Editorial Commentary

Is adjuvant olaparib standard of care in all high-risk HER2-negative early breast cancer presenting *gBRCA1/2* mutations?

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OlympiA trial is a phase 3, double-blind, multicentric, and randomized trial comparing 1 year of oral olaparib (OL) *vs.* placebo (PL) (1:1 ratio) in patients with high-risk human epidermal growth factor receptor 2 (HER2)-negative early breast cancer (EBC) and *BRCA1/2* germline pathogenic or likely pathogenic variants after local treatment (including radiotherapy) and neoadjuvant chemotherapy (NACT) or adjuvant chemotherapy (ACT). With a median follow-up of 2.5 years and 1,836 patients, it demonstrated a 3-year invasive disease-free survival (iDFS) of 85.9% with OL *vs.* 77.1% with PL [improvement of 8.8%; 95% confidence interval (CI): 4.5% to 13%] (1). Updated results presented at the San Antonio Breast Cancer Symposium 2024, with a follow-up of 6.1 years demonstrated a significant improvement of 6-year OS with OL of 4.3% (87.5% *vs.* 83.2%; 95% CI: 0.9% to 6.7%) leading to a HR of 0.72 (98.5% CI: 0.56 to 0.93) (2).

Patient-reported outcomes (PRO) in OlympiA have just been published (3). Fatigue and reduction of health-related quality of life (HRQOL) are common residual difficulties in the months following (N)ACT in EBC patients (4). Since fatigue is among the most prevalent side effects of OL (1), Ganz *et al.* hypothesized that adding 1 year of OL after (N)ACT might hinder or delay improvements in fatigue and HRQOL following chemotherapy (3). Therefore, they performed a PRO investigation of fatigue (primary endpoint) and functions of HRQOL (secondary endpoints) in patients of OlympiA trial. They also focused on digestive known side effects of OL [nausea and vomiting (NV), diarrhea, loss of appetite] (1).

They opted for Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale (5) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Core 30 item (EORTC QLQ-C30) (6) to obtain indication on fatigue and HRQOL, respectively.

Using FACIT-Fatigue scale, authors demonstrated at 6 and 12 months a statistically significant difference in fatigue severity, being higher in OL arm. However, this difference was not clinically meaningful. No difference was observed at 18 and 24 months (*Table 1*). In both NACT and ACT patients, no clinically meaningful differences in HRQOL were observed at any time between the OL and PL groups for physical, emotional scales or again the Global Health Status/Quality of Life.

Using the EORTC QLC-C30, there was no clinically meaningful (difference of at least 5) impact of OL on diarrhea at any time in patients treated by NACT and ACT. On the opposite, OL led to more clinically meaningful NV

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Table 1 Primary endpoint evaluation: OL-PL: difference of score using FACIT-Fatigue score in OL and PL groups

Months for evaluation	NACT		ACT	
	OL-PL (95% CI)	P value	OL-PL (95% CI)	P value
0 (baseline)	−0.3 (−1.7 to −1.1)	0.64	0.1 (−1.1 to 1.4)	0.82
6	−1.3 (−2.4 to −0.2)	0.02*	−1.3 (−2.3 to −0.2)	0.02*
12	−1.6 (−2.8 to −0.3)	0.02*	−1.3 (−2.4 to −0.2)	0.03*
18	−0.1 (−1.4 to 1.1)	0.82	−0.3 (−1.4 to 0.8)	0.58
24	−0.4 (−1.7 to 0.8)	0.52	−0.3 (−1.4 to 0.9)	0.66

*, statistically significant differences. ACT, adjuvant chemotherapy; CI, confidence interval; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; NACT, neoadjuvant chemotherapy; OL, olaparib; PL, placebo.

at 6 months in both settings [NACT: 6.0 (95% CI: 4.1 to 8.0); P<0.001; ACT: 5.3 (95% CI: 3.4 to 7.2), P<0.001] and at 12 months in NACT group [NACT: 6.4 (95% CI: 4.4 to 8.3), P<0.001; ACT: 4.5 (95% CI: 2.8 to 6.1), P<0.001]. No clinically meaningful differences in NV were seen at 18 and 24 months in either chemotherapy group. OL was also reported to induce more loss of appetite during the active treatment (up to 1 year) which wasn't mentioned later.

Globally the study led by Ganz *et al.* is well conducted. They have a good 83.7% ratio of the patients randomized in the OlympiA trial who fulfilled all the assessment at different time point (with reasonable collection windows and possibility to include in sensitivity analyses patients who answered outside of these windows). The study ensured confidence in interpreting changes over time by achieving a very strong balance in baseline PRO data, with no evidence that treatment-related or demographic factors impact the results. However, some small differences exist between the OL and PL groups. In the ACT setting, patients in OL group were slightly younger and had less radiotherapy, but not to a degree that would cast doubt on the results. In the NAC setting, fewer patients in the OL group received platinum-based chemotherapy, while the opposite trend was observed for radiotherapy. Once again, the differences are minor and don't lead to questioning the results. Authors themselves mention some demographics and treatment-related cofactors which might have influenced the results. Notably, predictable differences in treatment patterns were found between the NACT setting where platinum-based chemotherapy was more frequently administered and ACT setting where conservative surgery was more performed. The large sample size and careful stratification ensured a balanced distribution of variables between treatment arms, making the study's findings applicable to a global population meeting the trial's eligibility criteria. Finally, as acknowledged by authors, the small number of patients with hormone receptor-positive EBC included in the trial limited the ability to thoroughly evaluate this subgroup.

Adherence rates of participants in this study are convincing. At 6 months, the lowest adherence was in the OL group of ACT setting (91.2%). At 12 months, it was 86.9% (OL group in NACT setting). The lowest adherence at 18-month was also found in the OL group of NACT setting (75.7%) while it was in the PL group of NACT setting at 24 months (69%).

The PRO study found no evidence of clinically significant increase in fatigue severity after (N)ACT in high risk EBC patients treated with OL compared to PL, either during the drug administration phase and the following year after discontinuing therapy. Interestingly, mean fatigue levels in the PL group remained stable from baseline to 12 months, indicating a slow recovery from intensive schemes used in EBC treatments.

The FACIT-Fatigue scale is a commonly used tool to evaluate fatigue in patients with chronic diseases including cancers. It has multiple advantages. It has been used in numerous clinical trials and it is one of the rare tools measuring fatigue (with the EORTC QOL—Fatigue Questionnaire 12 and the Fatigue Symptom Inventory) which demonstrated high evidence for addressing all the eight psychometric properties of the COSMIN (COnsensus-based Standards for the selection of health Measurement INstruments) consensus: internal consistency, test-retest, content validity, item tool correlation, convergent/divergent validation, known groups, cross-cultural validity, and responsiveness (7). It is easy to perform since the scale is concise and has only 13 items, taking less than 5 minutes to complete. Moreover, it is sensitive to

change over time, allowing monitoring of fatigue following a treatment or an intervention. It is patient-centered, focusing on how fatigue impacts daily functioning and quality of life from the patient's perspective. All these advantages make the FACIT-Fatigue scale suitable for both clinical practice and research. Nevertheless, it also has some limitations. It may not capture the full multidimensional nature of fatigue (e.g., emotional, cognitive, and motivational aspects), which other tools like the Multidimensional Fatigue Inventory (MFI) might cover. Since it is self-reported, it is subject to patient bias, including underreporting or overreporting of symptoms based on individual perception or recall limitations. Although it has been translated into multiple languages (ensuring that patients answer in their own native languages), the cultural appropriateness of the translations in some contexts is not ideal with some items not fully reflecting the experience of fatigue in different cultural settings. Finally, the FACIT-Fatigue scale has floor or ceiling effects, where the scale may fail to differentiate between patients with extremely low or extremely high levels of fatigue (5,8). Therefore, using at least one another scale developed specifically for measuring fatigue (different then than the subscale on fatigue of the EORTC-QLC C30) would have improved the quality of the study, especially for investigating the multidimensional aspect of fatigue. However, we recognize that this might have decreased the adherence to the study by demanding more effort to the patients.

In summary, this PRO study in OlympiA is giving more insurance to physicians in terms of impact of OL on quality of life and fatigue after chemotherapy in high-risk EBC. Nevertheless, the question of how to treat *gBRCA1/2m* carriers with high-risk EBC remains difficult.

Before the results of the KEYNOTE-522 trial, a residual disease following NACT in EBC triple-negative breast cancer (TNBC) was really indicative of a poor prognostic with an estimated 5-year event-free survival (EFS) of 57% and overall survival (OS) of 47% in absence of pathological complete response (pCR) *vs.* and 5-year EFS of 90% and 5-year OS of 84% when pCR was achieved (9). Therefore, residual disease became the key factor to determine the need for additional adjuvant therapy. The CREATE-X trial was the first trial to prove the improved disease-free survival (DFS) in HER2-negative EBC without pCR after NACT including the TNBC subgroup. Adjuvant capecitabine for 6 to 8 cycles led in this subgroup to a 69.8% 5-year DFS of *vs.* 56.1% in the control group (HR, 0.58; 95% CI: 0.39 to 0.87) and 5-year OS of 78.8% *vs.* 70.3% (HR, 0.52; 95% CI: 0.30 to 0.90) (10). The KEYNOTE-522 trial demonstrated that adding pembrolizumab [an immune checkpoint inhibitor (ICI)] to NACT significantly increased the pCR rate (64.8% *vs.* 51.2%) compared to PL. Nine cycles of adjuvant pembrolizumab were given regardless of pCR status. The 3-year EFS in case of residual disease was higher in the pembrolizumab arm (67.4% *vs.* 56.8%) (11). Recently, both the 5-year OS (86.6% *vs.* 81.7%) and 5-year EFS (81.2% *vs.* 72.2%) (HR, 0.65; 95% CI: 0.51 to 0.83) were proven in favor of pembrolizumab (12). No adjuvant capecitabine was given in the KEYNOTE-522 trial since it was not a standard treatment during the trial's design (12). Phase 2 studies investigating combination of capecitabine and immunotherapy in metastatic TNBC didn't show new safety issues (13). Therefore, in the absence of pCR, it is reasonable to use capecitabine in combination with pembrolizumab, especially if the latter one was well tolerated in the neoadjuvant setting. However, no randomized data currently demonstrates the superiority of multi-agent therapy in this situation.

Treating the *gBRCAm* TNBC in case of residual disease is even more complex. Physicians can opt between OL, pembrolizumab, or capecitabine. Considering improved OS in OlympiA, adjuvant OL is favored since the efficacy of capecitabine is not specifically known in *gBRCAm* patients. Combination of OL and capecitabine is to avoid giving their shared toxicities, especially cytopenias (14). Inhibitors of the poly(adenosine diphosphate ribose) polymerase (PARPi) such OL activate the cGAS/STING pathway enhancing T cell recruitment, increasing tumor neoantigens, and upregulating PD-L1 expression. These effects pave the way to combine PARPi and ICI targeting the PD-1/PD-L1 axis. The PARPi-ICI combination has been well tolerated in phase 2 studies in metastatic setting with clinical benefit, especially in case of *BRCAm* (15-17). Therefore, trials investigating this combination in case of absence of pCR would be of high interest, especially if they consequently aim to discover biomarkers predictive of longer iDFS.

For high-risk *gBRCAm* hormone receptor+ EBC, beside endocrine therapy, the adjuvant treatment must be chosen between OL for 1 year or abemaciblib/ribociclib for 2/3 years. The optimal sequence is unknown. Majority of experts recommend starting by OL. Indeed, if only 18% of OlympiA trial patients are hormone receptor+ (n=325), the data of MonarchE and Natalee trials have not reached maturity for OS analysis, especially in *gBRCAm* patients. The combination of CDK4/6i and PARPi is discouraged

regarding common toxicity (cytopenias) (18). Nevertheless, panelists of 2023 St Gallen International Consensus Conference suggested a sequential approach where OL would be given for one year and CDK4/6i introduced directly after (expert opinion only) (19).

The place of PARPi in neoadjuvant setting remains putative. The phase 3 BrighTNess trial didn't show a higher pCR in breast and lymph nodes with the addition of veliparib to carboplatin-paclitaxel before doxorubicin-cyclophosphamide regimen in TNBC patients (53% *vs.* 58% in absence of veliparib, P=0.36) and failed to prove an advantage in *gBRCAm* cases (20). The phase 2/3 PARTNER trial obtained similar results but using OL (twice daily 150 mg days 3 to 14) whose addition to carboplatin-paclitaxel before anthracyclines in TNBC *gBRCAm* patients led to similar pCR rates (51% *vs.* 52% without, P=0.753) (21). The phase 2 GeparOLA explored use of OL instead of carboplatin in combination to paclitaxel before epirubicin-cyclophophamide in HER2-negative breast cancers with homologous recombination deficiency (HRD). Despite similar pCR rates (55.1% and 48.6%), the replacement by OL tended to inferior 4-year iDFS (76% *vs.* 88.5%) mainly driven by patients without *g/tBRCAm* since no difference was seen in *g/tBRCAm* carriers. Since OL was significantly better tolerated, and some subgroups have stronger pCR with it (52.6% *vs.* 20% in hormone receptor+ patients, 76.2% *vs.* 45.5% in <40 years patients) (22), we consider its capacity to replace carboplatin in well-selected patients worths further investigations rather than adding it to carboplatin-paclitaxel. As monotherapy, 24-week neoadjuvant talazoparib (phase 2 NEOTALA trial), led to 53% pCR rate TNBC *gBRCA1/2m* cases (23), a rate similar to rates obtained before the use of immunotherapy. Therefore, investigation of neoadjuvant use of OL in *BRCAm* TNBC (or HR-low HER2) patients is ongoing in the phase 2 OlympiaN trial. In case of low risk of recurrence (T1b–c/N0) OL monotherapy may be sufficient. Conversely, for those at higher risk (T2/N0 or T1/N1) of recurrence, investigators add immunotherapy (durvalumab). A de-escalation with sparing patients from chemotherapy would represent an important improvement in this setting for selected patients.

Defining biomarkers of response to PARPi remains very important. Among non-*BRCAm* patients, some patients might have a clinical benefit if they have pathogenic variants leading to an HRD (in genes such as: *RAD51*, *CHEK2*, *ATM*, *PALB2*, or *PTEN*). It is also likely that other biomarkers might help to determine which *gBRCAm* patients will benefit or not of PARPi and which patients might present more side effects. More preclinical and clinical investigations are required to perfectly delimit the spectrum of activity/toxicity of PARPi (24).

Finally, experience in ovarian cancer indicated higher risk of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) with OL, especially when platinum and alkylating drugs had been used previously. In SOLO-1 trial, OL was given for 2 years after the platinum-based chemotherapy. After 7 years of follow-up, MDS/AML incidence was 1.5% in OL arm *vs.* 0.8% in PL (25). After follow-up of 6 years in OlympiA there are six cases of MDS/AML in PL group *vs.* four in OL group (2). Adjuvant OL is the new standard of care for HER2-negative EBC presenting *gBRCA1/2* mutations based on OlympiA trial but further studies are needed concerning the optimal integration with other systemic therapies.

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Footnote

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