Impact of TP53 mutations on Treatment Duration with CDK 4/6 Inhibitors and Immune Checkpoint Inhibitors in ER-positive/HER2-negative Breast Cancer: Insights from Real-World Data

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INTRODUCTION

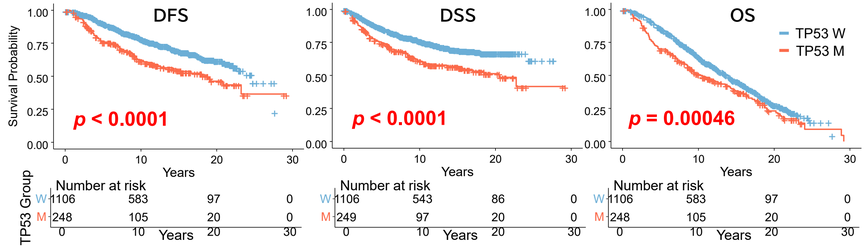
- TP53 mutation is a key driver of breast cancer. However, its clinical impact remains unclear. This study investigates the relationship between TP53 mutations and response to CDK 4/6 inhibitors (CDK4/6i) and immune checkpoint inhibitors (ICI) in breast cancer using real-world data (RWD) from the C-CAT (Center for Cancer Genomics and Advanced Therapeutics) cohort, with particular focus on age-related differences. The duration of treatment was used as a surrogate of unresponsiveness to treatment and progression of disease during treatment.

METHODS

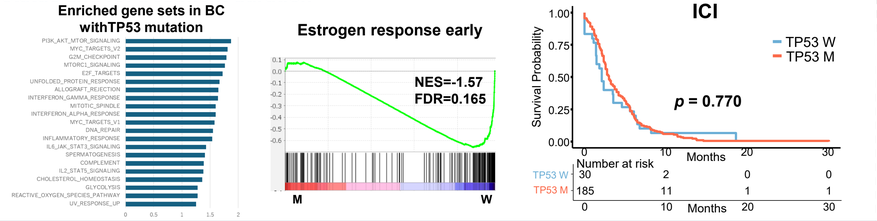
- We used METABRIC data for initial survival analysis and performed Gene Set Enrichment Analysis (GSEA) to identify pathway enriched in TP53-mutated ER-positive/HER2-negative breast cancers. We also investigated the relationship of TP53 mutations and durations of CDK4/6i and ICI treatments in the C-CAT cohort, a database that includes clinical and genomic data of metastatic breast cancer patients from Japan. To evaluate treatment resistance in metastatic breast cancer, we used treatment duration as a clinical endpoint. The CCAT cohort was stratified by age into four groups: Adolescent and Yong Adults (AYA: 15-39 y.o.), perimenopausal (40-54 y.o.), menopausal (55-64 y.o.), and old (over 65 y.o.).

Results

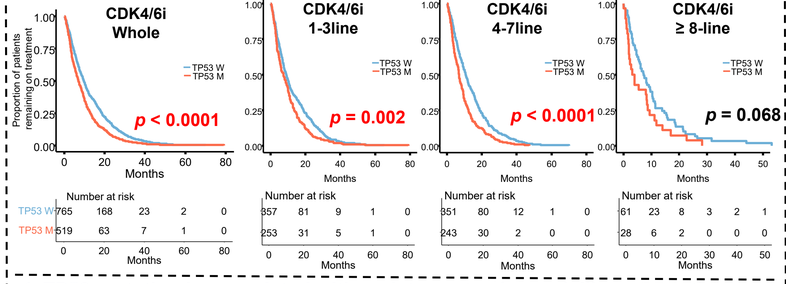
1. Prognostic impact of TP53 mutations in ER-positive/HER2-negative breast cancer



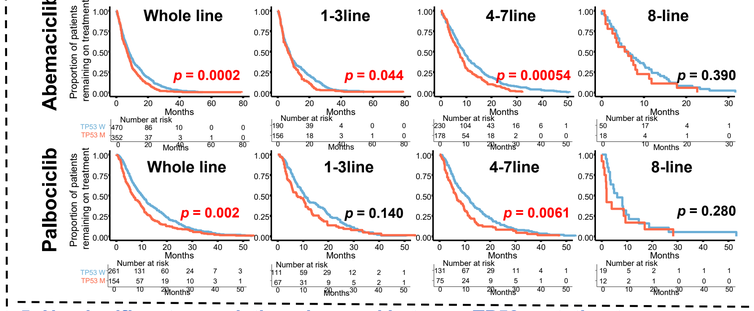
2. Biological characterization of TP53 and no significant difference between TP53 mutation status and ICI treatment duration



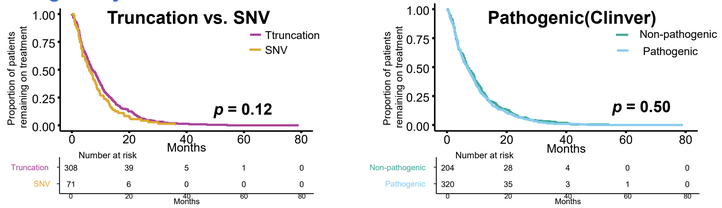
3. TP53 mutation shortens CDK4/6i treatment duration in early line, but not difference in late line



4. TP53 mutation is associated with resistance to abemaciclib more so than palbociclib in ER-positive/HER2-negative breast cancer

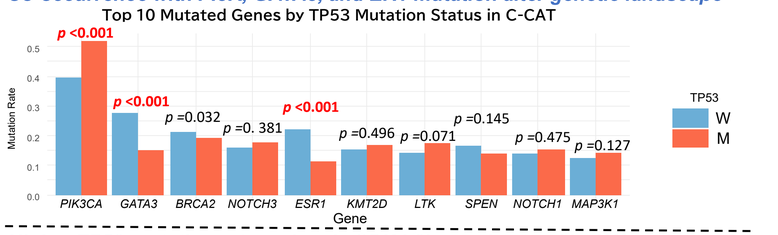


5. No significant association observed between TP53 mutation type or pathogenicity and treatment duration

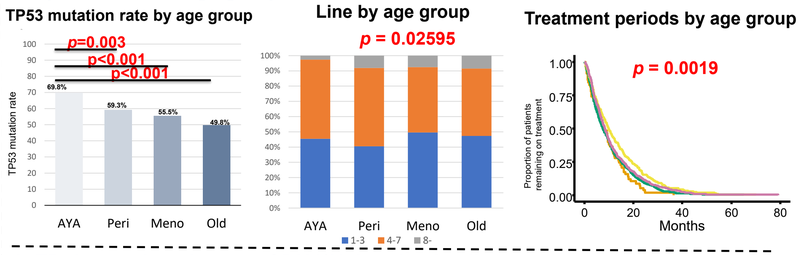


*SNV, single-nucleotid variant

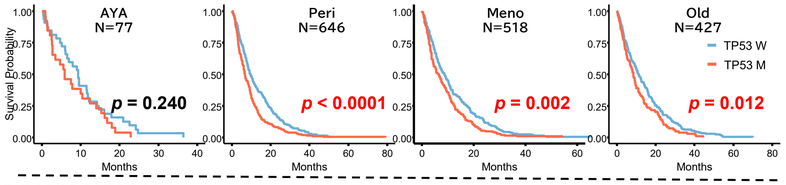
6. Co-occurrence with PI3K, GATA3, and ER1 mutation alter genetic landscape



7. Higher TP53 mutation rate and early CDK4/6i use observed in AYA patients compared to older age groups



8. TP53 mutation shortens CDK4/6i duration in all age groups without



CONCLUSION

- This study demonstrated that TP53 mutation is associated with shorter duration of CDK4/6i treatment, particularly in the early stages, with similar trends observed for Abemaciclib and Palbociclib. These findings highlight the need for personalized treatment strategies based on TP53 mutation status. While the impact of TP53 mutations on ICI treatment duration was not significant, it suggests that other factors may influence ICI efficacy. Additionally, age-specific therapeutic strategies should be considered, as the impact of TP53 mutations on treatment duration varies by age group.

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