Genomic and Transcriptomic Landscape of HER2-Low Breast Cancer

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BACKGROUND

- Breast cancer has pioneered precision medicine with prognostic and predictive subtypes.
- HER2-low (H2L) has emerged as a novel therapeutic entity.
- H2L defined: HER2 IHC 1+ or 2+ with negative in-situ hybridization (ISH) assay.
- H2L represents about 50% of all breast cancer.
- Investigation into the mutational landscape of H2L compared to historical subtypes will shape understanding of the clinical and biologic factors driving mechanisms of resistance and consideration of post-progression treatment options within H2L populations.

METHODS

Data Source: H2L breast tumors identified in the Caris Life Sciences database of >11,000 samples.

Outcomes:

- Mutations detected by DNA next-generation sequencing (NextSeq 592 gene panels or NovaSeq whole exome sequencing).
- PD-L1 IHC expression (SP142 IC ≥ 1%).
- Tumor mutational burden (TMB), total somatic mutations per-tumor (high ≥ 10 mutations per megabase).

Analysis: Fisher's-Exact/Mann Whitney/$\chi 2$ tests, significance determine by Benjamini-Hochberg-correction-adjusted p-value (q value) <0.05.

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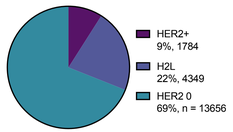
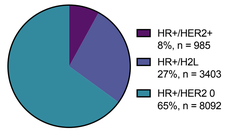
RESULTS

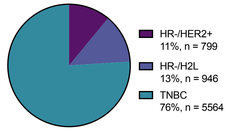
22% of tumors tested with HER2 staining were Identified as H2L (n= 4349)



Whole Cohort by Her2 Staining
Figure 1



HR+ Cohort by Her2 Staining
Figure 2



HR- Cohort by Her2 Staining
Figure 3

HR-/H2L similar to TNBC and are immune "hot" compared to HR+/H2L tumors

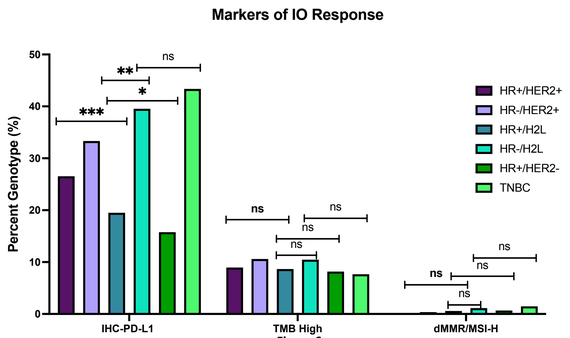


Figure 6

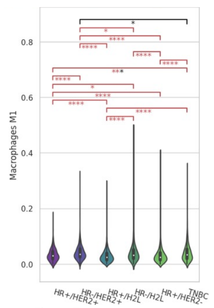


Figure 7

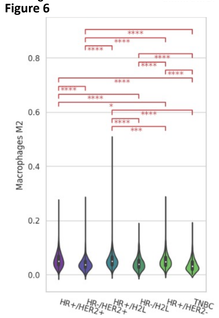


Figure 8

PIK3CA is higher in HR-/H2L vs. TNBC

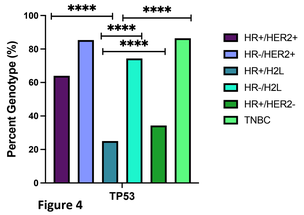


Figure 4

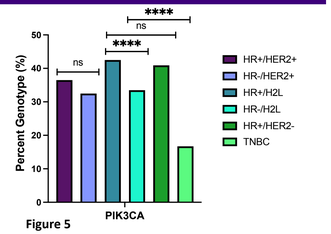


Figure 5

Overall H2L breast cancer similar to classic molecular subtype of either HR+ or TNBC

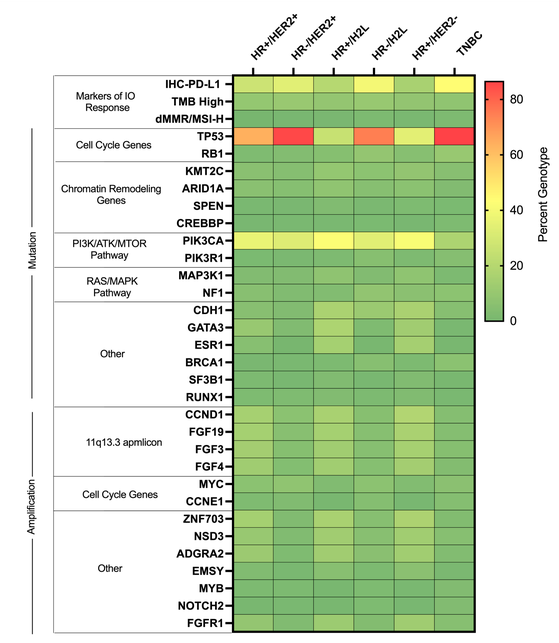


Figure 9

SUMMARY

- 22% of all tumors were identified as H2L; 27% of HR+ and 13% of HR- tumors are H2L (Figure 1).
- Increased frequency of amplifications in HR+/H2L tumors compared to HR-/H2L in CCND1 (15.6% vs 5.0 %), FGF3 (13.3% vs 4.7%), FGF4 (13.3% vs 4.2%), FGF19 (14.4% vs 4.7%), ZNF703 (15.6% vs 4.4 %), NSD3 (12.9% vs 5.2%), ADGRA2 (13.1% vs 5.3%), FGFR1 (11.7% vs 3.6%), and EMSY (5.2% vs 1.4%)(all q<0.05, Figure 9).
- TP53 mutations were significantly higher in HR-/H2L (75.4% vs 25%; q < 00001) compared to HR+ H2L.
- PIK3CA mutations were higher in HR-/H2L compared to TNBC (33.4% vs 16.7% q < 00001) (Figure 4, 5).
- Markers of IO response (PD-L1 positivity and TMB-H) similar between HR-/H2L and TNBC subtype.(Figure 6).
- M1 and M2 macrophage abundance differs between HER2 subtypes (Figure 7).

CONCLUSIONS

- With some exceptions, H2L breast cancer shared genomic features with its more classically defined subset of either HR+ or HR- disease.
- Notable differences in PIK3CA (an actionable mutation warrant additional assessment, as do the differences in gene amplification between groups.
- Our findings confirmed that H2L Breast cancer is not a separate entity, but is driven largely by a classic subset.
- As such, future trial designs in H2L breast cancer should be developed, either escalating or de-escalating therapy, evaluating resistance, or post-progression therapy.