The Molecular and Immune Landscape of HER2 Positive Breast Cancer

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INTRODUCTION

Recent molecular profiling advances have transformed breast cancer treatment. These breakthroughs have largely benefited patients with hormone receptor–positive and triple-negative breast cancers, while HER2-positive (HER2+) breast cancer remains less understood molecularly. We evaluated the tumor immune microenvironment of HER2+ breast cancer, assessing immune cell infiltration, TMB, PD-L1 status, and HLA allele prevalence, to uncover biomarkers for treatment.

METHODS

- Tempus Lens was used to identify 455 female patients with HER2+ breast cancer and xT and xR testing.
- Patients were classified as having localized (stage 1-3, N = 124) or de novo metastatic disease (stage 4, N = 331).
- Wilcoxon rank sum, Fisher's exact, and Pearson's Chi-squared tests were used to compare groups, as appropriate.
- Immune cell proportions were estimated using quanTIseq. TMB, PD-L1, and HLA were also analyzed.
- Risk-set adjusted real-world overall survival (rwOS) was calculated from first line treatment start to death from any cause.

SUMMARY

Our findings suggest a potential therapeutic benefit of incorporating immunotherapy into the treatment paradigm for HER2+ breast cancer, in both localized and metastatic disease settings. Moreover, the ethnically enriched HLA polymorphisms within our patient cohort may help elucidate observed disparities in clinical outcomes and offer valuable insights for the development of population-tailored immunotherapeutic strategies.

RESULTS

Cohort Characteristics

	Overall (N = 455)	De Novo Metastatic (N = 331)	Localized (N = 124)	p-value
Age at Diagnosis Median (Q1, Q3)	55 (44, 65)	56 (45, 65)	54 (42, 63)	0.14
Race				0.3
White	217 (71%)	169 (73%)	48 (63%)	
Black or African American	46 (15%)	30 (13%)	16 (21%)	
Other Race	31 (10%)	23 (10%)	8 (11%)	
Asian	13 (4%)	9 (4%)	4 (5%)	
Unknown	148	100	48	
HR Status at Diagnosis				0.4
HR+	301 (67%)	222 (68%)	79 (64%)	
HR-	151 (33%)	106 (32%)	45 (36%)	
Unknown	3	3	0	

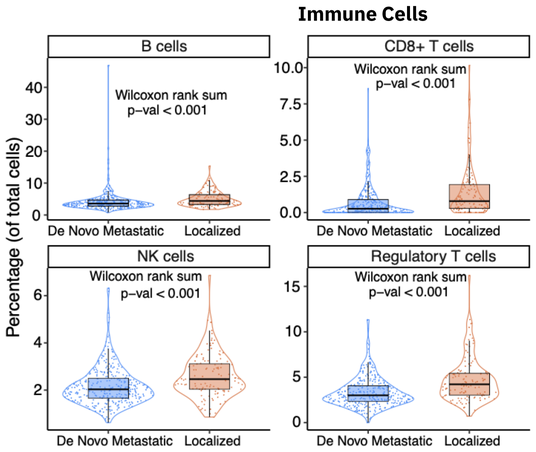

Figure 1. Tumor-infiltrating B cells, natural killer (NK) cells, CD8+ T cells, and regulatory T cells all had increased infiltration in the localized patients compared to the de novo metastatic patients (all p<0.001).

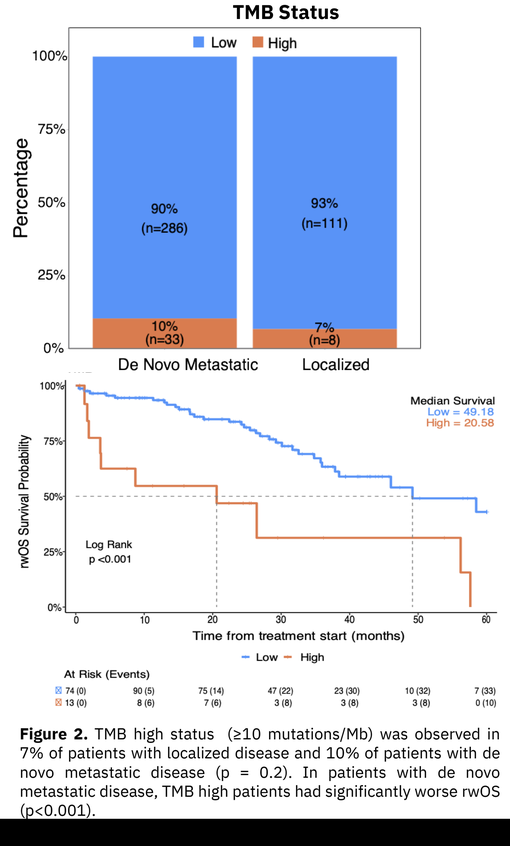

Figure 2. TMB high status (≥10 mutations/Mb) was observed in 7% of patients with localized disease and 10% of patients with de novo metastatic disease (p = 0.2). In patients with de novo metastatic disease, TMB high patients had significantly worse rwOS (p<0.001).

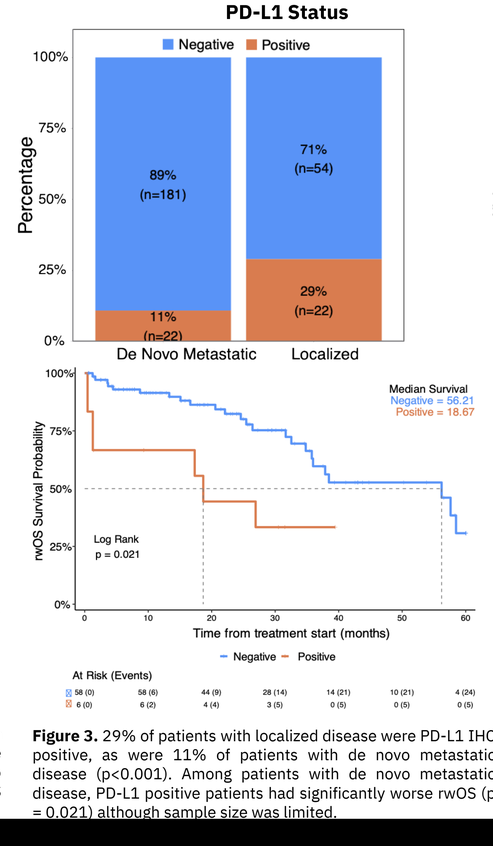

Figure 3. 29% of patients with localized disease were PD-L1 IHC positive, as were 11% of patients with de novo metastatic disease (p<0.001). Among patients with de novo metastatic disease, PD-L1 positive patients had significantly worse rwOS (p = 0.021) although sample size was limited.

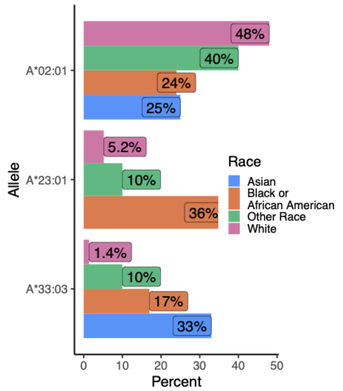

Figure 4. Across all patients with patient-reported race information available, the HLA-A *02:01 allele exhibited the highest overall frequency (43%). Stratified by race, this allele was most prevalent in White patients (48%), with significantly lower frequencies observed in Asian (25%) and Black (24%) patients (p=0.018). In contrast, the HLA-A *33:03 allele demonstrated a higher frequency in Asian patients (33%), and lower prevalence in Black (17%) and White (1.4%) patients (p<0.001). Similarly, the HLA-A *23:01 allele was more frequently observed in Black patients (36%) compared to White (5.2%) and Asian (0%) patients (p<0.001).

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