Dana-Farber Cancer Institute | Susan F. Smith Center for Women's Cancers

Dana-Farber Breast Oncology Center

Updated Consensus Statement Regarding the Use of Adjuvant Olaparib in High-Risk, Early-Stage Breast Cancer Patients with a Pathogenic or Likely Pathogenic Variant in *BRCA1*, *BRCA2*, or *PALB2*

Consensus: Obtained at Breast Oncology Center Meetings on 5/6/2022, 5/20/2022, 6/1/2022, 8/5/2022, 4/18/2025, and 5/15/2026.

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Q2. Should olaparib and pembrolizumab be given concomitantly?	When both olaparib and pembrolizumab are considered, concurrent administration should be preferred, if adequately tolerated.
Q3. Should both capecitabine and olaparib be offered and given sequentially?	Olaparib should be preferred over capecitabine in patients with TNBC and residual disease after neoadjuvant therapy. Sequential administration of olaparib and capecitabine may be offered to patients at "very high" risk of recurrence.
Q4. Should olaparib be considered in TNBC patients with poor response to platinum?	Olaparib should be considered in patients with TNBC regardless of response to platinum (i.e., residual disease despite neoadjuvant platinum).
Q5. Which patients with TNBC should receive adjuvant olaparib after adjuvant chemotherapy?	Adjuvant olaparib after adjuvant chemotherapy should be recommended for patients with stage II-III TNBC, according to the OlympiA criteria. Adjuvant olaparib should not be recommended for patients with stage I TNBC.

2. Consensus statements for the use of adjuvant olaparib in g*BRCA* carriers with early-stage, hormone receptor (HR)-positive/HER2-negative (HR+/HER2-) breast cancer

Clinical Question	Consensus Statement
Q6: What treatment should be recommended after adjuvant chemotherapy for g*BRCA*m patients with HR+/HER2- breast cancer and ≥4 positive axillary lymph nodes?	Adjuvant olaparib should be preferred over adjuvant abemaciclib or ribociclib after adjuvant chemotherapy in g*BRCA*m patients with early-stage, HR+/HER2- breast cancer and ≥4 positive axillary lymph nodes. Sequential administration of olaparib and abemaciclib or ribociclib may be considered in very high-risk patients.
Q7: What treatment should be recommended after adjuvant chemotherapy for g*BRCA*m patients with HR+/HER2- breast cancer and 1-3 positive axillary lymph nodes?	Adjuvant olaparib should be considered after adjuvant chemotherapy in g*BRCA*m patients with early-stage, HR+/HER2- breast cancer and 1-3 positive axillary lymph nodes. Abemaciclib or ribociclib may be considered as an alternative.
Q8. What treatment should be recommended after adjuvant chemotherapy for g*BRCA*m patients with high-risk, node-negative HR+/HER2- breast cancer?	Adjuvant olaparib should generally not be recommended for patients with early-stage, node-negative, HR+/HER2− breast cancer following adjuvant chemotherapy, except for those with a g*BRCA*m who meet NATALEE eligibility criteria but not monarchE, particularly in the presence of high-risk features such as Ki-67 ≥20% or an Oncotype DX Recurrence Score ≥26, and who have received (neo)adjuvant chemotherapy. In this

	subset, the group favored olaparib over ribociclib or endocrine therapy alone.
Q9: What treatment should be recommended after neoadjuvant chemotherapy for g*BRCA*m patients with early-stage, HR+/HER2- breast cancer and ≥4 positive axillary lymph nodes at surgery?	Adjuvant olaparib should be recommended after neoadjuvant chemotherapy in g*BRCA*m patients with early-stage, HR+/HER2- breast cancer and ≥4 positive axillary lymph nodes. Sequential administration of olaparib and abemaciclib or ribociclib may be considered in high-risk patients.
Q10: What treatment should be recommended after neoadjuvant chemotherapy for g*BRCA*m patients with early-stage, HR+/HER2- breast cancer and 1-3 axillary lymph nodes at surgery?	Adjuvant olaparib should be considered after neoadjuvant chemotherapy in g*BRCA*m patients with early-stage, HR+/HER2- breast cancer and 1-3 positive axillary lymph nodes. Abemaciclib or ribociclib should be considered as an alternative. Sequential administration of adjuvant olaparib followed by abemaciclib or ribociclib may be considered in high-risk patients.
Q11: What treatment should be recommended for patients with high-risk, node-positive HR+/HER2- breast cancer who do not receive chemotherapy?	Adjuvant olaparib could be considered for patients with high-risk, node-positive, HR+/HER2- disease who do not receive chemotherapy. Sequential administration of olaparib followed by abemaciclib or ribociclib may be considered for high-risk patients.
Q12: Should olaparib be administered concurrently with endocrine therapy?	Adjuvant olaparib and endocrine therapy should be administered concurrently.
Q13: If both CDK4/6 inhibitors (CDK4/6i) and olaparib are considered, which agent should be offered first?	Administration of olaparib followed by CDK4/6i should be preferred when sequential administration of both agents is considered.
Q14: What is the preferred adjuvant approach for patients with HR+/HER2− breast cancer who carry a g*BRCA*m and are eligible for NATALEE, but do not meet monarchE criteria?	In patients with high-risk early-stage HR+/HER2- breast cancer with a g*BRCA*m who are eligible for NATALEE but do not meet MonarchE criteria, especially those with node-negative tumors and high-risk features such as Ki-67 ≥20% or an Oncotype DX RS ≥26 or tumors ≥ 5 cm, and who have received (neo)adjuvant chemotherapy, the group favored olaparib over ribociclib. This decision should take into consideration factors such as patient age, prior chemotherapy, patient preferences, and overall risk assessment.

3. Consensus statements for the use of adjuvant olaparib in g*BRCA* carriers with early-stage ER-low breast cancer

Clinical Question	Consensus Statement
Q15. Should olaparib be offered to g*BRCA* carriers with ER-low breast cancer according to the OlympiA inclusion criteria defined for TNBC or HR-positive patients?	Olaparib should be offered to g*BRCA* carriers with ER-low breast cancer according to the OlympiA inclusion criteria defined for TNBC (i.e., non-pCR after neoadjuvant chemotherapy; ≥pT2 and/or node-positive disease after surgery and adjuvant chemotherapy).
Q16. Should adjuvant olaparib be administered with endocrine therapy in patients with ER-low breast cancer?	When adjuvant endocrine therapy is considered, adjuvant olaparib should be administered concurrently in g*BRCA*m carriers with ER-low breast cancer.

Q17. If neoadjuvant pembrolizumab was administered to g*BRCA* carriers with ER-low breast cancer and residual disease at surgery, should pembrolizumab, endocrine therapy and olaparib be administered concurrently as post-neoadjuvant therapy?	Concurrent administration of adjuvant pembrolizumab, endocrine therapy and olaparib should be considered. Sequential administration of adjuvant olaparib followed by abemaciclib or ribociclib may be considered in high-risk patients.

4. Consensus statements for the use of adjuvant olaparib in g*PALB2* carriers with early-stage HER2- breast cancer

Clinical Question	Consensus Statement
Q18. Should adjuvant olaparib be considered in g*PALB2*m patients with HER2-negative early breast cancer according to the OlympiA criteria?	Adjuvant olaparib may be considered in g*PALB2*m carriers with HER2-negative early breast cancer according to the OlympiA criteria and MonarchE criteria.
Q19. What is the preferred adjuvant approach for patients with HR+/HER2− breast cancer who carry a g*PALB2*m and meet the NATALEE/monarchE eligibility criteria?	In high-risk HR+/HER2− early breast cancer patients with a g*PALB2*m who are eligible for NATALEE but do not meet MonarchE criteria, especially those with high-risk features such as Ki-67 ≥20% or an Oncotype DX RS ≥26, and who have received (neo)adjuvant chemotherapy, the group favored olaparib over ribociclib or endocrine therapy alone. This decision should take into consideration factors such as patient age, prior chemotherapy, patient preferences, and overall risk assessment.

5. Consensus statements for the use of adjuvant olaparib and the impact on fertility

Clinical Question	Consensus Statement
Q20. Should adjuvant olaparib be considered independently of future pregnancy plans?	Decisions regarding fertility preservation and timing of subsequent pregnancy should be guided by existing data on fertility after standard cytotoxic therapy, patient age, and individual preferences, while acknowledging the uncertainty in this area. A minimum waiting period of six months after completing cytotoxic treatment is generally recommended before attempting conception.

6. Consensus statements on germline genetic testing in patients with early breast cancer

Clinical Question	Consensus Statement
Q21. Which patients should be tested for g*BRCA* status?	Germline genetic testing should be offered to patients according to the NCCN criteria, including those who may be eligible for adjuvant olaparib. In parallel, ASCO guidelines recommend offering germline *BRCA1/2* testing to all newly diagnosed breast cancer patients ≤65 years, with selective testing in older patients

	or in the recurrent setting when results inform PARPi eligibility, risk assessment, or clinical management.

7. Consensus statements on toxicity monitoring and management in g*BRCA*m carriers with early breast cancer receiving adjuvant olaparib

Clinical Question	Consensus Statement
Q22. What monitoring should be used for patients receiving adjuvant olaparib?	Patients receiving adjuvant olaparib should be monitored according to the OlympiA protocol, i.e., complete blood count (CBC) and comprehensive metabolic panel (CMP) bi-weekly for 1 month, then monthly for 5 months. CBC monitoring after the first 6 months of treatment should be personalized based on tolerance.

Background

Evidence in support of use of adjuvant olaparib for germline *BRCA1/2* carriers with early breast cancer

The randomized, double-blind, phase 3 OlympiA trial evaluated adjuvant olaparib in patients with early-stage, human epidermal growth factor receptor 2 (HER2)–negative breast cancer with high risk of recurrence and germline *BRCA1* or *BRCA2* pathogenic or likely pathogenic (P/LP) variants. All participants had received neoadjuvant or adjuvant chemotherapy prior to enrollment. Patients with triple-negative breast cancer (TNBC) treated with adjuvant chemotherapy were required to have node–positive disease or an invasive primary tumor of at least 2 cm, whereas patients receiving neoadjuvant chemotherapy were required to have residual disease at surgery. Patients with hormone receptor (HR)–positive breast cancer receiving adjuvant chemotherapy were required to have at least four pathologically confirmed positive lymph nodes, whereas those receiving neoadjuvant chemotherapy were required to have residual disease and a CPS+EG score of 3 or higher.[1]

A total of 1,836 participants were randomized to receive 1 year of adjuvant olaparib or placebo. The primary endpoint was invasive disease-free survival (iDFS); secondary endpoints were distant disease-free survival (DDFS), overall survival (OS), and safety.[1]

At the first pre-planned interim analysis after a median follow up of 2.5 years, there was significant iDFS improvement, with a 3-year iDFS of 85.9% in the olaparib group and 77.1% in the placebo group (hazard ratio [HR] for invasive disease or death: 0.58, 99.5% CI: 0.41 - 0.82; $p < 0.001$)[1]. At the second planned interim analysis after a median follow up of 3.5 years, a significant OS benefit was reported (3-year OS: 92.8% with olaparib versus 89.1% with placebo; stratified HR: 0.68, 98.5% CI: 0.47 to 0.97; $p = 0.009$)[2]. At the third pre-planned interim analysis after a median follow-up of 6.1 years, an absolute OS benefit of 4.4% was reported with olaparib compared to placebo in the overall population (6-year OS: 87.5% with olaparib vs. 83.2% with placebo; stratified HR: 0.72, 95% CI: 0.56–0.93). The survival

benefit remained statistically significant across subgroups, regardless of breast cancer subtype, neoadjuvant or adjuvant setting, or prior exposure to platinum-based chemotherapy.[3]

Presently, 1 year of adjuvant olaparib is recommended by ASCO[4] and NCCN[5] guidelines for g*BRCA* carriers with high-risk, early-stage, HER2-negative breast cancer according to the inclusion criteria of the OlympiA study. On March 11, 2022, the US Food and Drug Administration (FDA) approved olaparib for the adjuvant treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated HER2-negative high-risk early-stage breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy[6].

Development of the Consensus Statements

Dana-Farber Cancer Institute's Breast Oncology Center (BOC) held multidisciplinary meetings on May 6, 2022, May 20, 2022, June 1, 2022, and April 18, 2025, to discuss recommendations for the use of olaparib in patients with P/LP g*BRCA1* or *gBRCA2* mutations (g*BRCA*m) and high-risk early-stage breast cancer. Gathered evidence on the use of adjuvant olaparib was presented for discussion to a multidisciplinary group, which included Dana-Farber physicians, nurses, clinical investigators, lab investigators, translational researchers, administrators, and patient advocates at the BOC weekly staff meetings. The discussion and suggestions for improvements continued via email exchanges following the meeting. The final consensus statements were consolidated in July and August of 2022. The updated consensus statements were consolidated in April 2026.

The consensus statements can be subject to future variations and periodic updates, based on emerging evidence and new reports from ongoing clinical studies. Therefore, the information provided in this document should not be considered as being complete or inclusive of all proper assessments, treatments or methods of care or as a statement of the standard of care. This information does not mandate any particular course of medical care and is not intended to be a substitute for the independent professional judgment of a health care provider. The document is based on the opinion of a multidisciplinary team at Dana-Farber but does not represent the official institutional position and overall must be considered as a consensus based on the positions and ideas of Dana-Farber providers.

Clinical Questions

Adjuvant olaparib for g*BRCA* carriers with early-stage triple negative breast cancer

Q1. What should be the initial recommended treatment strategy for g*BRCA*m patients who received neoadjuvant chemoimmunotherapy and had residual disease at surgery?

Evidence in support: Neoadjuvant pembrolizumab plus anthracycline, taxane, and carboplatin-based chemotherapy, followed by adjuvant pembrolizumab, is recommended for patients with high-risk, stage II-III TNBC based on the pathologic complete response (pCR), event-free survival (EFS), and overall survival (OS) benefit showed in the KEYNOTE-522 (KN522) study.[7-9] In this study, g*BRCA* status was reported only for 17.9% of patients, with 54 known g*BRCA* carriers enrolled (40 in the experimental arm and 14 in the placebo arm). g*BRCA* status was missing/undetermined in 82.1% of patients.[10] In the IMpassion130 study, which randomized patients with metastatic TNBC to receive first-line nab-paclitaxel with or without atezolizumab, the benefit of the addition of immunotherapy was observed regardless of g*BRCA* status.[11]

Administration of pembrolizumab was not allowed in the OlympiA study, as it was not standard of care when the study was designed. Analogously, adjuvant olaparib was not allowed in the KN522 study.

The lack of pCR after neoadjuvant chemo-immunotherapy for TNBC is associated with high risk of relapse.[12] Despite the lack of data in this setting, the consensus within the BOC group was to recommend adjuvant olaparib after neoadjuvant chemo-immunotherapy in patients with residual disease considering the strong OS benefit shown by the OlympiA study.[3]

Consensus Statement 1
One year of adjuvant olaparib is recommended for g*BRCA*m patients who received neoadjuvant chemo-immunotherapy and had residual disease at surgery. Concurrent adjuvant pembrolizumab may be considered.

Q2. Should olaparib and pembrolizumab be given concomitantly?

Evidence in support: There are currently no safety and efficacy data available regarding concurrent administration of PARP inhibitors (PARPi) and immunotherapy in patients with early-stage breast cancer. A number of trials that investigated their co-administration in the metastatic setting showed good tolerability (i.e., TOPACIO,[13] MEDIOLA,[14] KEYLYNK-007[15] trials), although none of the trials compared efficacy of PARPi monotherapy versus PARPi plus immunotherapy. Recent neoadjuvant data also support the biological feasibility of PARPi–PD-1 co-administration in early-stage disease. In the phase 2 TBCRC 056 study, 18 weeks of concurrent niraparib and dostarlimab therapy in patients with g*BRCA*m HR+/HER2− breast cancer resulted in a pCR rate of 18.8% and was associated with an early increase in stromal tumor-infiltrating lymphocytes, with a manageable safety profile.[16] In

the randomized phase 2 ETCTN 10020 trial (NCT02849496) in patients with advanced g*BRCA*m breast cancer, the addition of atezolizumab to olaparib did not significantly improve PFS or OS compared with olaparib alone, although both regimens showed clinically meaningful activity and the combination was associated with a higher rate of adverse events.[17]

When considering administration of both olaparib and pembrolizumab, the BOC group favored concurrent administration of both agents, if adequately tolerated.

Consensus Statement 2
When both olaparib and pembrolizumab are considered, concurrent administration should be preferred, if adequately tolerated.

Q3. Should both capecitabine and olaparib be offered and given sequentially?

Evidence in support: In the randomized phase 3 CREATE-X study,[18] 6-8 cycles of adjuvant capecitabine were shown to increase both iDFS and OS in patients with early-stage TNBC and residual disease after neoadjuvant chemotherapy. Prior to the approval of adjuvant olaparib, post-neoadjuvant capecitabine was standard practice in both g*BRCA*m and g*BRCA* wild-type (wt) patients. Administration of capecitabine was not allowed in the OlympiA and KN522 studies.

There are no data directly comparing adjuvant capecitabine and olaparib in this setting. Correlative data from the GEICAM[19] study suggested that the benefit of capecitabine is mainly experienced by patients with non-basal-like subtypes and is lower in patients with basal-like tumors, as most g*BRCA*-associated TNBC. Similarly, in the EA1131 study, patients with non-basal subtypes seemed to derive a higher benefit from capecitabine than platinum-based chemotherapy, although the finding was not significant[20].

In the EMBRACA[21] and OlympiAD[22,23] studies, a progression-free survival (PFS) benefit of PARPi over physician's choice of chemotherapy was observed for g*BRCA*m patients with advanced breast cancer. Capecitabine was the most frequently administered chemotherapy in both trials.

The BOC group favored administration of olaparib over capecitabine in TNBC patients with residual disease after neoadjuvant chemotherapy. Sequential administration of the two agents was endorsed only for patients considered at "very high" risk. The BOC group recommended against concurrent administration given the overlapping toxicity profile of capecitabine and olaparib.

Consensus Statement 3
Olaparib should be preferred over capecitabine in patients with TNBC and residual disease after neoadjuvant therapy. Sequential administration of olaparib and capecitabine may be offered to patients at "very high" risk of recurrence.

Q4: Should olaparib be considered in TNBC patients with poor response to platinum?

Evidence in support. Data regarding the efficacy of PARPi in g*BRCA*m patients with poor response to platinum are limited. The OlympiAD[23] and EMBRACA[24] trials did not allow enrollment of platinum-refractory patients, although patients with prior exposure and no progression on platinum were allowed to participate. In the BrighTNess study,[25] which investigated the addition of carboplatin to neoadjuvant chemotherapy in patients with early-stage TNBC, there was no significant difference in pCR among treatment arms by *BRCA* status.

In the OlympiA study, all patients treated with neoadjuvant chemotherapy had residual disease per inclusion criteria, including those receiving platinum (~26%).[1] Although the absence of pCR might be interpreted as suboptimal response to platinum, the subgroup analysis showed that the benefit of olaparib was maintained also in platinum pre-treated patients.

The BOC group acknowledged that there are insufficient data to recommend against the use of olaparib in patients with a suboptimal response to platinum.

Consensus Statement 4
Olaparib should be considered in patients with TNBC regardless of response to platinum (i.e., residual disease despite neoadjuvant platinum).

Q5: Which patients with TNBC should receive adjuvant olaparib after adjuvant chemotherapy?

Evidence in support. In the OlympiA study, patients with TNBC who enrolled after adjuvant chemotherapy were required to have invasive disease at surgery of at least 2 cm in the breast or axillary lymph node involvement.[1] The FDA approved adjuvant olaparib for high-risk patients after (neo)adjuvant chemotherapy, thus extending eligibility to patients with stage I TNBC treated with adjuvant chemotherapy.

Most stage I TNBC patients have very good outcomes.[26] The use of adjuvant olaparib after chemotherapy may thus represent an overtreatment for many of these patients.

The BOC group recognized the lack of data so far supporting the use of adjuvant olaparib in stage I TNBC. Whether olaparib might instead replace chemotherapy in this subgroup of patients warrants further investigation.

Oppositely, the BOC group recognized that some high-risk patients with TNBC might not receive chemotherapy, such as those with comorbidities that contraindicate chemotherapy or due to patient's decision. Considering the high risk of recurrence, olaparib should be considered for early-stage TNBC patients who do not receive chemotherapy but otherwise meet OlympiA criteria.

Consensus Statement 5
Adjuvant olaparib after adjuvant chemotherapy should be recommended for patients with stage II-III TNBC, according to the OlympiA criteria. Adjuvant olaparib should not be recommended for patients with stage I TNBC.

Adjuvant olaparib for g*BRCA* carriers with early-stage hormone receptor (HR)-positive/HER2-negative (HR+/HER2-) breast cancer

Evidence in support: Based on the iDFS and OS benefit showed in the monarchE trial,[27-29] 2 years of adjuvant abemaciclib is recommended for patients with high-risk early-stage HR+/HER2- breast cancer regardless of g*BRCA* status. Adjuvant olaparib was not allowed in the monarchE study, as it was not standard practice when the study was designed.

There are no data directly comparing adjuvant abemaciclib to olaparib in high-risk, HR+/HER2- early-stage breast cancer. Although both are currently approved in this setting, inclusion criteria of the monarchE and OlympiA trials differed and overlapped only partially. Prior treatment with chemotherapy was not required by the monarchE study, though 95% of enrolled patients received chemotherapy.[28] To be eligible for the monarchE study, patients were required to have more than 4 axillary lymph nodes involved at surgery, or 1-3 positive lymph nodes and either grade 3 or tumor size larger than 5 cm or a Ki-67 ≥20%. There was no distinction between patients receiving neoadjuvant or adjuvant chemotherapy.

In the OlympiA study,[1] patients with HR+ tumors receiving adjuvant chemotherapy were eligible only if they had more than 4 positive axillary lymph nodes. Patients treated with neoadjuvant chemotherapy were eligible if there was residual disease at surgery and a CPS-EG score equal to or higher than 3.

The CPS+EG is a prognostic score estimating the risk of recurrence after neoadjuvant chemotherapy.[30] It is based on clinical stage, pathologic stage, estrogen receptor status, and nuclear grade on pretreatment tumor biopsy. Although all patients with CPS+EG≥3 have high-risk tumors, the opposite is not confirmed, and some high-risk tumors have CPS+EG score lower than 3. For instance, clinical stage III, grade II ER+ tumors with pathological stage III after neoadjuvant chemotherapy have a CPS+EG score of 2. Updated long-term follow-up from the OlympiA trial continues to demonstrate durable benefit from 1 year of adjuvant olaparib in g*BRCA1/2* carriers with high-risk early-stage HER2- breast cancer, including the HR+ subgroup. With approximately 6 years of median follow-up, improvements in iDFS and DDFS are sustained, and the OS benefit persists (87.5% vs 83.2%; HR: 0.72, 95%: CI 0.56–0.93; absolute difference 4.4%),[3] without new safety concerns and with a very low incidence of acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS).[31]

The most recent update of the monarchE trial (median follow-up: 76.2 months) confirms that adding 2 years of abemaciclib to endocrine therapy provides sustained reductions in early and late recurrences. In this analysis, OS also reached statistical significance (86.8% vs 85.0%; HR: 0.842, 95% CI: 0.722–0.981; absolute difference 1.8%). The safety profile remained consistent with previous reports and did not reveal new toxicity signals.[29] These data support abemaciclib as a standard adjuvant option for patients with anatomically or biologically high-risk disease.

The phase 3 NATALEE trial evaluated adjuvant ribociclib combined with endocrine therapy for patients with stage II–III HR+/HER2- breast cancer, enrolling a broader population than previous CDK4/6 inhibitor trials by including selected node-negative tumors with high-risk features (grade 3 disease or grade 2 tumors with high-risk features such as Ki-67 ≥20% or an Oncotype DX Recurrence Score ≥26; node-negative tumors >5 cm were eligible without the need for additional high-risk features). Ribociclib was administered at 400 mg (3 weeks on, 1 week off) for 36 months in combination with a nonsteroidal aromatase inhibitor for at least 5 years, plus ovarian suppression for premenopausal women. In the updated analysis, ribociclib significantly improved iDFS (HR: 0.716, 95% CI: 0.618–0.829; absolute difference 4.5%), with consistent benefit across stage III and a smaller yet clinically meaningful effect in stage II disease. OS remains immature but shows a favorable trend (HR: 0.800, 95% CI: 0.637–1.003). Safety outcomes were consistent with known CDK4/6 inhibitor toxicities, and no new safety issues were identified. Overall, these results establish ribociclib as an adjuvant option for a broad HR+/HER2- population, including patients who would not have met monarchE eligibility criteria.[32]

When the NATALEE trial was initiated, adjuvant olaparib had not yet been approved for patients with germline g*BRCA*. Based on the 2024 FDA approval,[33] ribociclib now carries an adjuvant indication for stage IIA disease with additional risk factors, as well as stages IIB and III. As a result, a new subgroup of patients has emerged: individuals with relatively high-risk HR+/HER2- early-stage breast cancer who are also g*BRCA* carriers and meet eligibility for both adjuvant ribociclib and olaparib based on current approvals.

This therapeutic overlap raises important clinical questions regarding the optimal treatment strategy, specifically, whether ribociclib or olaparib should be prioritized in eligible patients, or whether a sequential approach could provide incremental benefit. At present, there are no data directly comparing adjuvant abemaciclib, olaparib, and ribociclib in this population, and cross-trial comparisons are inherently limited by difference sin study design and patient selection. Prospective studies are therefore needed to inform treatment selection, define optimal sequencing strategies, and ultimately optimize long-term outcomes for these patients.

Q6: What treatment should be recommended after adjuvant chemotherapy for g*BRCA*m patients with HR+/HER2- breast cancer and ≥4 positive axillary lymph nodes?

Q7: What treatment should be recommended after adjuvant chemotherapy for g*BRCA*m patients with HR+/HER2- breast cancer and 1-3 positive axillary lymph nodes?

Q8. What treatment should be recommended after adjuvant chemotherapy for g*BRCA*m patients with high-risk, node-negative HR+/HER2- breast cancer?

Evidence in support: Patients with more than 3 positive lymph nodes at surgery receiving adjuvant chemotherapy were included in both the OlympiA[1] and monarchE trial,[28] whereas patients with 1-3 positive lymph nodes were excluded from OlympiA and their inclusion in monarchE was dependent on tumor grade, Ki-67, or tumor size. Patients with node-negative disease were not included in the OlympiA nor in the monarchE trials. Although these patients were eligible for the NATALEE trial—which required grade 3 disease or grade 2 tumors with high-risk features (such as Ki-67 ≥20% or an Oncotype DX Recurrence Score ≥26)—node-negative tumors >5 cm were eligible without the need for additional high-risk features.[32]

The FDA label of adjuvant olaparib allows its administration to all patients considered at "high-risk" of recurrence after neoadjuvant chemotherapy, independently of the number of nodes involved.[6] g*BRCA* carriers are more likely to have HR+ breast cancer with a high Oncotype DX Recurrence Score.[34] Thus, they are candidates to receive adjuvant chemotherapy independently of nodal status.

The OS benefit observed in the OlympiA study was maintained in the HR+ positive population.[3] Updated OS data from the monarchE trial showed a survival benefit (HR: 0.842, 95%: CI 0.722–0.981).[29]

The BOC group favored olaparib over abemaciclib for patients with HR+ breast cancer and 4 or more positive lymph nodes. For patients with 1-3 positive nodes, the BOC group recognized the lack of data supporting adjuvant olaparib, although it was discussed that these patients might derive a benefit from olaparib. The group also underlined the lack of data about benefit of abemaciclib among g*BRCA* carriers.

The BOC group agreed on the use of both drugs in sequence for high-risk patients.

Due to the lack of data in node-negative patients, the BOC group recommended against administration of adjuvant olaparib in this subgroup of patients.

Consensus Statement 6
Adjuvant olaparib should be preferred over adjuvant abemaciclib or ribociclib after adjuvant chemotherapy in g*BRCA*m patients with early-stage, HR+/HER2- breast cancer and ≥4 positive axillary lymph nodes. Sequential administration of olaparib and abemaciclib or ribociclib may be considered in very high-risk patients.

Consensus Statement 7
Adjuvant olaparib should be considered after adjuvant chemotherapy in g*BRCA*m patients with early-stage, HR+/HER2- breast cancer and 1-3 positive axillary lymph nodes. Abemaciclib or ribociclib may be considered as an alternative.

Consensus Statement 8
Adjuvant olaparib should generally not be recommended for patients with early-stage, node-negative, HR+/HER2− breast cancer following adjuvant chemotherapy, except for those with a g*BRCA*m who meet NATALEE eligibility criteria but not monarchE, particularly in the presence of high-risk features such as Ki-67 ≥20% or an Oncotype DX Recurrence Score ≥26, and who have received (neo)adjuvant chemotherapy. In this subset, the group favored olaparib over ribociclib or endocrine therapy alone.

Q9: What treatment should be recommended after neoadjuvant chemotherapy for g*BRCA*m patients with early-stage, HR+/HER2 breast cancer and ≥4 positive axillary lymph nodes at surgery?

Q10: What treatment should be recommended after neoadjuvant chemotherapy for g*BRCA*m patients with early-stage, HR+/HER2- breast cancer and 1-3 positive axillary lymph nodes at surgery?

Evidence in support: In the monarchE trial, inclusion criteria were equal for patients receiving neoadjuvant or adjuvant chemotherapy. Indeed, patients with early-stage HR+/HER2- breast cancer were eligible for study inclusion if they had more than 4 positive axillary lymph nodes or 1-3 positive nodes and additional risk factors.[28] The NATALEE trial evaluated adjuvant ribociclib plus endocrine therapy in a broad stage II–III HR+/HER2- population, including selected node-negative tumors with high-risk features.[32]

In the OlympiA study, enrollment for patients receiving neoadjuvant chemotherapy was dependent on the CPS+EG score,[1] although the FDA label allows treatment with adjuvant olaparib for all patients considered at high risk of recurrence, without specific consideration of the CPS+EG score.[6]

Considering the OS benefit observed with adjuvant olaparib and the limitations of the CPS+EG score in identifying all high-risk patients, the consensus of the BOC group favored adjuvant olaparib over abemaciclib or ribociclib. Sequential administration of olaparib followed by abemaciclib or ribociclib was endorsed for high-risk patients.

Consensus Statement 9
Adjuvant olaparib should be recommended after neoadjuvant chemotherapy in g*BRCA*m patients with early-stage, HR+/HER2- breast cancer and ≥4 positive axillary lymph nodes at surgery. Sequential administration of olaparib and abemaciclib or ribociclib may be considered in high-risk patients.

Consensus Statement 10
Adjuvant olaparib should be considered after neoadjuvant chemotherapy in g*BRCA*m patients with early-stage, HR+/HER2- breast cancer and 1-3 positive axillary lymph nodes. Abemaciclib or ribociclib should be considered as an alternative. Sequential administration of adjuvant olaparib followed by abemaciclib or ribociclib may be considered in high-risk patients.

Q11. What treatment should be recommended for g*BRCA*m patients with high-risk, node-positive disease who do not receive chemotherapy?

Evidence in support: According to the results of the RxPONDER trial,[35] there is no added benefit of adjuvant chemotherapy over endocrine therapy alone in postmenopausal patients with a low or intermediate Oncotype DX Recurrence Score, although an age-modifying effect was seen in premenopausal women. Accordingly, not all patients with node-positive early-stage HR+ breast cancer are candidates to receive adjuvant chemotherapy. However, most of them are still at moderate to high risk of recurrence.

Patients not receiving chemotherapy were not enrolled in the OlympiA study[1] and represented 5% of the population included in the monarchE study.[28] Despite the lack of representation of these patients in OlympiA, and the perception that the benefit of olaparib likely expands beyond the high-risk patients included in OlympiA, the BOC group favored administration of olaparib as well as sequential administration of olaparib followed by abemaciclib or ribociclib for very-high-risk patients who did not receive chemotherapy.

Consensus Statement 11
Adjuvant olaparib could be considered for patients with high-risk, node-positive disease who do not receive chemotherapy. Sequential administration of olaparib followed by abemaciclib or ribociclib may be considered for high-risk patients.

Q12. Should olaparib be administered concurrently with endocrine therapy?

Evidence in support: There are no data comparing efficacy of olaparib plus endocrine therapy versus olaparib alone.

A preliminary analysis of the D081CC00001 study[36] combining olaparib with endocrine therapy did not show clinically relevant drug-drug interaction between olaparib and tamoxifen, letrozole, or anastrozole. Based on these findings, g*BRCA*m patients with HR+ breast cancer in the OlympiA trial were allowed to receive endocrine therapy at any time during the study, and 87% of patients did receive concurrent administration. According to the OlympiA subgroup analyses, the benefit of adjuvant olaparib was maintained for both HR+ and TNBC patients and there was no concern for decreased clinical benefit with the addition of ET.[1]

Based on the OlympiA findings, the consensus from the group favored concurrent administration of olaparib and endocrine therapy.

Consensus Statement 12
Adjuvant olaparib and endocrine therapy should be administered concurrently.

Q13: If both CDK4/6 inhibitors and olaparib are considered, which agent should be offered first?

Evidence in support: There are no safety data available for the combination of abemaciclib/ribociclib and olaparib, which share partially overlapping toxicity profiles. The HOPE trial, testing the combination of a CDK4/6i (palbociclib), a PARPi (olaparib), and endocrine therapy (fulvestrant) in the metastatic setting, has shown preliminary antitumor activity but raised concerns about hematologic toxicity and feasibility of triple combination.[37] Therefore, when considering both abemaciclib and olaparib, these should not be given concomitantly.

In the monarchE trial, abemaciclib was allowed to be started up to 16 months after surgery.[28] In the OlympiA study, olaparib was allowed to be started up to 8 weeks after completion of primary therapy.[1]

There is no direct comparison between CDK4/6i and PARPi plus endocrine therapy. However, a correlative study from the Memorial Sloan Kettering Cancer Center suggests a reduced benefit from CDK4/6i in g*BRCA2* carriers with metastatic breast cancer.[38] A prospective study (NCT06380751) is currently underway to compare CDK4/6i versus PARPi plus endocrine therapy in patients with HR+/HER2- advanced breast cancer, highlighting the absence of definitive head-to-head data in this space.

Considering these data and OS benefit from olaparib, the BOC group recommended administration of olaparib first when both olaparib and CDK4/6i are considered.

Consensus Statement 13
Administration of olaparib followed by CDK4/6i should be preferred when sequential administration of both agents is considered.

Q14: What is the preferred adjuvant approach for patients with HR+/HER2− breast cancer who carry a g*BRCA*m and are eligible for NATALEE, but do not meet monarchE criteria?

Evidence in support: There are currently no safety data supporting the concurrent use of ribociclib and olaparib, and these agents have partially overlapping toxicity profiles. Experience from the metastatic setting further underscores this concern: the HOPE trial, which evaluated the combination of the CDK4/6i palbociclib, the PARPi olaparib, and fulvestrant, demonstrated preliminary antitumor activity but also highlighted substantial hematologic toxicity and challenges with the feasibility of triple therapy.[37] Taken together, these findings suggest that ribociclib and olaparib should not be administered concomitantly in early breast cancer, and any consideration of using both agents should involve sequential, and not overlapping, administration.

In the NATALEE trial, patients could have received any adjuvant or neoadjuvant endocrine therapy for up to 12 months before randomization.[32] In the OlympiA study, olaparib initiation was restricted to within 8 weeks after completion of primary therapy.[1]

There is no direct comparison between CDK4/6i and PARPi plus endocrine therapy. However, retrospective data from Memorial Sloan Kettering suggest a reduced benefit from CDK4/6 inhibition in *gBRCA2* carriers with metastatic breast cancer. A new prospective study (NCT06380751) is currently underway to compare CDK4/6i versus PARPi plus endocrine therapy in HR+/HER2- advanced breast cancer, highlighting the absence of definitive head-to-head data in this space.

Considering these data and the OS benefit demonstrated in OlympiA,[3] the group recommended prioritizing olaparib for patients with HR+/HER2- breast cancer and a g*BRCA*m who are eligible for NATALEE but do not meet monarchE criteria, in situations where both options are being considered. This subgroup of patients may receive either adjuvant olaparib or ribociclib, and treatment sequencing should rely on the current evidence until prospective data become available.

Consensus Statement 14

In patients with high-risk early-stage HR+/HER2- breast cancer with a g*BRCA*m who are eligible for NATALEE but do not meet monarchE criteria—especially those with node-negative tumors and high-risk features such as Ki-67 ≥20% or an Oncotype DX RS ≥26—and who have received (neo)adjuvant chemotherapy, the group favored olaparib over ribociclib. This recommendation should take into consideration factors such as patient age, prior chemotherapy, patient preferences, and overall risk assessment.

Adjuvant olaparib for g*BRCA* carriers with early-stage ER-low breast cancer

Q15. Should olaparib be offered to g*BRCA* carriers with ER-low breast cancer according to the OlympiA inclusion criteria defined for TNBC or HR-positive patients?

Q16. Should adjuvant olaparib be administered with endocrine therapy in patients with ER-low breast cancer?

Q17. If neoadjuvant pembrolizumab was administered to g*BRCA* carriers with ER-low breast cancer and residual disease at surgery, should pembrolizumab, endocrine therapy, and olaparib be administered concurrently as post-neoadjuvant therapy?

Evidence in support: In 2020, the ASCO/CAP guidelines on estrogen and progesterone receptor testing in breast cancer defined tumors with estrogen receptor (ER) expression between 1 and 10% as a new reporting category: ER low positive.[39] This statement was based on the limited data about endocrine therapy benefits for cancers with low expression of ER.

ER-low breast tumors have pathologic features intermediate between ER>10% and ER-negative tumors. When compared to ER>10%, ER-low tumors are more frequently basal-like and high-grade.[40-43] Most of ER-positive tumors occurring in g*BRCA* carriers are ER-low, especially among *BRCA1* carriers.[40]

Retrospective studies showed a similar risk of recurrence and death for ER-low and TNBC, although the outcomes for the ER-low breast cancer patients receiving endocrine therapy were better compared to patients not treated with endocrine therapy.[44]

In the OlympiA study, g*BRCA* carriers with ER-low breast cancer were included in the HR-positive population and were eligible for inclusion according to those criteria.[1] Most patients received concurrent endocrine therapy. However, no subgroup analysis of treatment patterns and outcomes according to ER level of expression has been published.

According to BOC internal guidelines, neoadjuvant pembrolizumab plus chemotherapy (KN522 regimen) followed by adjuvant pembrolizumab may be considered for patients with ER-low breast cancer.

Considering available data about the biology, treatment patterns, and outcomes of ER-low breast cancers, the BOC group agreed that adjuvant olaparib recommendations for this group of patients should follow the OlympiA inclusion criteria for TNBC. Our group agreed on recommending adjuvant olaparib for g*BRCA* carriers with ER-low breast cancer receiving the KN522 neoadjuvant regimen with residual disease at surgery. Coadministration of adjuvant pembrolizumab and endocrine therapy should be considered.

Consensus Statement 15
Olaparib should be offered to g*BRCA* carriers with ER-low breast cancer according to the OlympiA inclusion criteria defined for TNBC (i.e., non-pCR after neoadjuvant chemotherapy; ≥pT2 and/or node-positive disease after surgery and adjuvant chemotherapy).

Consensus Statement 16
When adjuvant endocrine therapy is considered, adjuvant olaparib should be administered concurrently in g*BRCA*m carriers with ER-low breast cancer.

Consensus Statement 17
Concurrent administration of adjuvant pembrolizumab, endocrine therapy and olaparib should be considered. Sequential administration of adjuvant olaparib followed by abemaciclib or ribociclib may be considered in high-risk patients.

Adjuvant olaparib for germline *PALB2* carriers with early-stage HER2- breast cancer

Q18. Should adjuvant olaparib be considered in g*PALB2*m patients with HER2-negative early breast cancer according to the OlympiA criteria?

Evidence in support: Germline *PALB2* (g*PALB2*) carriers with early-stage, HER2- breast cancer were not included in the OlympiA trial.[1]

TBCRC 048 was a phase 2 trial investigating olaparib in metastatic breast cancer patients carrying either a germline mutation in a homologous recombination (HR)-related gene

other than *BRCA1/2* or a somatic mutation in a HR-related gene. Among patients with a g*PALB2* mutation, 82% had an objective response.[45]

Despite the lack of data in patients with early-stage breast cancer, the BOC group recognized that data available in the metastatic setting suggest that g*PALB2* carriers with early breast cancer are likely to derive benefit from adjuvant olaparib.

Consensus Statement 18

Adjuvant olaparib may be considered in g*PALB2*m carriers with HER2-negative early breast cancer according to the OlympiA criteria and MonarchE criteria.

Q19: What is the preferred adjuvant approach for patients with HR+/HER2− breast cancer who carry a g*PALB2*m and meet the NATALEE/monarchE eligibility criteria?

Evidence in support: g*PALB2*m carriers with early-stage, HER2- breast cancer were not included in the OlympiA trial.[1] There are no safety data available for the combination of abemaciclib/ribociclib and olaparib, which share partially overlapping toxicity profiles. Therefore, when considering both abemaciclib/ribociclib and olaparib in early-stage breast cancer, these agents should not be administered concomitantly.

Although data in early-stage breast cancer are limited, the BOC group acknowledged that evidence from the metastatic setting supports the potential benefit of adjuvant olaparib in g*PALB2*m carriers. We recommend prioritizing olaparib for patients with HR+/HER2− disease and a g*PALB2*m who meet NATALEE or monarchE criteria, in cases where both options are under consideration.

Consensus Statement 19

In high-risk HR+/HER2− early breast cancer patients with a g*PALB2*m who are eligible for NATALEE but do not meet MonarchE criteria, especially those with high-risk features such as Ki-67 ≥20% or an Oncotype DX RS ≥26, and who have received (neo)adjuvant chemotherapy, the group favored olaparib over ribociclib or endocrine therapy alone. This decision should take into consideration factors such as patient age, prior chemotherapy, patient preferences, and overall risk assessment.

Adjuvant olaparib and fertility

Q20. Should adjuvant olaparib be considered independently of future pregnancy plans?

Evidence in support: A secondary analysis of the COST-LESS study revealed significantly lower response to ovarian stimulation among breast cancer patients with a g*BRCA1* mutation.[46] However, clinical studies have not shown significant differences in fertility outcomes between *gBRCA* carriers and non-carriers.[47] The impact of adjuvant olaparib on

fertility remains uncertain, as no clinical data are available. A preclinical study in rats did not demonstrate adverse effects on mating or fertility rates after short-term olaparib exposure.[48]

However, a recent *in vivo* study showed that olaparib induces ovarian toxicity, thus reducing follicle number and quality, impairing granulosa cell function, and decreasing fertilization rates. These effects were largely reversible after a 3-week washout, though some reduction in oocyte yield persisted,[49] supporting the FDA recommendation for a 6-month contraception period after olaparib.[50]

In the latest update from the OlympiA study, pregnancy outcomes were reported: 41 patients in the olaparib arm had a total of 51 pregnancies, compared to 40 patients with 51 pregnancies in the placebo arm. Full-term pregnancies occurred in 32 patients receiving olaparib and in 39 patients receiving placebo.[31] Further data are needed to draw definitive conclusions.

Given these findings, fertility preservation should be discussed with young patients before starting olaparib, and decisions about timing of pregnancy should consider the available evidence on standard chemotherapy, patient age, and cancer risk.

Consensus Statement 20.
Decisions regarding fertility preservation and timing of subsequent pregnancy should be guided by existing data on fertility after standard cytotoxic therapy, patient age, and individual preferences, while acknowledging the uncertainty in this area. A minimum waiting period of six months after completing cytotoxic treatment is generally recommended before attempting conception.

Criteria for germline genetic testing in patients with early-stage breast cancer

Q21. Which patients should be tested for g*BRCA* status?

Evidence in support: Most guidelines recommend germline testing for high-penetrance genes associated with breast cancer according to the pre-test probability of carrying a germline alteration, thus on the basis of tumor subtype, age, and patient and family history.[51] Several retrospective analyses outlined the limitation of these criteria. For instance, NCCN criteria were shown to fail to detect 9% of pathogenic variants in *BRCA1/2* given an age cutoff of 60 years for testing and 12% given a 65-year age cutoff. On the other hand, prevalence of g*BRCA* variants among patients not meeting NCCN guidelines was low (1.9% $\leq$60; 1.7% $\leq$65) and the incremental yield if all patients were tested for *BRCA1/2/PALB2* was only 0.36%-0.42%.[52,53]

More recently, NCCN recommendations for germline testing have expanded to inform adjuvant treatment decisions, including eligibility for olaparib. In parallel, ASCO guidelines now recommend offering germline *BRCA1/2* testing to all newly diagnosed breast cancer patients aged $\leqslant$65 years, with selective testing in older individuals and broader use in the

recurrent setting when results may impact PARP inhibitor eligibility, risk assessment, and clinical management.[5,54]

Despite the low prevalence of g*BRCA* variants in older patients, the BOC group acknowledged that the survival benefit observed in the OlympiA trial justifies extending testing to all patients meeting the OlympiA criteria. Considering the additional benefit in terms of surgical management, screening for secondary tumors and family involvement, the group agreed that testing may be considered for all patients with HER2- early breast cancer.

Consensus Statement 21
Germline genetic testing should be offered to patients according to the NCCN criteria, including those who may be eligible for adjuvant olaparib. In parallel, ASCO guidelines recommend offering germline *BRCA1/2* testing to all newly diagnosed breast cancer patients aged ≤65 years, with selective testing in older patients or in the recurrent setting when results inform PARPi eligibility, risk assessment, or clinical management.

Adjuvant olaparib: toxicity monitoring and management

Q22. What monitoring should be used for patients receiving adjuvant olaparib?

Evidence in support: In the OlympiA trial, the safety profile of adjuvant olaparib was consistent with known side effects of olaparib, with no excess serious adverse events or adverse events of special interest. Most frequent side effects were nausea (57%), fatigue (40%), anemia (23.5%), vomiting (22.6%), headache (19.8%). Hematological toxicities represented the most common high grade (grade≥3) adverse events: anemia (8.7%), decreased neutrophil count (4.8%), decreased white-cell count (3.0%).[1,2]

In the metastatic setting, administration of PARP inhibitors has been associated with an increased risk of developing myelodysplastic syndrome (MDS) and/or acute myeloid leukemia (AML).[55,56] After a median follow up of 6.1 years, the incidence of MDS/AML was similar between the two arms (4 events in the olaparib arm and 6 in the placebo arm). [31]

In the OlympiA trial, complete blood count (CBC) and comprehensive metabolic panel (CMP) were checked every 2 weeks during the first month, monthly during months 2-6, then every 6 months during the last 6 months of treatment.

The FDA label recommends CBC monitoring at baseline and monthly thereafter.

In case of myelotoxicity, olaparib was interrupted, reduced or permanently discontinued according to Table 1.

Table 1. Management of hematological toxicity on olaparib	
CTCAE grade 1-2	Continue olaparib or withheld per investigator's judgement
Repeat CTCAE grade 1-2	Withheld olaparib until recovery to grade 1; Reduce olaparib dose to 250 mg BID If a further dose reduction is required, reduce to 200 mg BID
CTCAE grade 3-4	Withheld olaparib until recovery to grade 1; Reduce olaparib dose to 200 mg BID
Repeat CTCAE grade 3-4	Permanently discontinue olaparib

In case of prolonged hematological toxicity (see below), patients were monitored with weekly CBC, including reticulocytes and peripheral blood smear:

- ≥2-week interruption/delay in study treatment due to CTC grade ≥3 anemia and/or development of blood transfusion dependence
- ≥2-week interruption/delay in study treatment due to CTC grade ≥3 neutropenia (ANC < 1 x 109/L)
- ≥2-week interruption/delay in study treatment due to CTC grade ≥3 thrombocytopenia (Platelets < 50 x 109/L). In case of toxicity lasting more than 4 weeks after dose interruption (6 weeks for hemoglobin recovery), the patient discontinued permanently study treatment and was referred to a hematologist for further investigations.

The BOC group agreed on monitoring CBC according to the OlympiA trial, thus with CBC every two weeks in the first month and monthly thereafter for the first 6 months. Monitoring in the following 6 months should be based on individual tolerance.

Consensus Statement 22
Patients receiving adjuvant olaparib should be monitored according to the OlympiA protocol, i.e., complete blood count (CBC) and comprehensive metabolic panel (CMP) bi-weekly for 1 month, then monthly for 5 months. CBC monitoring after the first 6 months of treatment should be personalized based on tolerance.

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