Genomic evaluation of tumor mutational burden-high (TMB-H) versus TMB-low (TMB-L) metastatic breast cancer to reveal unique mutational features

Sarah Sammons[1,2], Andrew Elliott[3], Jeremy Meyer Force[1,2], Nicholas C. DeVito[1,2], Paul Kelly Marcom[1,2], Sandra M. Swain[4], Antoinette R. Tan[5], Evanthia T. Roussos Torres[6], Jia Zeng[7], Mustafa Khasraw[1,2], Justin M. Balko[8], Wolfgang Michael Korn[7], Carey K. Anders[1,2]; Duke University Medical Center[1], Duke Cancer Institute, Durham, NC[2]; CARIS Life Sciences, Irving, TX[3]; Georgetown University Medical Center and MedStar Health, Washington, DC[4]; Levine Cancer Institute, Atrium Health, Charlotte, NC[5]; University of Southern California, Keck School of Medicine, Department of Oncology, Los Angeles, CA[6]; Caris Life Sciences, Phoenix, AZ[7]; Vanderbilt University Medical Center, Nashville, TN[8]

Abstract

Background:
Tumor mutational burden (TMB) has emerged as an imperfect biomarker of immune checkpoint inhibition (ICI) outcomes in solid tumors. Despite the approval for pembrolizumab in all TMB-high (TMB-H) solid tumors, the optimal clinical approach to TMB-H advanced/metastatic breast cancer (MBC) is unknown with sparse prospective data.

We hypothesized that TMB-H MBC will have unique genomic alterations, mutational signatures, and immune profiles compared to TMB-low (TMB-L) breast cancer that could inform novel therapeutic approaches.

Methods:
- Tumor samples (N = 5621) obtained from patients with MBC were analyzed by next-generation sequencing (NGS) of DNA (592-gene panel or whole exome sequencing) and RNA (whole transcriptome sequencing) at Caris Life Sciences (Phoenix, AZ).
- TMB was calculated based on recommendations from the Friends of Cancer Research TMB Harmonization Project[1], with the TMB-H threshold set to ≥ 10 muts/Mb.
- IHC was performed for PD-L1 (Ventana SP142 ≥1% immune cells).
- Deficient mismatch repair (dMMR)/high microsatellite instability (MSI-H) was tested by IHC and NGS, respectively.

Results

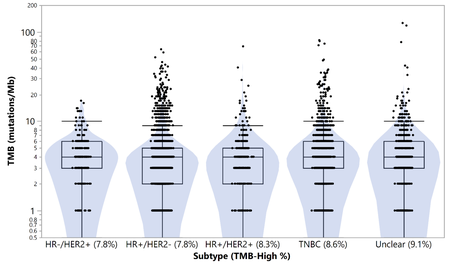


FIGURE 1a. TMB-H was identified in 8.2% (n = 461) of MBC samples, with similar frequencies observed across molecular subtypes.

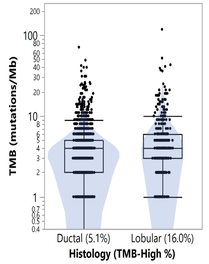


FIGURE 1b. The frequency of TMB-H was significantly increased in lobular (16%, n = 116) versus ductal (5%, n = 56) MBC (p < 0.01).

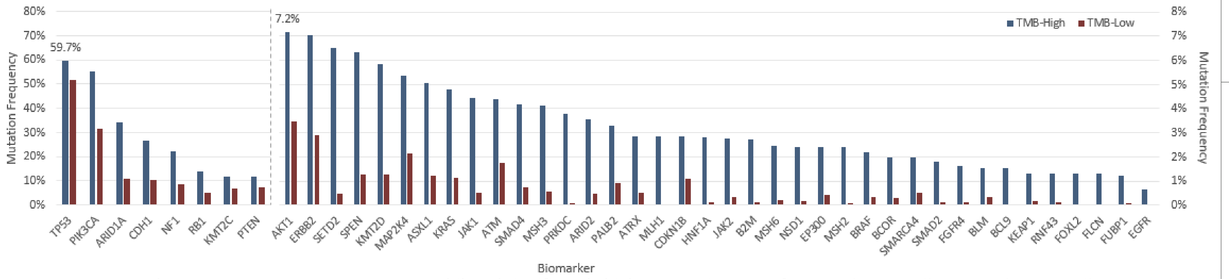


FIGURE 2. Compared to TMB-L tumors, TMB-H tumors exhibited significantly higher mutation rates for TP53 (60 v 52%), PIK3CA (55 vs 31%), ARID1A (34 vs 11%), CDH1 (27 vs 11%), NF1 (22 vs 9%), RB1 (14 vs 5%), KMT2C (12 vs 7%), PTEN (12 vs 7%), ERBB2 (7 vs 2.9%), and PALB2 (3.3 vs 1%) genes (p < 0.05 each).

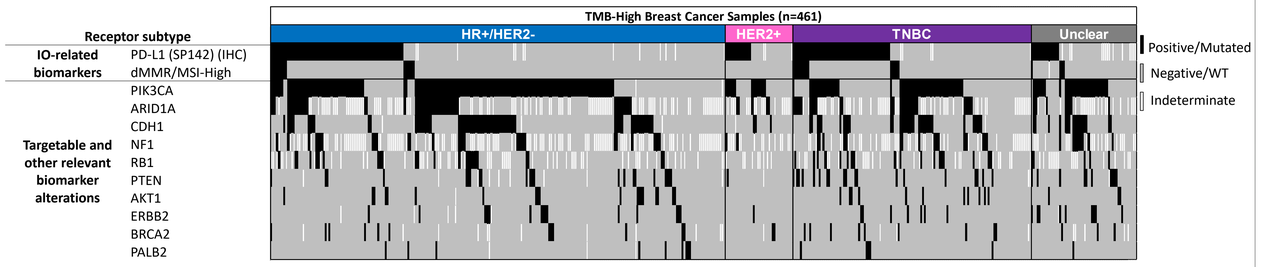


FIGURE 3. TMB-H breast tumors have diverse co-occurring targetable alterations within MBC subtypes. RB1 mutations, linked to CDK4/6 resistance (cite), are enriched in TMB-H HR+/HER2- MBC. PTEN mutations, linked to ICI resistance are increased in TNBC subset.[2,3]

Results

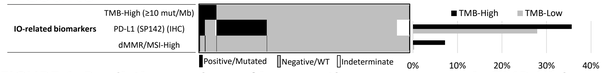
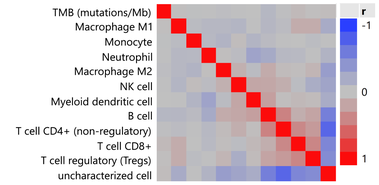


FIGURE 4. Predictive markers of immunotherapy response in TMB-High vs TMB-Low BC. dMMR/MSI-High (7.2 vs 0.3%, p < 0.01) and PD-L1 positivity (36 vs 28%, p < 0.05) frequencies were significantly increased in TMB-H tumors. Minimal overlap between TMB-H and PDL-1 tumors.



Abundance of immune and stromal cell populations determined by deconvolution of cell-specific transcriptional markers using quanTIseq.[4]

FIGURE 5. TMB weakly correlates with markers of immune cell infiltration. Heatmap of correlations between TMB and immune and stromal cell population abundance. (r=Pearson correlation coefficient)

Conclusions

- TMB-H tumors represent 8.2% of all breast cancers and are enriched in lobular breast cancers
- TMB-H breast cancers contain a unique genomic profile enriched with targetable mutations such as PIK3CA, ARID1A, NF1, PTEN, ERBB2, and PALB2
- HR+/HER2- TMB-H breast cancers have higher rates RB1 mutations, linked to CDK4/6 and endocrine resistance
- Concurrent predictive biomarkers of response to immune checkpoint inhibition such as MSI-H and PDL-1 positivity are also more prevalent in TMB-H MBC.
- These findings suggest novel combination strategies within TMB-H MBC could be explored
- TMB is weakly correlated with immune cell population abundance/fractions and immune signatures

References

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