Germline BRCA1/2 and other high-risk estrogen-receptor/HER2- breast cancer (BC) patients treated with endocrine therapy (ET) with or without palbociclib: A secondary analysis from the PENETO-BL study

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Background

The PENETO-BL trial (1) did not show an improved invasive disease-free survival (DFS) by adding palbociclib to ET in high-risk HER2- BC. In a HER2+/HR-positive population germline (g) BRCA1/2 mutations were observed in approximately 14% and BRCA1/2 plus other BC predisposition genes in 20%. In metastatic BC COG 6/6 inhibitors may have greater activity in patients with a BRCA mutation detected in ctDNA. Here, we aimed to investigate the incidence of mutations in gBRCA1/2 and other BC disposition genes (expected to be 10% and 13%, gBRCA1 and gBRCA2, respectively) in their impact on outcome in gBRCA1/2 patients.

Materials and Methods

Blood samples from 898 of the 1250 PENETO-BL patients were available. 445 patients were sampled following a case-cohort design (2) at all 20 defined disease events during follow-up (220 randomly selected patients without any event) and analysed by targeted next generation sequencing (NGS) for germline variants in BRCA1/2 and 16 non-BRCA1/2 cancer predisposition genes: ATM, BARD1, BRIP1, CDH1, CHEK2, FANCA, FANCC, FANCD2, FANCJ, FANCN, PALB2, PTEN, RAF53, RAD51C, RAD51D, STK11, TP53, BRCC2.

The primary definition of mutational status was the presence of a pathogenic variant (pv) (in mt) in one or more analyzed BC predisposition genes. Statistical analyses were based on inverse probability weighting. For time-to-event endpoints (DFS, OS and disease-free survival [DFS]), and overall survival (OS) weighted Cox proportional hazard models and weighted Kaplan–Meier estimators were used. Confidence intervals (CI) for 3-year survival rates and hazard ratios as well as interaction p-values were created by resampling.

Conclusions

This case-analysis of 442 enrolled patients in the PENETO-BL trial is the largest investigation that analyzed BC predisposition genes in HR- patients. The detection of BC predisposition genes was lower than expected. In this subset of patients from the PENETO-BL trial, patients with gBRCA1/2 or other BC disposition genes had a comparable outcome to non-carriers overall and irrespective of treatment.

References


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