune cell populations in PB and all non-breast sites (exception NK cells, all else p<0.05). Notably, HR+/HER2- breast cancer had lower proportions of CD8+ T cells across PB and all non-breast sites compared to TNBC (all, p<0.001). Liver, bone, and brain/CNS metastases had lower CD8+ T cell proportions compared to lung, breast, and LN.



[1] n (%)
[2] Kruskal-Wallis rank sum test

Figure 3. Regression model of proportion of CD8+ T cells according to disease site in entire cohort. TNBC has higher CD8+ T cell proportions compared to HR+/HER2. Besides breast and LN, lung, pleura, and peritoneum have higher CD8+ T cell proportions compared to other disease sites.

Variable		N	Estimate	p
Hormone subtype	HR+/HER2–	5715		Reference
	TNBC	2346	1.31 (1.12, 1.50)	<0.001
Tissue site of testing	Breast	3911		Reference
	Liver	886	−1.25 (−1.55, −0.96)	<0.001
	Bone	685	−1.30 (−1.63, −0.96)	<0.001
	Axilla	697	0.94 (0.63, 1.26)	<0.001
	Skin/chest wall	429	−0.17 (−0.57, 0.22)	0.387
	Lymph nodes	319	0.93 (0.48, 1.38)	<0.001
	Lung	283	−0.04 (−0.52, 0.44)	0.877
	Other	301	0.01 (−0.45, 0.48)	0.950
	Brain/CNS	219	−0.18 (−0.72, 0.36)	0.520
	Pleura	169	0.60 (−0.00, 1.21)	0.050
	GI	56	−0.44 (−1.47, 0.58)	0.396
	Peritoneum	60	0.53 (−0.46, 1.52)	0.292
	GYN	46	−1.40 (−2.52, −0.27)	0.015
Stage	Stage I–III	1162		Reference
	Stage IV	5343	−0.65 (−0.93, −0.36)	<0.001
	Unknown	1556	−0.17 (−0.46, 0.12)	0.258
Race	White	3897		Reference
	Black or African American	792	−0.68 (−0.97, −0.39)	<0.001
	Asian	242	0.39 (−0.11, 0.89)	0.130
	Other Race	447	−0.13 (−0.51, 0.25)	0.509
	Unknown	2683	−0.06 (−0.25, 0.13)	0.532
Age at sample collection		8061	−0.01 (−0.02, −0.00)	0.003

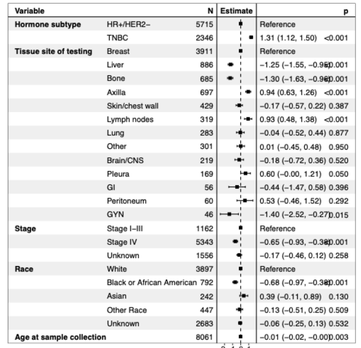


Table 2. IPS score according site of disease in HR+/HER2- and TNBC. Besides breast and LN, lung had the highest IPS score for both HR+/HER2- and TNBC.

	HR+/HER2-								TNBC							
	Overall N = 5,282[1]	Breast N = 3,038[1]	Liver N = 866[1]	Bone N = 753[1]	Lymph nodes N = 283[1]	Lung N = 225[1]	Brain/CNS N = 117[1]	p-value[2]	Overall N = 2,178[1]	Breast N = 1,413[1]	Liver N = 251[1]	Bone N = 92[1]	Lymph nodes N = 142[1]	Lung N = 163[1]	Brain/CNS N = 117[1]	p-value[2]
IPS score								<0.001								<0.001
Median (Q1, Q3)	44 (35, 52)	46 (38, 54)	42 (34, 50)	33 (26, 43)	49 (38, 63)	46 (40, 54)	31 (25, 43)		42 (31, 52)	43 (33, 54)	36 (28, 45)	31 (24, 46)	48 (37, 63)	44 (35, 52)	25 (16, 35)	
Min, Max	-2, 111	9, 111	11, 88	0, 84	2, 94	23, 86	-2, 70		-3, 107	6, 88	7, 92	4, 76	7, 107	1, 85	-3, 70	
Unknown	1,091	527	224	163	89	75	13		414	216	65	29	42	51	11	

CONCLUSION

- In HR+/HER2- and TNBC, the TIME significantly differed according to site of metastatic disease, with HR+/HER2- breast cancer less immunogenic across all disease sites.
- Although more commonly TMB high, liver, bone, and brain/CNS metastases had lower proportions of CD8+ T cells compared to lung and breast in HR+/HER2- breast cancer and TNBC.
- Besides breast and LN metastases, lung, pleura and the peritoneum had the highest proportions of CD8+ T cells in both subtypes, with lung also more likely to be IPS-high, indicating a subset of patients with HR+/HER2- breast cancer that could be enriched for ICI response.
- The TIME profile varies between metastatic sites and the impact this has on guiding patient selection for ICI is warranted in prospective clinical trials.

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