P1.05.25

Prognostic implications of oncogenetic pathway alterations in advanced male breast cancer

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BACKGROUND

Male breast cancer (MaBC) encompasses 1% of all BCs. In a previous work (Trapani et al, SABCS 2023), we reported that MaBC recapitulates a unique mutational repertoire. However, prognostic implications of altered pathways in MaBC vs female BC (FeBC) have not been reported before.

- In this work, we analyzed the **prognostic implication of single alterations on MaBC-related survival**.

METHODS

- 17,759 breast tumors were tested by next-generation sequencing (592, NextSeq; WES, NovaSeq) and whole-transcriptomics sequencing (NovaSeq; Caris Life Sciences, Phoenix, AZ).
- **Real world overall survival** (rwOS) was obtained from insurance claims and calculated from treatment start to last contact using Kaplan-Meier estimates.

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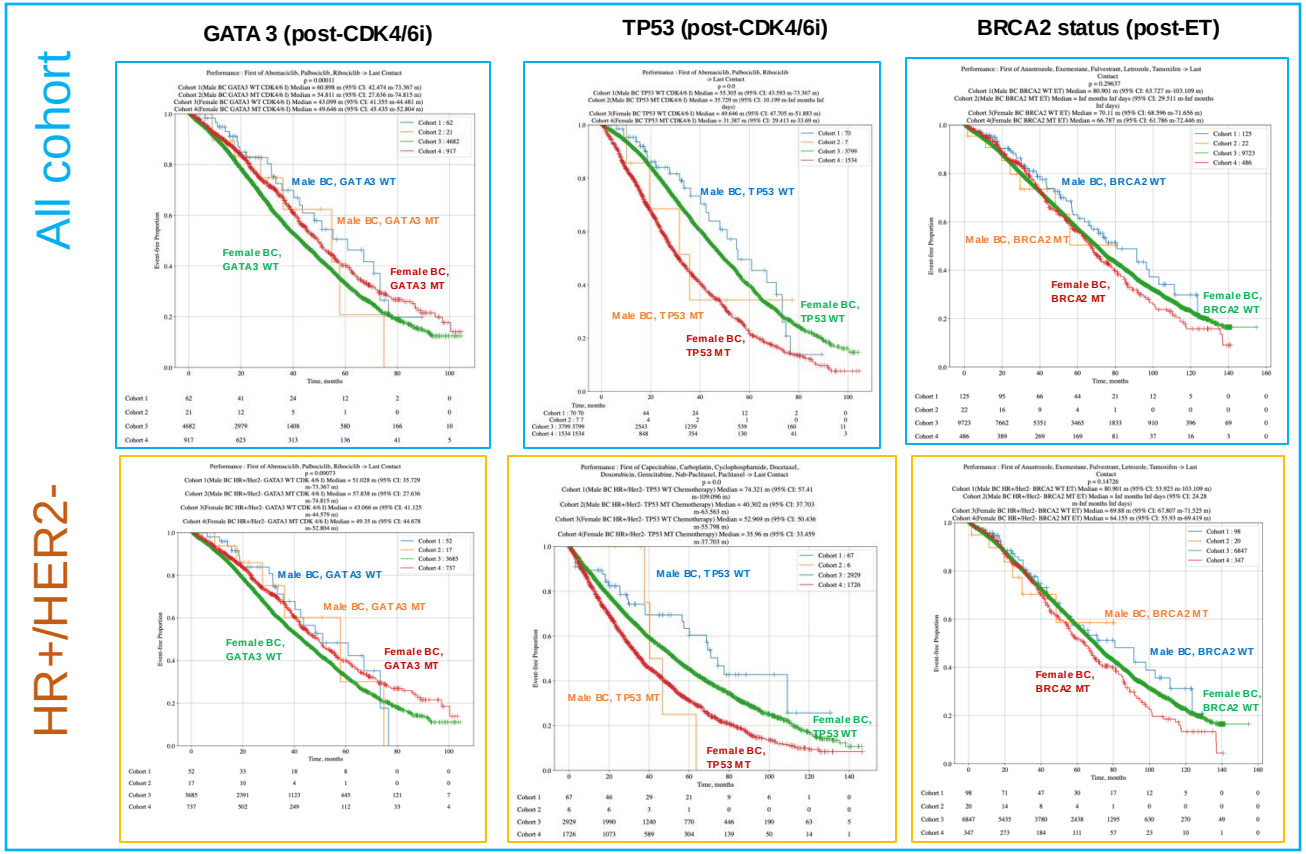
RESULTS

Figure 1. rwOS in patients undergoing treatment with endocrine therapy (ET) with/out CDK4/6i according to selected gene alterations.



The proportion of HR+/HER2- subtype was 72.12% in MaBC and 54% in FeBC.

- **Results in the HR+/HER2-MaBC subgroup were consistent with those reported in the overall cohort**. **Figure 1.**
- The number of HR+/HER2- MaBC with mutations in ESR1 (n=7), AKT1 (n=2), PTEN (n=8), mTOR (n=0), CDK4 (n=0), Rb1 (n=2) were very infrequent.

We identified **226 (1.3%) MaBC** and 17,533 (98.7%) FeBC. in FeBC.

- **GATA3** mutations (MT) were associated with better OS post-endocrine therapy (mOS: 49.6 vs. 43.1 months, HR 0.83, 95% CI 0.71-0.9, p<0.01) compared to GATA3 wild type (WT), whereas in MaBC, GATA3-MT was not associated with survival post-endocrine therapy (mOS: 54.8 vs. 60.8 months, HR 1.4, 95% CI 0.63-3.2, p=0.39) compared to GATA3-WT. **Figure 1.**
- The presence of **TP53** mutations was adversely associated in FeBC but not in MaBC. Poorer outcomes in TP53-MT vs WT were observed in FeBC patients post-endocrine therapy (FeBC: Δ mOS 25.2 months, HR 1.7, 95% CI 1.6-1.7, p<0.01 vs MaBC: Δ mOS 16.3 months, HR 1.08 95% CI 0.43-2.7, p=0.85), with CDK4/6 inhibitor (FeBC: Δ mOS 18.2 months, HR 1.7, 95% CI 1.6-1.9, p<0.01 vs MaBC: Δ mOS 19.5 months, HR 1.35, 95% CI 0.46-2.7, p=0.57) and in the post-chemotherapy setting (FeBC: Δ mOS 18 months HR 1.3, 95% CI 1.3-1.4, p<0.01 vs MaBC: Δ mOS 34 months HR 1.7, 95% CI 0.93-3.4, p=0.07).
- **CDH1, BRCA2 and PIK3CA mutations appeared to have no prognostic role in both MaBC and FeBC.**

CONCLUSIONS

MaBC may recapitulate a unique tumorigenic trajectory that might differ from FeBC, as suggested by the dissimilar prognostic significance of selected genomic alterations. The data warrant further confirmation, to understand the **sex-defined differences in BC**, thus yield tailored therapeutic strategies.