GS1-09: OlympiA: A phase 3, multicenter, randomized, placebo-controlled trial of adjuvant olaparib after (neo)adjuvant chemotherapy in patients w/ germline BRCA1 & BRCA2 pathogenic variants & highrisk HER2-negative primary breast cancer: longerterm follow

Presenting Author(s): Judy Garber

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Title

OlympiA: A phase 3, multicenter, randomized, placebo-controlled trial of adjuvant olaparib after (neo)adjuvant chemotherapy in patients with germline BRCA1 and/or BRCA2 pathogenic variants and high risk HER2-negative primary breast cancer: longer term follow-up.

Background

The OlympiA trial (NCT02032823) compared 1 year of adjuvant oral poly(adenosine diphosphateribose) polymerase inhibitor olaparib (OL) to matching placebo (PL) in a randomized trial of 1836 patients (pts) with pathogenic or likely pathogenic variants in germline BRCA1 or BRCA2 (gBRCApv) and high-risk human epidermal growth factor receptor 2 (HER2)-negative primary breast cancer (BC) who had completed all (neo)adjuvant chemotherapy, surgery and radiation. The first pre-specified interim analysis (IA) demonstrated statistically significant improvements in invasive disease-free survival (IDFS) and distant disease-free survival (DDFS). The second IA demonstrated statistically significant improvement in OS and maintained improvement in IDFS and DDFS, irrespective of hormone receptor status, prior platinum administration, timing of prior chemotherapy or type of gBRCApv. No excess acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) was observed. This updated analysis reports the results of the third pre-specified IA with median follow-up (MFU) of 6.1 years (maximum, 9.6 years).

Methods

Descriptive analyses are presented with longer-term follow-up comparing the primary endpoint IDFS, and key secondary endpoints DDFS and OS, across two arms: oral OL 300mg BID versus PL. Estimates of the hazard ratio (HR) based on the stratified Cox's Proportional Hazards Model and 95% confidence intervals (CI) are presented for each endpoint with event rates reported at the 6 year (yr) MFU. Safety analyses including adverse events of special interest (AESIs) and all deaths are highlighted.

Results

With longer follow-up, the benefit of OL in terms of IDFS, DDFS and OS was maintained with effect sizes similar to those reported in previous analyses. For IDFS, HR=0.65 (95% CI: 0.53, 0.78); 6-yr IDFS percents (OL vs PL): 79.6% vs 70.3% (diff. 9.4%; 95% CI, 5.1%, 12.7%). For DDFS, HR=0.65 (95% CI: 0.53, 0.81); 6-yr DDFS percents (OL vs PL): 83.5% vs 75.7% (diff. 7.8%; 95% CI, 3.8%,

11.5%). For OS, HR 0.72 (95% CI: 0.56, 0.93); 6-yr OS percents (OL vs PL): 87.5% vs 83.2% (diff. 4.4%; 95% CI, 0.9%, 6.7%). Total deaths/pts were 107/921 vs 143/915 in OL and PL, respectively. OL benefit was consistent across all key subgroups, including for pts with high-risk, hormone-receptor-positive disease. Fewer BRCA-associated cancers were reported with OL vs PL: contralateral invasive BC (31 vs 40); contralateral non-invasive BC (3 vs 4), new primary ovarian cancer (3 vs 9), new primary fallopian tube cancer (1 vs 4). The percent of pts experiencing AESIs was lower with OL vs PL (6.3% vs 9.3%), comprising MDS or AML (OL, n=4; PL, n=6), pneumonitis (OL, n=9; PL, n=13), and fewer new primary cancers overall (OL, n=45; PL, n=68).

Conclusions

At 6.1 years MFU, one year of adjuvant OL after (neo)adjuvant chemotherapy continues to demonstrate meaningful improvements in IDFS, DDFS and OS in pts with gBRCApv and high-risk, HER2-negative primary BC, including all key subgroups, and with acceptable toxicity and no evidence of increased risk of MDS or AML. These data continue to highlight the importance of gBRCApv testing in high-risk, HER2-negative primary BC.