GS3-01: Circulating tumor DNA surveillance in ZEST, a randomized, phase 3, double-blind study of niraparib or placebo in patients w/ triple-negative breast cancer or HER2+ BRCA-mutated breast cancer with molecular residual disease after definitive therapy

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Background: Circulating tumor DNA (ctDNA) testing in plasma offers the opportunity to identify early breast cancer (BC) recurrence in patients (pts) who, despite completion of definitive therapy, have molecular residual disease (MRD). ZEST is a randomized, phase 3, double-blind trial evaluating whether niraparib can enhance disease-free survival in pts with BC and ctDNA detection (ctDNA+) without evidence of radiographic recurrence after completion of curative intent therapy.
Methods: Pts with stage I–III triple negative breast cancer (TNBC) or BRCA-mutated HER2– BC were eligible. A personalized, tumor-informed ctDNA assay (Signatera) was designed based on whole-exome sequencing of tumor tissue and matched normal blood. Testing for ctDNA-based MRD began any time after the end of definitive treatment (EODT); pts with HR+ disease were allowed concurrent endocrine therapy (stable regimen). Upon ctDNA+, radiographic staging was performed. Those without evidence of metastatic disease were randomized (1:1) to niraparib (200 or 300 mg/day, depending on weight and platelet count) or placebo (PBO). Imaging was performed every 12 weeks. The primary endpoint was safety of niraparib; disease-free survival (measured as time from randomization to recurrence or death from any cause) was also assessed.

Results: As of May 8, 2024, a total of 2746 pts were prescreened; 1901 pts had ≥1 ctDNA test result (ctDNA+, 147 [8%]). Of the 1901 pts, median age was 52 (range, 22–88) years; 1683 pts (89%) had TNBC (ctDNA+, 135), and 218 (11%) had BRCA-mutated HR+ disease (ctDNA+, 12); 620 (33%) pts received neoadjuvant therapy, 643 (34%) received adjuvant therapy, and 593 (31%) received both neoadjuvant and adjuvant therapy. Due to low rates of ctDNA+, study enrollment was terminated early.
ctDNA+ was 5.2% on first test of pts with ≥1 test, and 4.4% on second or subsequent test of pts with ≥2 tests. Of pts with ctDNA+ (n=147), 66% had ctDNA+ on the first test, 91% on the first or second test, and 59% were ≤6 months from EODT. Compared with pts with ctDNA undetected, pts with ctDNA+ tended to have positive lymph nodes, T3/T4 tumor size, stage III disease, residual disease after neoadjuvant therapy, and received both neoadjuvant and adjuvant therapy. Of the 147 pts with ctDNA+, 72 (49%) had radiographic recurrence upon initial staging before randomization. The rate of radiographic recurrence was 52% (51/98) at first ctDNA+ test and 44% (21/48) at second or later ctDNA+ test.
Of pts with ctDNA+, 40 were enrolled and randomized (niraparib, 18; PBO, 22); 36 pts (90%) had TNBC, and 4 pts (10%) had BRCA-mutated HR+ disease. At data cutoff, 6 pts in the niraparib arm and 4 pts in the PBO arm remained on study without radiographic recurrence. Median disease-free

survival was 11.4 (95% CI, 5.7–18.2) months for niraparib vs 5.4 (95% CI, 2.8–9.3) months for PBO (hazard ratio, 0.64; 95% CI, 0.30–1.39). No new safety signals were observed for niraparib. Conclusions: The ZEST study was terminated early because of infeasibility of completing enrollment due to a low rate of ctDNA+ and a high rate of metastatic disease at the time of ctDNA+. Although ctDNA testing began any time after EODT, ctDNA+ occurred most frequently on the first test and ≤6 months from EODT. Pts, predominantly those with TNBC, had a high rate of radiographic recurrence at time of ctDNA+, consistent with early recurrence typical of TNBC. These findings have implications for future trial design, emphasizing the importance of early ctDNA testing, and careful selection of criteria defining risk of recurrence. Updated survival data and on-treatment ctDNA dynamics will be presented.