PS1-08-10 Adherence to Guidelines Recommended Germline Testing and Mutational Status of *BRCA1/2* Genes and Beyond as a Predictor of Response to CDK4/6 Inhibition in Advanced Breast Cancer

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Objective:
Cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) combined with endocrine therapy are the standard first-line treatment for hormone receptor-positive/HER2-negative advanced breast cancer (HR+ HER2- ABC). Germline *BRCA1/2* mutation (*gBRCAm*) has been associated with poorer treatment outcomes in this setting, but the predictive value of other germline breast cancer susceptibility gene mutations (beyond-*BRCAm*) remains unexplored.

Methods:
We aimed to compare time to treatment failure (TTF) in *gBRCAm* and beyond-*BRCAm* vs. patients without confirmed germline mutations treated with CDK4/6i at the Department of Oncology of the University Hospital Centre Zagreb from 2018 to 2023. Clinical data were collected retrospectively and prospectively depending of the timing of germline testing. TTF, defined as discontinuation due to progression, toxicity, or patient preference, was analyzed using Kaplan-Meier estimates, and group comparisons were assessed with the log-rank test.

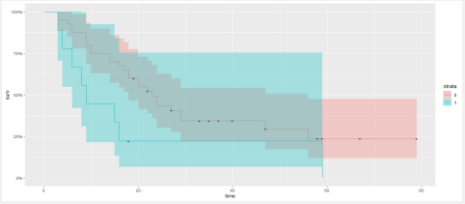


Figure 3. Kaplan-Meier TTF curve with 95% CI for the *gBRCAm* (1, n=9) and non-*gBRCAm* cohort (0, n=40)

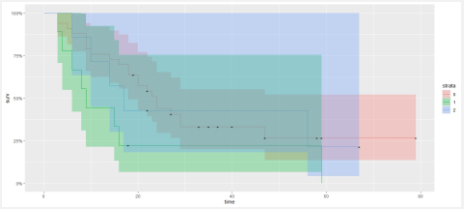


Figure 4. Kaplan-Meier TTF curve with 95% CI for the *gBRCAm* (1, n=9), beyond-*BRCA* (2, n=7) and no confirmed germline mutation cohort (0, n=33)



Figure 1. CONSORT diagram of the study

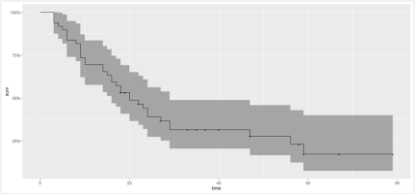


Figure 2. Kaplan-Meier TTF curve with 95% CI for the entire cohort (n=49)

Results:
Among 389 patients treated with CDK4/6i at our institution in advanced setting, only 49 of them (12.6%) underwent germline genetic testing. Of these, 9 (18.4%) were *gBRCAm* (2 *BRCA1*, 4 *BRCA2*, 3 *PALB2*), 7 (14.3%) were beyond-*BRCA* (*ATM, CHEK2, FANCI, FANCC, AIP, LZTR1*, and *MYC*), and the remaining 33 (67.3%) were without confirmed germline mutations. (Figure 1.)
Treatment failure occurred in 35 out of 49 patients. The overall median TTF was 20 months (95% CI, 16-29), with a mean TTF of 31.3 months (95% CI, 23.3-39.3). (Figure 2.)
In the *gBRCAm* cohort (n=9), treatment failure occurred in 8 patients. Median TTF was 9 months (95% CI, 6-NA), and mean TTF was 19.9 months (95% CI, 6.0-33.8). In the non-*gBRCAm* cohort (n=40), treatment failure occurred in 27 patients. Median TTF was 23 months (95% CI, 18-56), and mean TTF was 34.6 months (95% CI, 25.4-43.8). (Figure 3.)
TTF was significantly shorter in *gBRCAm* subgroup (log-rank χ^2 = 4.7, p = 0.03).

In the beyond-*BRCA* subgroup (n=7), treatment failure occurred in 5 patients. Median TTF was 17 months (95% CI, 10-NA), and mean TTF was 35.6 months (95% CI, 13.9-57.3). In the group without confirmed germline mutations (n=33), treatment failure occurred in 22 patients. Median TTF was 24 months (95% CI, 18-NA), and mean TTF was 35.2 months (95% CI, 24.9-45.5). (Figure 4.) Log-rank comparison for the three subgroups yielded χ^2 = 4.7, p = 0.09.

Conclusion:
In this single-institution cohort, *gBRCAm* patients demonstrated significantly shorter TTF when treated with CDK4/6i combined with endocrine therapy, suggesting outcomes consistent with results of previous studies in this specific patient population. Patients with beyond-*BRCAm* showed TTF outcomes comparable to those without confirmed germline mutations, although interpretation is limited by the small sample size. Notably, only 12.6% of patients underwent germline genetic testing, highlighting a need to adhere to *BRCA1/2* testing guideline recommendations for ABC to optimize individualized treatment strategies in HR+/HER2- ABC. Expanded genetic testing and further studies are warranted to clarify the predictive value and underlying mechanisms of resistance for both *gBRCAm* and beyond-*BRCAm*.

References:
Antonio Giordano, MD, PhD. Poor Outcomes of CDK4/6 Inhibitors in BRCA-Mutant Breast Cancer: What Mechanisms Might Be Responsible? ASCO Dly News [Internet]. Available from: https://dailynews.ascopubs.org/do/poor-outcomes-cdk4-6-inhibitors-brca-mutant-breast-cancer-mechanisms-might-responsible

All authors declare that they have no conflicts of interest.