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Supplementary information

The PARTNER trial of neoadjuvant olaparib with chemotherapy in triple-negative breast cancer

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Supplementary Information

Summary from protocol

Randomised, phase II/III, 3 stage trial to evaluate the safety and efficacy of the addition of olaparib to platinum-based neoadjuvant chemotherapy in breast cancer patients with TNBC

1. Details of study stages

This was an open label randomised 3-stage phase II/III trial. Eligible patients with early breast cancer were assessed for basal status using the following immune-histological assessments: CK5/6 and/or EGFR and if appropriate Androgen receptor.

In Stage 1 and 2, patients were randomised with a ratio 1:1:1 to either control or one of the two research arms. At the end of Stage 2, one of the two research arms was dropped. The recruitment continued into all three arms while waiting for the results of analysis of Stage 1 and Stage 2. One research group (olaparib on day 3 to day 14) was selected following the recommendation of the independent data safety monitoring committee (IDSMC), based on pre-specified criteria. Patients were then randomised with a ratio 1:1 to either control arm or the selected research arm (olaparib on day 3 to day 14). It was planned to recruit a minimum of 780 patients in total. The recruitment of patients with TNBC gBRCAwt and patients with gBRCA mutated (gBRCAm) breast cancer were completed independently. It was planned to recruit a minimum of 478 TNBC non-gBRCAwt and 188 gBRCAm patients.

Stage 1 (n=75, 25 patients in each of the two research arms) – Safety.

The primary outcome measure in stage 1 was safety within the research arms. Although all toxicities were considered, particular considerations were given to CTCAE grade 3 and 4 toxicities that appeared to be associated with olaparib especially grade 3 and 4 febrile neutropenia and thrombocytopenia, or events that require dose reduction or discontinuation of olaparib. If there was no evidence that the grade 3 and 4 adverse events as specified above exceeded 35% (i.e. more than 14 out of 25 patients for each of the research arm, or more than 24 out of 50 patients combining both research arms), the trial was continued to Stage 2. Otherwise, the research regimens would be amended. Safety was also compared between the control and experimental arms in an exploratory manner.

Stage 2 (n=159, 53 in each of the two research arms) – Selection of a research arm

Pathological complete response rate (pCR) rate post-surgery was taken together with completion rate of olaparib protocol treatment. It was a “pick-the winner” design with 53 patients in each research arm. This had a 90% power, 5% one-sided significance level to test null hypothesis of pCR ≤ 35% versus an alternative hypothesis of pCR ≥ 55% in each of the research arms.

Recruitment continued while waiting for the results of the analysis based on the 106 patients randomised in both research arms. Assuming that it would take 9 months (6 month to surgery + 3 months data cleaning and analysis) from the date when 106 patients were randomised in both research arms to the date when decision on Stage 2 was made, there were approximately 90 patients randomised in the trial (60 between the two research arms). All 166 patients randomised to the two research arms until end of Stage 2 are being followed-up, and thus provide information between the two research arms; a difference of pCR around 18% between the two research arms could be detected with a 10% significance level (two-sided) and 80% power.

Stage 3 (n=666 between control and the research arm selected in Stage 2) - Efficacy

The primary outcome measure was pCR. Based on the evidence from GeparSixto and CALGB 40603 [1–3] the anticipated pCR was ~45-55% for TNBC gBRCAwt patients and ~50-60% for gBRCA mutated patients, receiving platinum-based chemotherapy. The trial was powered to detect an absolute improvement of 15% for TNBC gBRCAwt and 20% for gBRCAm patients by adding olaparib to chemotherapy.

References:

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