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Review Article

Adjuvant Olaparib for Germline BRCA Carriers With HER2-Negative Early Breast Cancer: Evidence and Controversies

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Abstract

In the OlympiA study, 1 year of adjuvant olaparib significantly extended invasive disease-free survival and overall survival. The benefit was consistent across subgroups, and this regimen is now recommended after chemotherapy for germline *BRCA1/2* mutation (g*BRCA1/2*m) carriers with high-risk, HER2-negative early breast cancer. However, the integration of olaparib in the landscape of agents currently available in the post(neo) adjuvant setting—ie, pembrolizumab, abemaciclib, and capecitabine—is challenging, as there are no data suggesting how to select, sequence, and/or combine these therapeutic approaches. Furthermore, it is unclear how to best identify additional patients who could benefit from adjuvant olaparib beyond the original OlympiA criteria. Since it is unlikely that new clinical trials will answer these questions, recommendations for clinical practice can be made through indirect evidence. In this article, we review available data that could help guide treatment decisions for g*BRCA1/2*m carriers with high-risk, early-stage breast cancer.

Key words: germline BRCA; early breast cancer; olaparib; adjuvant; OlympiA.

Implications for Practice

In the OlympiA trial, 1 year of adjuvant olaparib improved the survival of germline BRCA mutation (gBRCAm) carriers with high-risk, HER2-negative early-stage breast cancer. However, novel agents became available since this study was designed, and evidence about how these options should be utilized is lacking. In patients with triple-negative tumors, clinicians must decide whether and how to combine olaparib, pembrolizumab, and capecitabine. Similarly, which option should be preferred between olaparib and abemaciclib for estrogen receptor-positive disease is unknown. In the absence of direct evidence, we review available data that could help guide treatment decisions for gBRCAm carriers with early-stage breast cancer.

Introduction

Approximately 5%-10% of breast tumors occur in patients harboring a germline pathogenic or likely pathogenic (P/LP) variant (defined mutation hereafter) in cancer susceptibility genes, with *BRCA1* and *BRCA2* (*BRCA1/2*) alterations being the most frequent.[1,2] Clinicopathologic features are usually distinct in *BRCA1/2*-associated breast cancers. Breast tumors in germline *BRCA1* mutation (g*BRCA1*m) carriers are more frequently triple-negative, basal-like, and are diagnosed at younger ages. Germline *BRCA2* mutation (g*BRCA2*m)-associated breast cancers are instead more commonly estrogen receptor (ER)-positive and diagnosed at older ages compared with those in g*BRCA1*m carriers, although earlier than in non-carriers.[3,4] Both g*BRCA1*m and g*BRCA2*m-associated breast cancers are higher grade than sporadic tumors.[3]

In the metastatic setting, PARP inhibitors (PARPi) are effective in the treatment of gBRCAm carriers with HER2-negative breast cancer. In the OlympiAD study, olaparib resulted in

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a significant improvement in median progression-free survival (mPFS) and health-related quality of life compared to non-platinum chemotherapy treatment of physician's choice (TPC).[5] Although an improvement in overall survival (OS) was not observed, the final analysis showed a greater benefit among patients who had not received prior chemotherapy in the metastatic setting (OS 22.6 versus 14.7 months; hazard ratio [HR] 0.51; 95% [CI]: 0.29-0.90).[6] In the EMBRACA trial, talazoparib similarly led to an improvement in mPFS compared with TPC, but did not translate into an OS benefit, including in the first-line setting.[7]

For early breast cancer (eBC), recommendations for systemic therapy to date have been mostly independent of g*BRCA1/2* status, and genetic testing has been primarily offered to tailor locoregional management, screening, and risk reduction strategies.[8,9]

The Olympia Trial

OlympiA was a phase III, double-blind trial in which 1836 patients with a g*BRCA1/2*m and stages II–III, HER2-negative breast cancer were randomized 1:1 to receive 1 year of adjuvant olaparib or placebo.[10] Patients were required to have completed local treatment and received at least 6 cycles of (neo)adjuvant chemotherapy. Of note, axillary management for patients with node-positive disease included axillary dissection or radiation therapy, in line with contemporary algorithms. Only high-risk patients were eligible, and inclusion criteria differed according to therapy setting and tumor subtype (Fig. 1).

The population enrolled was relatively young, with a median age of 42 years. Most patients had a g*BRCA1*m (72.3% versus 27.7% g*BRCA2*m) and triple-negative breast cancer (TNBC) (82% versus 18% ER-positive). The proportion of patients treated in the neoadjuvant and adjuvant setting was equivalent in the 2 arms, and 24% of patients received prior platinum. Interestingly, the original protocol from 2014 included only patients with TNBC. The first patient with ER-positive eBC was enrolled 1 year later, after regulators accepted the combination of olaparib and endocrine therapy, which may partially explain the higher proportion of TNBC and g*BRCA1*m carriers.[10]

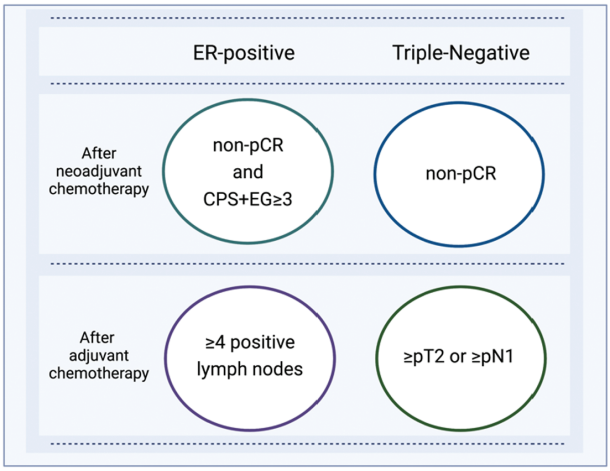

Figure 1. Inclusion criteria of the OlympiA study according to tumor subtype and treatment setting. Created with BioRender.com. ER, estrogen receptor; pCR, pathologic complete response.

A significant reduction of invasive disease recurrence or death with olaparib was observed at the first interim analysis, reaching the study's primary endpoint (HR 0.58; $P < .0001$).[10] This benefit was confirmed at the second interim analysis, with an absolute invasive disease-free survival (iDFS) benefit of 7.3% at 4 years. OS was also improved by olaparib (HR 0.68; $P = .009$) with an absolute 3.4% benefit at 4 years,[11] and both iDFS and OS benefits were consistent across all subgroups. Following these results, adjuvant olaparib was approved by both the U.S. Food and Drug Administration (FDA) and the European Medical Agency (EMA) and is recommended by international guidelines for gBRCAm carriers with high-risk, early-stage, HER2-negative breast cancer.[12,13]

However, questions remain related to the systemic management of gBRCAm-associated eBC. Many drugs have become available in the adjuvant setting for high-risk patients since the OlympiA study was originally designed—eg, capecitabine[14] and pembrolizumab[15] for TNBC; abemaciclib[16] for ER-positive eBC—and data about how these options should be prioritized and/or integrated are lacking. It is also unclear which patients should be candidates to receive adjuvant olaparib since trial eligibility, existing guidelines, and drug labeling do not completely overlap. Finally, whether and to what extent indications for germline testing should be broadened following approval of adjuvant olaparib is debated.

Triple-Negative Breast Cancer

The Post-Neoadjuvant Setting: Evidence on Olaparib and Pembrolizumab

Following the event-free survival (EFS) benefit observed in the KEYNOTE-522 (KN522) study, neoadjuvant pembrolizumab plus anthracycline, taxane, and carboplatin-based chemotherapy followed by adjuvant pembrolizumab is recommended for patients with stage II-III TNBC.[15] The statistical plan of this study did not include a subgroup analysis based on *BRCA1/2* status and, according to the EMA assessment report, g*BRCA1/2* status was missing/undetermined in 82.1% of patients.[17] Only 54 known gBRCAm carriers were enrolled (40 in the experimental and 14 in the placebo arm).[17] Due to such small numbers, it is not possible to determine if efficacy differed according to gBRCAm status. In the IMpassion130 study, the only phase III study of chemo-immunotherapy reporting a subgroup analysis according to gBRCA status so far, the benefit of adding atezolizumab to first-line chemotherapy in metastatic TNBC was maintained irrespective of gBRCA status.[18]

In the OlympiA trial, administration of pembrolizumab was not allowed[10]; in the KN522 study, adjuvant olaparib was not allowed.[19] There are no data to inform whether adjuvant olaparib should be recommended after the KN522 regimen. Per inclusion criteria of the OlympiA study, patients with TNBC treated with neoadjuvant chemotherapy were eligible if they had residual disease at surgery.[10] In the KN522 study, with a median follow up of 39.1 months, 96 of 290 patients with residual disease at surgery (35% of the intention-to-treat population) had an event or died at 36 months despite adjuvant pembrolizumab.[15] Because of the high risk of recurrence of these tumors and the OS benefit observed in the OlympiA study, olaparib is likely to provide a meaningful benefit to gBRCAm carriers with residual disease after chemo-immunotherapy (Fig. 2).

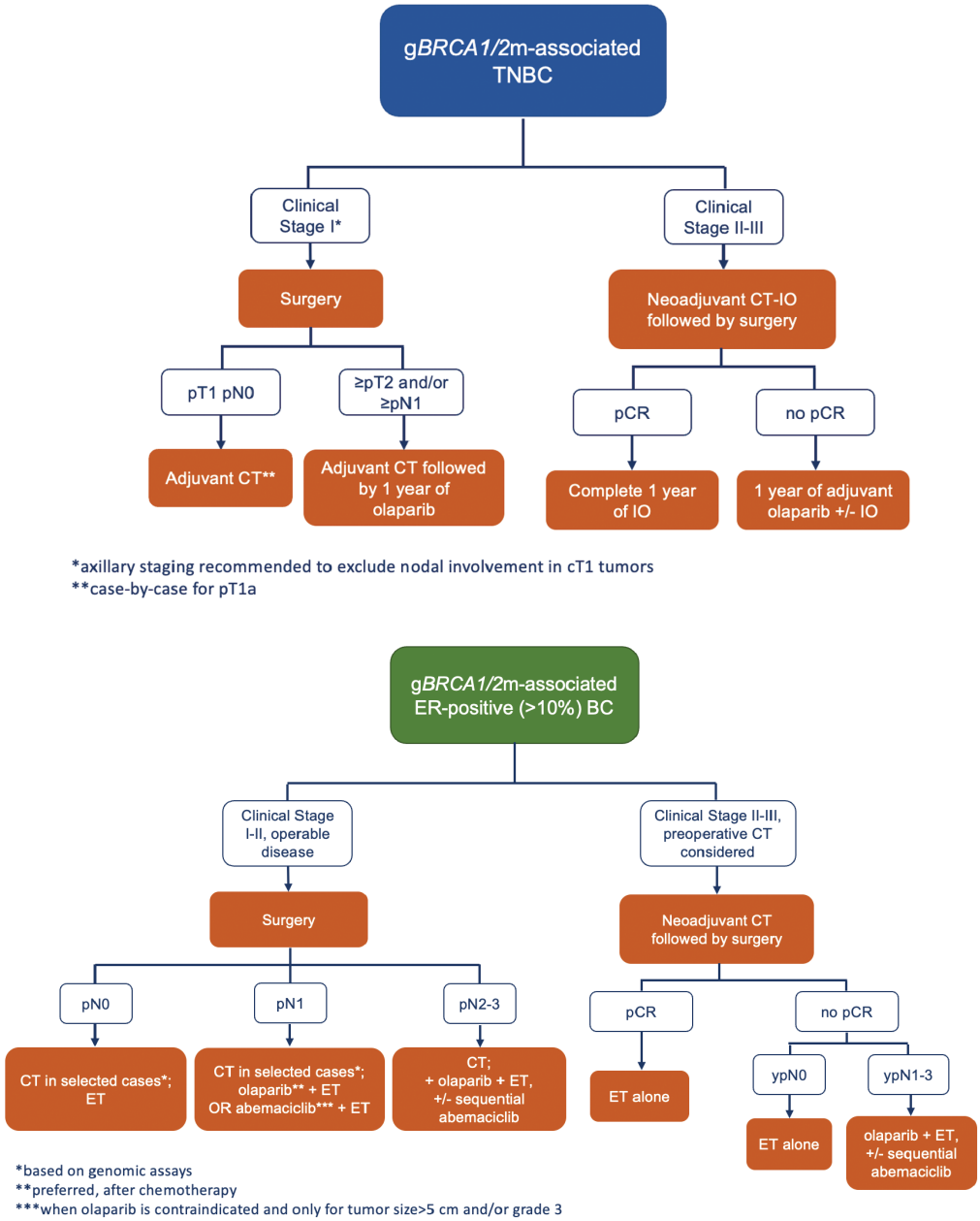

Figure 2. Management of early breast cancer in g*BRCA1/2*m carriers. CT, chemotherapy; ER, estrogen receptor; ET, endocrine therapy; IO, immunotherapy; g*BRCA1/2*m, germline *BRCA1/2* mutation; pCR, pathologic complete response.

Whether olaparib and pembrolizumab should be administered concurrently is debated. Multiple trials have evaluated combinations of PARPi and immune checkpoint inhibitors in the metastatic setting (ie, TOPACIO,[20] MEDIOLA,[21] KEYLYNK-007,[22] and JAVELIN PARP Medley[23] trials), with an acceptable toxicity profile (Table 1). However, none compared the efficacy of PARPi monotherapy with PARPi plus immunotherapy. The ETCTN10020 trial, investigating olaparib with or without atezolizumab in gBRCAm-associated HER2-negative advanced breast cancer, has completed enrollment and results are pending (NCT02849496). Although it is still unknown whether the addition of immunotherapy to PARPi improves outcomes compared to single-agent PARPi, safety data in the metastatic setting suggest the combination is tolerable. Even if not evidence-based, data extrapolation thus supports co-administration of adjuvant pembrolizumab and olaparib in high-risk patients with residual disease after chemo-immunotherapy.

The Post-Neoadjuvant Setting: The Role of Capecitabine

Before results from the KN522 study became available, capecitabine was standard treatment for patients with residual disease after neoadjuvant chemotherapy, as the CREATE-X study showed an iDFS and OS benefit from 6 to 8 cycles of capecitabine after surgery.[14] How to integrate results of the CREATE-X and KN522 studies is debated,[24,25] though the combination of capecitabine and pembrolizumab in patients with residual disease is safe and frequently chosen for gBRCA-wild type patients with residual disease. Similarly, whether olaparib should be favored over capecitabine is unknown, as no direct comparisons are available.

Subgroup analyses of the CREATE-X study did not include gBRCA status, but correlative data from other trials do suggest a reduced benefit from capecitabine in gBRCAm carriers (Table 2). A correlative analysis of the GEICAM study, which also did not report outcomes in gBRCAm carriers, showed a decreased benefit from capecitabine in patients with basal-like tumors, which comprise the majority (~90%) of gBRCAm-associated breast cancer.[26,27] The EA1131 study, which compared capecitabine to platinum in the post-neoadjuvant setting, failed to demonstrate non-inferiority of platinum in both basal and non-basal tumors and showed a worse outcome for basal tumors. A trend toward a higher iDFS benefit from capecitabine in non-basal tumors was also observed, though not statistically significant.[28]

In the metastatic setting, capecitabine and PARPi have been compared head-to-head in the EMBRACA[7,29] and OlympiAD[6,5] studies. In both trials, a PFS benefit of PARPi over TPC was observed, and capecitabine was the most frequent chemotherapy used. Translated in the early-stage setting, these findings may favor olaparib over capecitabine.

Co-administration of olaparib and capecitabine is unfeasible due to overlapping toxicity profiles.[6,7,14] In patients considered at very high risk of recurrence, both agents in sequence may be considered, although without evidence supporting the benefit. As olaparib was initiated within 2 months after primary therapy in the OlympiA trial[10] and capecitabine was allowed to start later, up to 4 months in the CREATE-X trial,[14] olaparib should be administered first when both agents in sequence are considered.

Olaparib After Platinum Chemotherapy

All patients receiving neoadjuvant chemo-immunotherapy are now treated with platinum as part of the KN522 regimen. Little is known about the efficacy of PARPi in gBRCAm patients with poor response to platinum, with available data suggesting potential cross-resistance mechanisms.[30] The OlympiAD[5] and EMBRACA trials did not allow enrollment of platinum-refractory patients. In the BrighTNess study, which investigated the addition of carboplatin to neoadjuvant chemotherapy in early-stage TNBC, the pathologic complete response (pCR) rate did not differ according to

Table 1. Safety profile of immune-checkpoint inhibitors plus PARPi in patients with metastatic breast cancer.

Characteristic	TOPACIO[20] (n=55)	MEDIOLA[21] (n=34)	KEYLYNK-007[22] (n=168)	JAVELIN PARP Medley[23] (n=34)
Treatment	Pembrolizumab + Niraparib	Durvalumab + Olaparib	Pembrolizumab + Olaparib	Avelumab + Talazoparib
TNBC	47 (100%)	18 (53%)	N/A (multiple tumor types included)	22 (100%)
gBRCAm carriers	15 (32%)	100%	N/A	N/A
ORR	21%	63%	6.3%-28.6%	8%
DoR	NR	9.2 months	N/A	N/A
PFS	2.3 months (8.3 months in gBRCAm carriers)	8.2 months	N/A	N/A
Grades 3-4	58%	32%	35.7%	47.4%
Discontinuation for AE	N/A	9%	2.4%	N/A
Most common AE	Nausea (55%), Fatigue (44%), Anemia (35%), Thrombocytopenia (25%), Constipation (24%)	Fatigue (65%), Nausea (59%), Anemia (41%), Diarrhea (35%)	Nausea (39.3%), Anemia (30.4%), Fatigue (15.5%)	Anemia (57.9%), Nausea (26.3%), Fatigue (21.1%), Thrombocytopenia (21.1%)

Abbreviations: AE, adverse events; gBRCAm, germline BRCA mutation; DoR, duration of response; N/A, not available; ORR, overall response rate; P/LP, pathogenic/likely pathogenic; PARPi, PARP inhibitor; PFS, progression-free survival; TNBC, triple-negative breast cancer.

Table 2. Trials investigating adjuvant capecitabine.

Characteristic	CREATE-X (*n*=286)[14]	GEICAM (*n*=876)[26]	EA1131 (*n*=410)[28]
Population	Non-pCR	>T1c and/or N+	>1 cm RD
Setting	Post-neoadjuvant	Post-adjuvant or -neoadjuvant	Post-neoadjuvant
Arms	Capecitabine vs observation	Papecitabine vs. observation	Platinum vs. capecitabine
5-year DFS	69.8% vs. 56.1%	79.6% vs. 76.8%	3-yr RFS 46% vs. 49%
5-year OS	78.8% vs. 70.3%	86.2% vs. 85.9%	3-yr OS 58% vs. 66%
gBRCAm	N/A	N/A	N/A
Basal	N/A	74%; HR 0.94 (0.69-1.27)	78%; HR 1.06 (0.62-1.81)
Non-basal	N/A	26%; HR 0.53 (0.31-0.91)	22%; HR 1.94 (0.69-5.45)

Abbreviations: DFS, disease-free survival; gBRCAm, germline BRCA mutation; HR, hazard ratio; N/A, not available; pCR, pathologic complete response; RD, residual disease; RFS, relapse-free survival; OS, overall survival.

gBRCA status.[31] Of note, all patients receiving neoadjuvant chemotherapy in the OlympiA study had residual disease, including those treated with platinum (~26%).[10] The absence of pCR might be interpreted as a suboptimal response to platinum, but in the subgroup analysis the benefit of olaparib was maintained in platinum pre-treated patients. Therefore, olaparib is likely to be beneficial even in patients with suboptimal response to platinum, although this is still an area of research.

The Adjuvant Setting

In the OlympiA study, patients enrolled after adjuvant chemotherapy were required to have at least tumors larger than 2 cm (T2) or node-positive disease.[10] There are currently no data to recommend adjuvant olaparib for stage I patients. Patients with stage I TNBC generally have a relatively good prognosis, with 5-year iDFS >90% across different series.[32,33] Furthermore, a trend toward better outcomes has been reported for g*BRCA1*m-associated TNBC, which might be related to increased sensitivity to chemotherapy and earlier diagnosis driven by more intense screening strategies.[34,35] Hence, olaparib may represent an overtreatment for most patients with stage I TNBC treated with adjuvant chemotherapy. On the other hand, whether olaparib could replace adjuvant chemotherapy for these patients is unknown. In the neoadjuvant setting, single-agent PARP inhibition showed a pCR rate similar to combination chemotherapy, with a favorable safety profile.[36] A clinical trial replacing chemotherapy with PARPi in gBRCAm carriers with stage I TNBC is warranted.

Hormone Receptor-Positive Breast Cancer

Hormone receptor-positive breast cancers are approximately 50%-60% of all gBRCAm-associated eBC.[37–39] Compared to sporadic tumors, ER-positive breast cancers in gBRCAm carriers are more frequently diagnosed at younger age, have higher grade, lower ER/progesterone receptor (PR) expression, and higher 21-gene recurrence score.[3,4,40,41] Prognosis also appears to be slightly worse in gBRCAm-associated ER-positive tumors than non-gBRCAm cancers.[37,42] In g*BRCA2*m carriers, long-term survival is similar for ER-positive and ER-negative tumors.[43]

In the OlympiA study, patients with ER-positive eBC were eligible if they had at least 4 positive axillary lymph nodes and received adjuvant chemotherapy, or if they had residual disease at surgery and a CPS+EG score greater than or equal to 3 after neoadjuvant chemotherapy.[10] Both the FDA and EMA approved olaparib for high-risk tumors, with no restrictions according to nodal or CPS+EG criteria.

The CPS+EG score is a prognostic tool developed to estimate the risk of recurrence after neoadjuvant chemotherapy across all breast cancer subtypes.[44,45] It is based on 4 variables: clinical stage at diagnosis, pathologic stage at surgery, ER status (positive vs. negative), and nuclear grade.[45] An online tool to calculate the CPS+EG score is freely accessible.[46]

Despite its proven prognostic value,[45,47] this score is infrequently calculated in clinical practice. As regulatory agencies approved olaparib without specific mention of the CPS+EG score, it is unclear whether providers will use this scoring system to inform decisions regarding adjuvant olaparib.

Evidence on Abemaciclib and Olaparib

In patients with ER-positive eBC, the integration of olaparib in the landscape of treatments currently available is controversial, especially after approval of adjuvant abemaciclib following results of the monarchE trial.[48]

The monarchE study was a phase III, randomized trial investigating the addition of 2 years of adjuvant abemaciclib to endocrine therapy in patients with high-risk, ER-positive breast cancer.[16] Prior treatment with chemotherapy was not required, although 95% of the intention-to-treat population received prior chemotherapy. Patients were eligible if they had 4 or more positive axillary lymph nodes at surgery or 1-3 positive lymph nodes and either grade 3 or tumor size larger than 5 cm or a Ki67 ≥20% (Fig. 3). After a median follow-up of 42 months, a significant iDFS benefit was observed in the experimental arm (HR 0.664; 95% CI, 0.58-0.76, $P < .0001$). Preliminary OS data did not show a survival benefit (HR 0.93; 95% CI, 0.74-1.15; $P = .50$) although data were still immature.[48] Whether gBRCAm carriers derive the same benefit from adjuvant abemaciclib as those who are BRCA wild type is unknown, as no subgroup analysis for gBRCA status is available.

Due to the timing of these trials, treatment with olaparib was not allowed in monarchE and abemaciclib was not allowed in OlympiA. The inclusion criteria of the studies overlapped only partially (Fig. 3). As there are no data comparing adjuvant abemaciclib to olaparib for patients with gBRCAm ER-positive eBC, which agent should be preferred or whether both should be considered in sequence is debated.

For patients with node-positive disease, 4 clinical scenarios may be hypothesized according to extent of disease (1-3 or ≥4 positive lymph nodes) and treatment setting (adjuvant vs. neoadjuvant) (Fig. 2):

- For patients receiving surgery upfront and adjuvant chemotherapy, the presence of ≥4 positive axillary lymph nodes detected by contemporary axillary evaluation algorithms satisfied the eligibility requirements of both the OlympiA and monarchE trials. As only the first showed a survival benefit so far, olaparib may be favored over abemaciclib in these patients, although this may change with more mature OS data from the monarchE study. Patients with 1-3 positive lymph nodes were excluded from the OlympiA trial and included in monarchE if they had other high-risk features (Fig. 3). However, olaparib is approved by the FDA and EMA for patients with eBC considered "high-risk" and treated with chemotherapy, and could thus be considered for patients with 1-3 positive lymph nodes. Although both agents may be offered in this setting, the survival benefit of the OlympiA study may still favor olaparib.
- For patients receiving chemotherapy upfront, defining eligibility for one or both trials is challenging, as monarchE considered pathologic stage whereas OlympiA applied the CPS + EG score. It is noteworthy that even patients with high nodal involvement may have been excluded from OlympiA due to a CPS + EG<3 (ie, patients with clinical stage IIIA, pathologic stage IIIA, and nuclear grade 2 ER-positive breast cancer have a CPS+EG score of 2). All the limitations of the CPS+EG score in identifying all high-risk patients should be thus acknowledged when choosing the best adjuvant regimen after neoadjuvant chemotherapy.

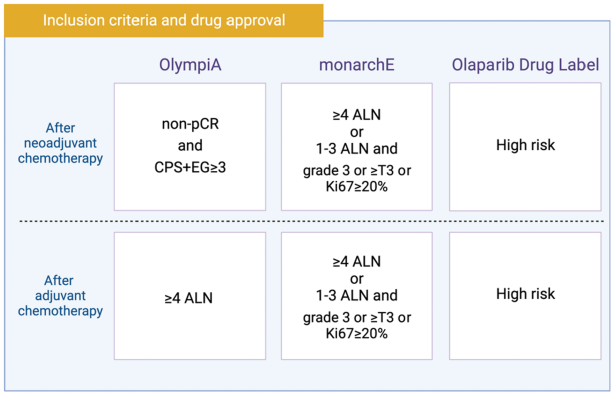

Figure 3. Comparison between OlympiA and monarchE populations and olaparib approval for ER-positive early breast cancer. Created with BioRender.com. ALN, axillary lymph node; ER, estrogen receptor; pCR, pathologic complete response.

Independent of the treatment setting, sequential administration of both agents could be eventually considered for selected, very high-risk patients. In this case, timing of administration in the registrational studies may help choosing the sequence. As olaparib was administered up to 2 months after primary therapy in OlympiA and abemaciclib was administered up to 16 months after definitive surgery in monarchE, olaparib should probably be started first. This strategy, however, has not been explored for efficacy or safety, so it should be recommended cautiously.

Patients with node-negative disease were excluded from both OlympiA and monarchE trials, as patients with ER-positive, node-negative disease have relatively good outcomes and are not considered high-risk.[49] However, retrospective studies showed that gBRCAm-associated tumors more frequently have a recurrence score greater than 26, and are more often treated with chemotherapy.[40,50] Although the absolute benefit that may be derived from olaparib after chemotherapy is likely to be small in patients with ER-positive, node-negative disease, a clinical trial investigating PARPi as a targeted treatment compared to chemotherapy would be of great interest.

ER-Low Breast Cancer

ER-low breast cancers account for 2%-3% of ER-positive tumors.[51] Defined as tumors with ER expression between 1% and 10%, ER-low breast cancer is recognized as a distinct reporting category by the 2020 American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines.[51] Although technically ER-positive, these tumors are often basal-like and poorly differentiated.[52] Retrospective studies showed a similar risk of recurrence and mortality for ER-low and TNBC, although some ER-low tumors appear to derive a benefit from endocrine therapy.[53,54] Many ER-positive tumors occurring in gBRCAm carriers are ER-low, especially among g*BRCA1*m carriers.[55]

In the OlympiA study, gBRCAm carriers with ER-low breast cancer were included in the ER-positive tumors group and were eligible according to those criteria. The number of ER-low tumors included in the OlympiA trial and whether their outcomes differed compared to ER > 10% tumors have not been reported.

To date, most ER-low eBC are treated as TNBC. Considering the biology, treatment patterns, and prognosis of these tumors, it is reasonable to consider adjuvant olaparib for ER-low eBC according to the same criteria used for TNBC.

Expanding Eligibility to *PALB2* Carriers

Patients with breast cancer carrying a germline *PALB2* mutation (g*PALB2*m) were not included in the OlympiA trial. However, indirect evidence from the metastatic setting suggests that these patients may benefit from adjuvant olaparib. The olaparib expanded study (TBCRC 048) was a phase II single-arm trial of olaparib in patients with metastatic breast cancer with either germline variants in non-*BRCA1/2* homologous recombination-related genes (cohort 1), or somatic variants in these genes or *BRCA1/2* (cohort 2). Eleven g*PALB2*m carriers were enrolled in cohort 1. The overall response rate (primary endpoint) was 33% in cohort 1, but 82% (9/11) across g*PALB2*m carriers. mPFS was 13.3 months in g*PALB2* carriers.[56] In a similar study that investigated talazoparib in g*PALB2*m carriers with breast or other solid tumors, the clinical benefit rate was 50% among 12 breast cancer patients.[57] Despite the lack of data in patients with eBC, based on evidence from the advanced setting, it is likely that g*PALB2*m could derive benefit from adjuvant olaparib.[58]

Expanding Criteria for Germline Testing

Most guidelines recommend germline testing according to the pre-test probability of carrying a germline alteration, considering the tumor subtype, patient age, and family history of cancer. However, some retrospective analyses proved the limitations of such an approach. In the Mayo series, National Comprehensive Cancer Network (NCCN) criteria failed to detect 12% of pathogenic variants in *BRCA1/2* patients diagnosed by the age of 65 and 9% of variants in patients diagnosed by the age of 60.[59,60] However, the prevalence of gBRCA variants among patients not meeting NCCN guidelines was low (1.9% <60 years; 1.7% <65 years).[59,60]

After results of the OlympiA study became available, NCCN guidelines were revised and testing is now recommended to identify patients who may benefit from adjuvant olaparib.[8] As benefits of olaparib did not differ by subtype in the OlympiA trial, identification of gBRCAm carriers is as important for those with ER-positive disease as it is for those with TNBC who may be candidates for adjuvant olaparib. Furthermore, advantages in terms of surgical management, screening for secondary tumors, and cascade testing may justify extending testing to all eBC patients, as recommended by some experts and surgical guidelines.[61–63]

Long-Term Toxicity

Myelodysplastic syndromes/acute myeloid leukemia (MDS/AML) have been observed in patients receiving PARPi across different tumor types. In OlympiA, at a median follow-up of 3.5 years, the incidence of MDS/AML was similar in the 2 arms, with only a few cases reported (2 in the olaparib arm and 3 in the placebo arm).[10,11]

In the metastatic setting, most MDS/AML cases observed in patients receiving PARPi are diagnosed within the first 2 years of therapy.[64,65] The heavier chemotherapy pretreatment of patients with metastatic breast cancer may partially

explain why most MDS/AML have been recorded during the first years of treatment, although the 7-year follow-up data from patients with ovarian cancer enrolled in the SOLO trial provided reassuring data, with low incidence and early occurrence of MDS/AML.[66] Ten years of follow-up are planned in the OlympiA trial, which will help elucidate the long-term safety of adjuvant PARPi.

As gBRCAm carriers are typically young and premenopausal, gonadal toxicity of PARPi and the impact on future pregnancies are also of concern. Preclinical studies in rats did not identify adverse effects on mating and fertility,[12] although others showed a depletion of ovarian reserve.[67] There are no clinical data on humans. Therefore, decisions surrounding fertility preservation and timing of subsequent pregnancy should probably mimic recommendations made for cytotoxic therapy, and take into account patient age, preferences, and tumor-related prognosis. If a patient is receiving ovarian suppression with chemotherapy for fertility preservation and tolerating this approach, it is reasonable to continue ovarian suppression during adjuvant olaparib, but acknowledging the lack of data on this approach.

Conclusion

Following the results of the OlympiA trial, 1 year of adjuvant olaparib is recommended for gBRCAm carriers with high-risk, HER2-negative eBC. However, how to define high-risk patients and how to integrate olaparib with all agents currently available is unclear. The survival benefit observed in the OlympiA trial, which was consistent across all subgroups, combined with favorable toxicity profile, strongly supports the use of olaparib in this patient population. In contrast, there are no clear data about the efficacy of pembrolizumab and abemaciclib in gBRCAm carriers specifically, and none has proven to increase survival in this setting so far.

According to the drug label, olaparib can be offered to high-risk patients after (neo)adjuvant chemotherapy, although "high-risk" is not specifically defined. As most gBRCAm carriers are treated with chemotherapy,[50,68] which patients should be considered "high-risk" and, therefore, candidates for adjuvant olaparib is mostly at physician's discretion.

All patients with TNBC were eligible to enroll in the OlympiA study except those with pCR or stage I disease. For patients with residual disease after neoadjuvant therapy, co-administration of olaparib and pembrolizumab showed to be safe in the metastatic setting and may be considered. Conversely, combination of capecitabine and olaparib is contraindicated due to overlapping toxicity. For patients with stage I TNBC, the absolute benefit of olaparib after chemotherapy is likely to be modest. The possibility that olaparib could replace chemotherapy for patients with stage I breast cancer warrants further investigation.

A slightly worse prognosis has been reported for ER-positive, *BRCA2*-associated tumors compared with sporadic tumors,[34,37] and inclusion criteria in the OlympiA study were more restrictive for ER-positive compared to TNBC. Risk of recurrence is substantial in node-positive, ER-positive disease. Therefore, olaparib could be eventually considered beyond the OlympiA eligibility criteria for patients with 1-3 involved nodes and/or CPS + EG <3, especially if there are other high-risk features. This is particularly relevant as current locoregional management favors radiation therapy over axillary dissection for patients with 1-2 positive sentinel lymph nodes, the exact extent of nodal involvment is frequently unknown.[69]

Breast cancer research is rapidly evolving in many directions, such that, the treatment landscape can change dramatically from the time when studies are designed to when results are available, especially in the adjuvant setting. Thus, treatment recommendations may need to be extrapolated from indirect evidence as it is unlikely that clinical trials will be able to answer all questions in a timely manner. Many novel agents became available in the post-(neo)adjuvant setting after the OlympiA study was launched, and it is now challenging to integrate all data from all available options in clinical practice. As no other agent has shown a comparable survival benefit in this setting thus far, olaparib now represents the cornerstone of adjuvant treatment for high-risk, gBRCAm-associated breast tumors, which may be integrated with other available agents according to risk of recurrence and estimated risk reduction, safety, and toxicity data, as well as patient preference and treatment availability.

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Conflict of Interest

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Author Contributions

Conception/design: S.M., S.M.T., F.L. Provision of study material or patients: S.M., S.M.T., F.L. Collection and/or assembly of data: S.M., F.L. Data analysis and interpretation: All authors. Manuscript writing: S.M., F.L. Final approval of manuscript: All authors.

Data Availability

No new data were generated or analyzed in support of this research.

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