Site specific Genomic and Immune Landscapes Underpinning in metastatic Male Breast Cancer

Dario Trapani[1], Sachin Kumar Deshmukh[2], Sharon Wu[2], Joanne Xiu[2], Nancy U. Lin[1], Giuseppe Curigliano[3], Philip Spanheimer[4], Pooja Advani[5], Priscilla Barreto Coelho[6], Maryam Lustberg[7], George W. Sledge Jr.[2], Sara M. Tolaney[1], Jose P. Leone[1]

Department of Medicine, Dana-Farber Cancer Institute, Boston, MA; Caris Life Sciences, Phoenix, AZ; European institute of oncology, University of Milan, department of oncology and hematology, Milan, Italy; University of North Carolina at Chapel Hill, Chapel Hill, NC Mayo Clinic, Jacksonville, FL; University of Miami, Coral Gables, FL; Yale School of Medicine, Yale University, New Haven, CT

BACKGROUND

- Male breast cancer (MBC) is a rare malignancy, accounting for approximately 1% of all breast cancer cases.
- Our previous studies suggest that MBC is biologically distinct from female breast cancer (FBC), exhibiting a unique mutational profile and immune-genomic microenvironment.
- While the impact of these molecular alterations on site-specific metastases has been explored in FBC, it remains poorly understood in MBC.
- This gap limits accurate risk stratification and prediction of disease trajectory in male patients.
- In this study, we investigated site-specific genomic and immune alterations across metastatic sites in MBC.

METHODS

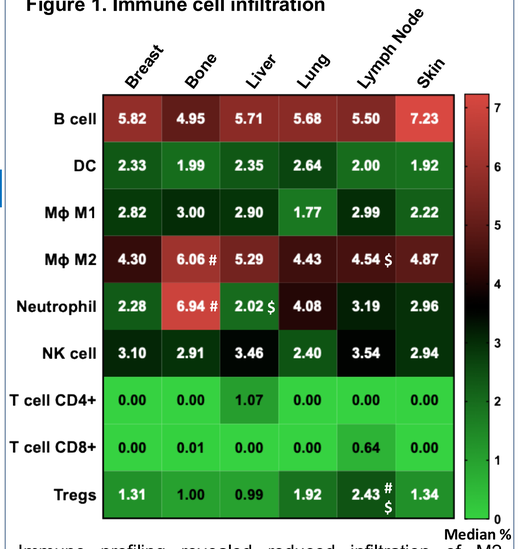
- 238 MBC samples were tested by NGS (592, NextSeq; WES, NovaSeq) and WTS (NovaSeq; Caris Life Sciences, Phoenix, AZ).
- We classified patients by site of biopsy/specimen site and performed analysis in hormone receptor-positive (HR+) and HER2-negative (HER2-) subtypes which are most common in male.
- Immune cells were estimated using WTS deconvolution (Quantiseq).
- Gene expression profiles were analyzed for T-cell inflamed score, interferon-gamma (IFN-gamma) score and MAPK Activation Score.
- Statistical significance was assessed with chi-square and Mann-Whitney U tests, p<0.05 is considered statistically significant.

RESULTS

Table 1. Patients' demographic information

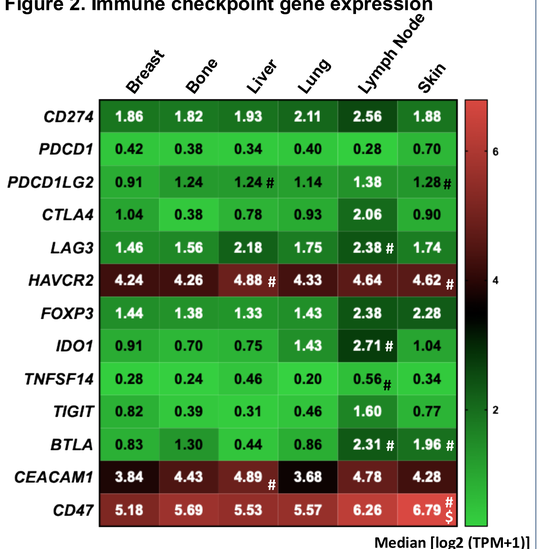
		Breast	Bone	Liver	Lung	Lymph node	Skin
Count (N)		39	15	8	8	7	9
Median Age [range]		63 [33-89]	67 [39-81]	71 [37-87]	62.5 [38-88]	64 [39-74]	68 [53-85]
Race	White	70% (21/30)	64.29% (9/14)	100% (6/6)	71.43% (5/7)	57.14% (4/7)	66.67% (4/6)
	African American	23.33% (7/30)	21.43% (3/14)	0% (0/6)	28.57% (2/7)	28.57% (2/7)	33.33% (2/6)
	Asian/PI	0% (0/30)	7.14% (1/14)	0% (0/6)	0% (0/7)	0% (0/7)	0% (0/6)
	Other	6.67% (2/30)	7.14% (1/14)	0% (0/6)	0% (0/7)	14.29% (1/7)	0% (0/6)
Ethnicity	Not Hispanic or Latino	96.67% (29/30)	100% (15/15)	87.5% (7/8)	80% (4/5)	100% (7/7)	100% (7/7)
	Hispanic or Latino	3.33% (1/30)	0% (0/15)	12.5% (1/8)	20% (1/5)	0% (0/7)	0% (0/7)
HER2 expression spectrum	HER2-null	48.72% (19/39)	66.67% (10/15)	75% (6/8)	75% (6/8)	57.14% (4/7)	55.56% (5/9)
	HER2 ultra-low	0% (0/39)	0% (0/15)	0% (0/8)	0% (0/8)	0% (0/7)	0% (0/9)
	HER2-low	51.28% (20/39)	33.33% (5/15)	25% (2/8)	25% (2/8)	42.86% (3/7)	44.44% (4/9)

Figure 1. Immune cell infiltration



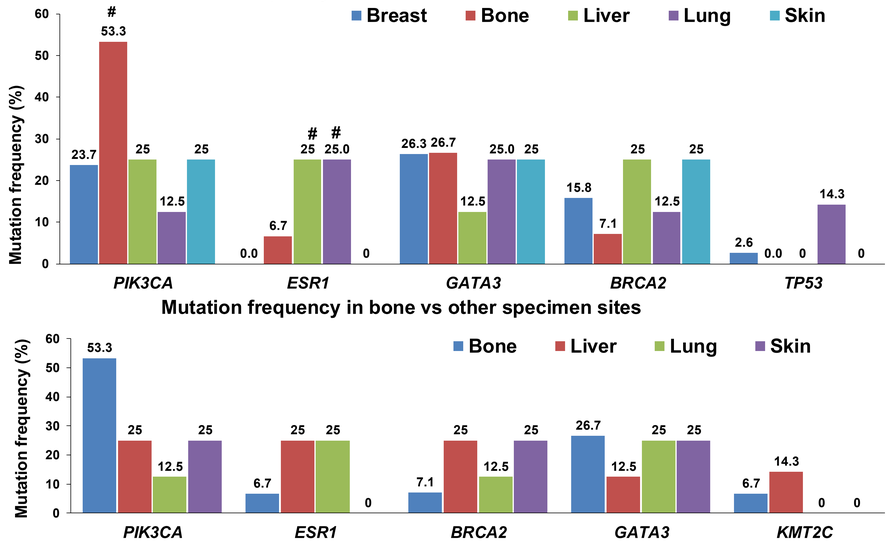
Immune profiling revealed reduced infiltration of M2 macrophages (4.3% vs. 6%) and neutrophil (2.2% vs. 6.9%) in pBC relative to bone Mets. Further, CD4+ T cells were lower in pBC compared to lymph nodes (0% vs. 2.4%). # p-value <0.05 is relative to breast biopsy, $ p-value <0.05 is relative to bone biopsy.

Figure 2. Immune checkpoint gene expression



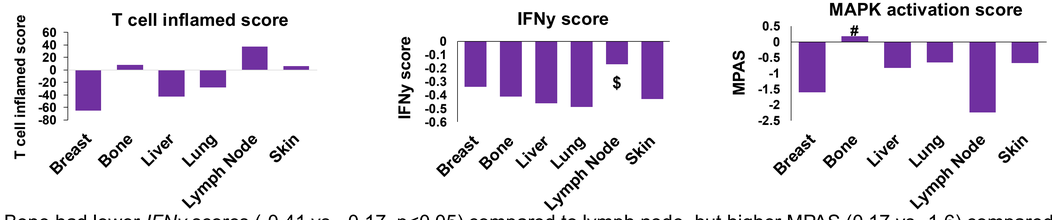
Breast site had lower expression of immune checkpoint genes (*PDCD1LG2, HAVCR2* and *CD47)* compared to other mets. Bone showed reduced expression of *CD47* (median TPM 50.6 vs. 109.9, p<0.05) compared to skin. # p-value <0.05 is relative to breast biopsy, $ p-value <0.05 is relative to bone biopsy.

Figure 3. Mutation analysis of MBC vs FBC patient treated with ADC



Breast biopsy showed a significantly lower prevalence of *PIK3CA* mutations (23.7% vs. 53.3%) compared to bone mets. *ESR1* mutations were absent in breast site but present in 25% of liver and 25% of lung met. # p-value <0.05

Figure 4. T-cell inflamed, IFNy and MAPK activation score



Bone had lower *IFNy* scores (-0.41 vs. -0.17, p<0.05) compared to lymph node, but higher MPAS (0.17 vs -1.6) compared to breast biopsy # p-value <0.05 is relative to breast biopsy, $ p-value <0.05 is relative to bone biopsy.

CONCLUSIONS

Distinct genomic and immune signatures characterize MBC metastases by site, suggesting that metastatic tropism shapes tumor evolution and may inform personalized treatment strategies.