Advanced breast cancer

PARP INHIBITORS FOR ADVANCED BC WITH GERMLINE BRCA MUTATIONS

TRIAL SUMMARY: Talazoparib safety and efficacy

Litton J, Rugo HS, Ettl J, et al. EMBRACA: A phase 3 trial comparing talazoparib, an oral PARP inhibitor, to physician's choice of therapy in patients with advanced breast cancer and a germline BRCA mutation. 2017 San Antonio Breast Cancer Symposium, December 2017. Abstract.

EMBRACA is an open-label, randomized, 2-arm, phase 3 trial comparing the efficacy and safety of talazoparib (1 mg/day) with standard single-agent physician's choice of therapy (PCT) (capecitabine, eribulin, gemcitabine or vinorelbine) in patients with advanced breast cancer (BC) and a germline BRCA1/2 mutation (gBRCAmut). Talazoparib (TALA) is

a potent, dual-mechanism poly-ADP ribose (PARP) inhibitor that inhibits the PARP enzyme and effectively traps PARP on single-stranded DNA breaks, preventing DNA damage repair and causing cell death in BRCA1/2-mutated cells. The primary endpoint in the study was progression-free survival (PFS) assessed by blinded independent central review. Secondary endpoints were overall survival (OS), overall response rate (ORR), clinical benefit rate at 24 weeks (CBR24), and safety. Patient-reported quality of life (QoL) was also explored. Patients included in the study were 18 years or older; had HER2-negative advanced BC, deleterious or suspected deleterious gBRCAmut; had already received ≤3 prior cytotoxic regimens; and had Eastern Cooperative Oncology Group (ECOG) performance status ≤2. Patients were randomized 2:1 and stratified by receptor status, extent of prior therapy, and central nervous system (CNS) metastases.

Results: A total of 431 patients were randomized (median age 46 years; 54% hormone receptor [HR]+ BC; 45% BRCA1+ and 55% BRCA2+; 55% ECOG PS=0; 38% chemo-naïve for advanced BC (18% prior platinum; 15% CNS metastases); 287 were assigned to TALA and 144 to PCT (1 TALA, 18 PCT patients were not treated). Median duration of exposure was 6.1 and 3.9 months, respectively; TALA had a relative dose intensity of 87%. At 62% PFS data maturity, clinical benefit was seen in all subsets, including those with HR+ BC (HR 0.47; 95% CI: 0.32–0.71) and CNS metastasis (HR 0.32; 95% CI: 0.15–0.88). There was a significant delay in the time to deterioration in global health status/QoL for TALA vs PCT (HR 0.38; 95% CI: 0.26–0.55; p<0.0001). Grade 3–4 hematologic adverse events (AEs) occurred in 55% of the TALA group (mainly anemia) vs 39% of the PCT group (mainly neutropenia). Grade 3–4 non-hematologic AEs were seen in 32% TALA/38% PCT; TALA was associated with fewer gastrointestinal disorders (5.6% vs 11.9%) and skin/subcutaneous tissue disorders (0.7% vs 5.6%) than PCT. Grade 3–4 serious AEs were observed in 26% TALA/25% PCT. AEs associated with permanent study drug discontinuation occurred in 8% TALA/10% PCT. AE resulting in death occurred in 2.1% TALA/3.2% PCT. Single-agent TALA significantly prolonged PFS by blinded independent central review in HER2-negative advanced BC patients with a gBRCAmut compared to PCT; all key secondary efficacy endpoints demonstrated benefit with TALA, with a significant delay in time to deterioration in global health status/QoL. TALA was generally well tolerated with minimal nonhematologic toxicity and few AEs associated with treatment discontinuations.

COMMENTARY: The PARP inhibitors are a novel therapeutic class that has shown efficacy in tumours with germline BRCA1/2 mutations (gBRCAmut); they include olaparib, rucaparib, niraparib, veliparib and talazoparib.[1] PARP is a necessary enzyme in single-stranded DNA repair, something already impaired in patients with gBRCAmut.[2] The first agent to achieve commercial success, olaparib, has been approved in Canada since 2016 for use in advanced ovarian cancers with gBRCAmut, but also has demonstrated efficacy in both metastatic prostate cancer and breast cancer with gBRCAmut,[3,4] received expedited approval from the Food and Drug Administration (FDA) for use in breast cancer[5] and was granted Health Canada approval for use in HER2 negative metastatic breast cancer with gBRCAmut on May 8, 2018.[6] In the phase 3 EMBRACA study, talazoparib reached its efficacy endpoints in advanced breast cancer patients with gBRCAmut. These results are promising, with a 3-month improvement in PFS and OS, despite not yet reaching maturity for OS data. The 62.6% response rate is slightly better than what was shown with olaparib (59%) in the same patient population[4] despite talazoparib reportedly having 100-fold greater PARP-DNA complex trapping ability.[1]

While the results of EMBRACA are interesting, they are not yet practice-changing. At the present time, none of the PARP inhibitors are under review with the pan-Canadian Oncology Drug Review,[7] meaning none have made it into provincial formularies and access is limited to clinical trials or expanded access programs. Many clinical trials are ongoing.[8] The Canadian Clinical Trials Group (CCTG) is examining olaparib's role in the adjuvant setting in HER2-negative breast cancer patients in the OlympiA trial (MA36/BIG 6-13), which is currently open and accruing patients.[9] In addition to the regulatory issues with PARP inhibitors, a practical issue is that we do not have information on BRCA status on all patients. PARP inhibitors are a promising class of targeted therapy with proven efficacy in metastatic gBRCAmut breast cancer, and will be a part of standard care for these patients once regulatory and access issues have been addressed.

IN BRIEF

Already known
- PARP inhibitors have shown efficacy in tumours with germline BRCA1/2 mutations.
- In Canada, PARP inhibitors are approved for use in advanced ovarian cancers with these mutations, but not for breast cancer.

What this study showed
- The EMBRACA study showed promising improvements in progression-free and overall survival in patients with advanced BRCA1/2 breast cancer with the PARP inhibitor talazoparib.

Next steps
- Continue accruing patients to clinical trials in Canada testing PARP inhibitors in advanced breast cancer.
- Gain more widespread testing for BRCA mutations.

References

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