QUALITY IN SPORT
eISSN 2450-3118 · Open Access · Peer-reviewed
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ZARAŃSKI, Bartosz, BACHURSKI, Patryk, CHMIEL, Gabriela, KALINOWSKI, Paweł, MIĘDLAR, Maja, MUDA, Martyna, PACEK, Szymon, PIERZGA, Elisabetta, WIŚNIEWSKI, Karol Paweł and WITKOWSKI, Paweł. Efficacy of Olaparib in Women With BRCA2-Mutated Breast Cancer: A Critical Review of Clinical Evidence. Quality in Sport. 2026.78.76517. https://doi.org/10.12775/QS.2026.78.76517

ARTICLE TIMELINE
Received: 07.10.2026.
Accepted: 15.10.2026.
Published: 06.11.2026.

INDEXING & EVALUATION
MEiN points: 20 Unique ID: 201398
Disciplines: Economics & Finance; Management & Quality Sciences

The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024 No. 32553. Unique Journal Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).

Punkty Ministerialne z 2019 — aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

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Efficacy of Olaparib in Women With BRCA2-Mutated Breast Cancer: A Critical Review of Clinical Evidence

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Abstract

Breast cancers associated with pathogenic BRCA2 variants have impaired homologous-recombination DNA repair and may be particularly vulnerable to poly(ADP-ribose) polymerase inhibition. Olaparib is the best-studied PARP inhibitor in this setting, but the evidence base is not equivalent across disease stages, mutation types, or treatment contexts. This review synthesizes randomized trials, prospective studies, secondary analyses, real-world cohorts, and meta-analyses identified in the completed literature search. The strongest evidence comes from germline BRCA1/2 populations: in high-risk HER2-negative early breast cancer, one year of adjuvant olaparib improved invasive disease-free, distant disease-free, and overall survival, with a consistent BRCA2 subgroup effect. In HER2-negative metastatic disease, OlympiAD demonstrated a clear progression-free survival and response advantage over physician-choice chemotherapy; the prespecified BRCA2 subgroup had a progression-free survival hazard ratio of 0.49, although overall-survival benefit was not statistically significant in the overall population or the BRCA2 subgroup. Neoadjuvant studies show substantial activity but are smaller, frequently combine BRCA1 and BRCA2 carriers, and have not established a definitive role for olaparib alone or in combination with chemotherapy before surgery. Evidence for somatic BRCA2 mutations is promising but remains based mainly on small, single-arm studies and pooled BRCA1/2 analyses. Real-world studies broadly reproduce clinical activity, while also showing the effect of later treatment lines, prior platinum exposure, and patient selection. Across the evidence base, olaparib improves disease control and progression-related outcomes more consistently than overall survival in metastatic disease. The central limitation is the scarcity of adequately powered BRCA2-specific analyses. Current evidence

supports olaparib as an effective targeted treatment for germline BRCA2-mutated, HER2-negative breast cancer, especially in high-risk early disease and metastatic disease, but it does not justify assuming that every result from a pooled BRCA1/2 population is a BRCA2-specific estimate.

Keywords: olaparib; BRCA2; breast cancer; PARP inhibitor; germline mutation; somatic mutation; metastatic breast cancer; early breast cancer; progression-free survival; systematic review

1. Introduction

BRCA2 is a central homologous-recombination repair gene. Pathogenic germline variants increase breast-cancer risk and create a biologically distinct group of tumors in which DNA-repair dependence may be therapeutically exploitable. The clinical rationale for PARP inhibition is based on synthetic lethality: inhibition of PARP-mediated repair and replication-fork protection can selectively compromise tumor cells that already have defective homologous-recombination repair. Early proof-of-concept work established that olaparib could produce tumor responses in advanced breast cancers carrying BRCA1 or BRCA2 mutations [1]. Subsequent phase II work confirmed activity in heavily pretreated germline BRCA-associated breast cancer, although response rates were lower in a later-line population and were not uniformly separated by BRCA1 versus BRCA2 status [2].

The clinical question is now more specific than whether olaparib works in BRCA-mutated breast cancer. The relevant question is how strongly the evidence supports efficacy in women with a BRCA2 mutation, in which disease settings, and under which treatment conditions. This distinction matters because many pivotal studies enrolled patients with either BRCA1 or BRCA2 mutations and reported pooled results. BRCA1 and BRCA2 tumors share homologous-recombination deficiency, but they differ in tumor phenotype, hormone-receptor distribution, genomic architecture, and possibly sensitivity to particular treatment sequences. A pooled BRCA1/2 estimate can therefore support the general use of olaparib while still being insufficient to quantify the treatment effect for BRCA2 alone.

The most influential randomized evidence comes from two settings. OlympiAD compared olaparib with physician-choice chemotherapy in HER2-negative metastatic breast cancer with a germline BRCA mutation and established a progression-free survival and response advantage [3]. OlympiA evaluated one year of adjuvant olaparib in high-risk, HER2-negative early breast cancer with a germline BRCA1 or BRCA2 pathogenic or likely pathogenic variant and showed a clinically important improvement in invasive disease-free survival [4]. Longer follow-up subsequently demonstrated an overall-survival benefit in the early-disease population [5]. In contrast, the metastatic OlympiAD population showed a numerical but not statistically significant overall-survival difference, although the first-line subgroup appeared to derive a larger benefit [6], [7].

This review examines the efficacy of olaparib specifically through a BRCA2-focused lens. It distinguishes germline from somatic BRCA2 alterations, separates early from metastatic disease, gives priority to randomized evidence, and treats neoadjuvant, combination, retrospective, and meta-analytic evidence according to its design strength. Safety and quality of life are included because the clinical value of efficacy depends on whether treatment can be delivered for a sufficient duration and without unacceptable toxicity.

2. Review approach and scope

This manuscript is an evidence synthesis based on the completed deep literature search titled Olaparib BRCA2 Breast Cancer Efficacy. The search identified 25 relevant scholarly records spanning foundational trials, randomized phase III trials, secondary subgroup analyses, neoadjuvant studies,

prospective real-world studies, retrospective cohorts, combination studies, systematic reviews, and meta-analyses. Primary efficacy studies were prioritized over secondary summaries. Full-text extraction was performed for the available PDFs; abstract-level or metadata-level evidence was used for records without an accessible full text and is identified as lower-certainty evidence where relevant.

The population of interest was women with breast cancer and a BRCA2 mutation. The evidence base includes both germline and somatic BRCA2 alterations because both are clinically relevant, but they are not treated as interchangeable. Studies enrolling mixed BRCA1/2 populations were included when they reported BRCA2-specific results or when they were essential to understanding the evidence supporting the broader indication. Outcomes of interest were overall survival, progression-free survival, invasive disease-free survival, distant disease-free survival, objective response, clinical benefit, pathological complete response, duration of response, quality of life, and treatment exposure. The review also considered prior platinum exposure, treatment line, hormone-receptor status, HER2 status, and mutation-testing strategy.

The search is comprehensive for the records identified in the completed workspace search, but this manuscript should not be presented as a formally registered PRISMA systematic review without additional protocol registration, duplicate screening, a reproducible database-level search strategy, formal risk-of-bias assessment, and a documented study-selection flow. The conclusions therefore use the language of a critical evidence review rather than implying that all methodological requirements of a registered systematic review have been completed.

3. Biological and clinical rationale for BRCA2-directed PARP inhibition

BRCA2 participates in homologous-recombination repair through its role in the loading and regulation of RAD51 at sites of DNA damage. Loss of functional BRCA2 can leave tumor cells dependent on alternative repair mechanisms and vulnerable to replication-associated damage. Olaparib inhibits PARP1 and PARP2 and can trap PARP on damaged DNA, producing lesions that are particularly difficult for homologous-recombination-deficient cells to resolve. The therapeutic rationale is therefore strongest when the BRCA2 alteration is pathogenic, functionally deleterious, and present in the tumor clone.

Clinical sensitivity is not determined by the gene label alone. Important modifiers include whether the mutation is germline or somatic, whether the second BRCA2 allele is inactivated, the type and pathogenicity of the variant, the presence of reversion mutations, prior platinum exposure, the number of previous treatment lines, tumor hormone-receptor status, and the burden and site of metastatic disease. The clinical studies reviewed here illustrate this complexity. Germline BRCA2 carriers were enrolled prospectively in OlympiAD and OlympiA, whereas somatic BRCA2 evidence comes mostly from molecularly selected, single-arm studies with small sample sizes [8], [9].

The distinction between efficacy and effectiveness is also important. Randomized trials estimate the effect of assigning olaparib under controlled eligibility criteria. Prospective real-world studies estimate outcomes in patients treated in routine practice, often with more comorbidity, more variable follow-up, and broader treatment histories. Neither design replaces the other. Randomized trials provide the clearest causal estimate, while real-world studies help determine whether the benefit remains clinically visible outside the trial population.

4. Olaparib in early breast cancer

4.1 The OlympiA trial

OlympiA was a phase III, double-blind, randomized trial in patients with HER2-negative early breast cancer, a germline BRCA1 or BRCA2 pathogenic or likely pathogenic variant, and high-risk clinicopathological features. Participants had completed local therapy and neoadjuvant or adjuvant chemotherapy. They were randomized to one year of oral olaparib at 300 mg twice daily or matching placebo [4]. This design is important because it tested olaparib as a postoperative risk-reduction treatment rather than as therapy for measurable metastatic disease.

At the prespecified interim analysis, 1,836 patients had been randomized. The three-year invasive disease-free survival rate was 85.9% with olaparib versus 77.1% with placebo, an absolute difference of 8.8 percentage points and a hazard ratio of 0.58 with a 99.5% confidence interval of 0.41 to 0.82. Three-year distant disease-free survival was 87.5% versus 80.4%, respectively, with a hazard ratio of 0.57 and a 99.5% confidence interval of 0.39 to 0.83. There were fewer deaths in the olaparib group, but the interim overall-survival analysis had not crossed its prespecified significance boundary [4].

The early-disease result is clinically meaningful for two reasons. First, the magnitude of the invasive disease-free survival difference is larger than would usually be expected from a small incremental disease-free survival difference is larger than would usually be expected from a small incremental chemotherapy effect. Second, the benefit was observed after completion of standard local and systemic therapy, suggesting that olaparib was not simply replacing chemotherapy but was reducing the risk of recurrence in a biologically selected population. The trial therefore established adjuvant olaparib as a disease-modifying treatment for appropriately selected high-risk germline BRCA-associated early breast cancer.

4.2 Longer follow-up and the BRCA2 subgroup

The second prespecified overall-survival analysis of OlympiA strengthened the case for adjuvant olaparib. With a median follow-up of 3.5 years, four-year overall survival was 89.8% with olaparib versus 86.4% with placebo. The overall-survival hazard ratio was 0.68, with a 98.5% confidence interval of 0.47 to 0.97 and a P value of 0.009. Four-year invasive disease-free survival was 82.7% versus 75.4%, with a hazard ratio of 0.63, and four-year distant disease-free survival was 86.5% versus 79.1%, with a hazard ratio of 0.61 [5].

The BRCA2-specific findings are particularly relevant to this review. In the initial OlympiA report, the BRCA2 subgroup included 230 patients in the olaparib group and 209 in the placebo group. Three-year invasive disease-free survival was approximately 88.6% with olaparib versus 78.0% with placebo, corresponding to a hazard ratio of 0.52 with a 95% confidence interval of 0.30 to 0.86 [4]. In the longer follow-up analysis, the BRCA2 subgroup had an overall-survival hazard ratio of 0.521 with a 95% confidence interval of 0.276 to 0.951. Four-year overall survival was 92.1% with olaparib versus 85.3% with placebo. The corresponding BRCA2 subgroup estimates were less precise for invasive disease-free survival, with a hazard ratio of 0.693, and remained favorable for distant disease-free survival, with a hazard ratio of 0.609 [5].

These results support a real adjuvant benefit in BRCA2 carriers, but the interpretation should remain appropriately cautious. The BRCA2 estimates are subgroup estimates within a trial designed primarily to test the pooled BRCA1/2 population. They are not independent trials powered to compare olaparib with placebo only in BRCA2 carriers. Confidence intervals are wider than those for the overall population, and subgroup analyses can be influenced by baseline imbalance and multiplicity. Nevertheless, the direction and size of effect are consistent with the biological rationale and with the pooled result.

The OlympiA findings also indicate that BRCA2-associated breast cancer should not be treated as an exclusively triple-negative disease. BRCA2 carriers are more likely than BRCA1 carriers to have hormone-receptor-positive tumors, and OlympiA included hormone-receptor-positive patients. Endocrine therapy could be administered concurrently with study medication. This matters clinically because the benefit of olaparib is not limited to triple-negative breast cancer when the patient meets the high-risk eligibility criteria.

4.3 Neoadjuvant evidence

Neoadjuvant evidence is less mature than the adjuvant OlympiA evidence. The PARTNER trial investigated a schedule designed to combine olaparib with carboplatin and paclitaxel while reducing overlapping hematologic toxicity. In the germline BRCA cohort, patients received carboplatin and paclitaxel with either a gap-schedule of olaparib or chemotherapy alone, followed by anthracycline-containing treatment [10].

The primary pathological complete response endpoint did not favor the olaparib arm. Pathological complete response was 64.1% in the research arm versus 69.8% in the control arm, with a difference of −5.7 percentage points and P = 0.586. The trial was stopped early for futility with respect to the prespecified pathological complete response objective. However, exploratory 36-month estimates favored the research arm for event-free survival, 96.4% versus 80.1%, and overall survival, 100% versus 88.2%, although the small cohort and early stopping make these secondary survival findings hypothesis-generating rather than definitive [10].

PARTNER did not provide a separate, adequately powered BRCA2 efficacy analysis. Consequently, it cannot establish whether the observed survival pattern is stronger, weaker, or equivalent in BRCA2 carriers. It does, however, provide two useful lessons. First, the lack of a pathological complete response advantage does not necessarily exclude a later disease-control benefit in germline BRCA-associated disease. Second, combining PARP inhibition with DNA-damaging chemotherapy requires careful scheduling because the treatment effect may be constrained by hematologic toxicity.

GeparOLA provides complementary but also limited neoadjuvant evidence. The study enrolled patients with HER2-negative early breast cancer and homologous-recombination deficiency, defined by a high HRD score and/or a germline or tumor BRCA1/2 mutation. Patients were randomized to paclitaxel plus olaparib or paclitaxel plus carboplatin, followed by epirubicin and cyclophosphamide [11]. Confirmed germline BRCA1/2 mutations were present in 56.2% of the study population, and 72.6% had triple-negative disease. The pathological complete response rate was 55.1% with paclitaxel/olaparib and 48.6% with paclitaxel/carboplatin. The study could not exclude a pathological complete response rate of 55% or lower in the olaparib arm, and it was not designed to provide a definitive BRCA2-specific treatment effect.

The neoadjuvant studies should therefore be interpreted as evidence of activity and feasibility rather than as proof that olaparib should replace standard neoadjuvant chemotherapy. They also reinforce the importance of distinguishing between a treatment regimen and a drug. The available data do not show that olaparib monotherapy, olaparib plus chemotherapy, or olaparib in a particular schedule is superior across all early BRCA2-mutated breast cancers. The strongest evidence for early disease remains postoperative olaparib in the high-risk OlympiA population.

4.4 Generalizability of early-disease findings

The Japanese OlympiA subset provides a useful external consistency analysis. Among 140 patients enrolled in Japan, 45 had BRCA2 mutations. The analysis was descriptive and not powered to detect population-specific differences. At the first data cutoff, the hazard ratio for invasive disease-free survival was 0.50 and the hazard ratio for distant disease-free survival was 0.41. At the later cutoff, the four-year overall-survival hazard ratio was 0.62, although the confidence interval was wide because of the small number of events [12].

These findings are consistent with the global OlympiA results but should not be interpreted as a separate BRCA2-specific confirmation. They show that the direction of benefit was maintained in a different national setting, while also highlighting how quickly precision declines when subgroup sample sizes become small.

5. Olaparib in metastatic breast cancer

5.1 The OlympiAD randomized trial

OlympiAD was the pivotal phase III trial for metastatic disease. It enrolled patients with germline BRCA-mutated, HER2-negative metastatic breast cancer who had received no more than two previous lines of chemotherapy for metastatic disease. Participants were randomized 2:1 to olaparib tablets at 300 mg twice daily or physician-choice single-agent chemotherapy, consisting of capecitabine, vinorelbine, or eribulin [3].

The primary OlympiAD report showed a clinically important progression-free survival advantage for olaparib. Median progression-free survival was approximately 7.0 months with olaparib versus 4.2 months with physician-choice chemotherapy, with a hazard ratio of 0.58. Objective response was also substantially higher with olaparib, approximately 59.9% versus 28.8%. The benefit was observed in a population that included both triple-negative and hormone-receptor-positive/HER2-negative disease, showing that germline BRCA-associated metastatic breast cancer is not a single-subtype condition [3].

The final subgroup analysis provides the most direct BRCA2-specific metastatic evidence. In the final analysis population of 302 patients, median investigator-assessed progression-free survival was 8.0 months with olaparib and 3.8 months with physician-choice chemotherapy, corresponding to a hazard ratio of 0.51 with a 95% confidence interval of 0.39 to 0.66. The prespecified BRCA2 subgroup had a progression-free survival hazard ratio of 0.49 with a 95% confidence interval of 0.33 to 0.74. The corresponding BRCA1 estimate was also 0.49, supporting a broadly consistent progression benefit across the two germline BRCA genes [13].

The BRCA2 result is important because it is not merely inferred from the pooled population. It is a prespecified subgroup estimate, and its confidence interval excludes no effect. At the same time, it remains a subgroup result from a trial that was not powered to test superiority separately in BRCA2

carriers. The correct conclusion is that the metastatic progression-free survival benefit is strongly compatible with a clinically meaningful olaparib effect in BRCA2 carriers, not that the BRCA2 hazard ratio is known with the same precision as the overall estimate.

Objective response was higher with olaparib across the reported subgroups, including BRCA2, hormone-receptor status, prior metastatic chemotherapy, and prior platinum exposure [13]. Patient-reported global health status and quality of life generally favored olaparib over physician-choice chemotherapy, which is clinically relevant because a progression-free survival advantage is more valuable when it is not accompanied by earlier deterioration in symptoms or daily function.

5.2 Overall survival in OlympiAD

The final overall-survival analysis of OlympiAD did not show a statistically significant difference in the overall population. Median overall survival was 19.3 months with olaparib versus 17.1 months with physician-choice chemotherapy, with a hazard ratio of 0.90, a 95% confidence interval of 0.66 to 1.23, and P = 0.513 [6]. The BRCA2 subgroup had an overall-survival hazard ratio of 0.90 with a 95% confidence interval of 0.56 to 1.48. This estimate is compatible with benefit, no difference, or modest harm and is therefore imprecise.

The absence of a statistically significant overall-survival benefit does not negate the progression-free survival result. Several factors complicate overall-survival interpretation in metastatic breast cancer, including crossover or subsequent treatment with PARP inhibitors, unequal post-progression therapy, limited event numbers in subgroups, and the use of different chemotherapy comparators. The first-line subgroup is particularly informative. In patients who had not received chemotherapy for metastatic disease, median overall survival was 22.6 months with olaparib versus 14.7 months with physician-choice chemotherapy, with a hazard ratio of 0.51 [6].

Extended follow-up produced a similar pattern. In the overall population, median overall survival remained 19.3 versus 17.1 months, with a hazard ratio of 0.89 and a 95% confidence interval of 0.67 to 1.18. Three-year survival was 27.9% with olaparib versus 21.2% with chemotherapy. In the first-line metastatic subgroup, median overall survival was 22.6 versus 14.7 months, with a hazard ratio of 0.55 and a three-year survival rate of 40.8% versus 12.8%. In the later-line subgroup, the hazard ratio was 1.00, with a 95% confidence interval of 0.76 to 1.47 [7].

These results suggest that earlier use of olaparib may produce a larger survival effect than later-line use, but this inference should not be treated as a randomized comparison between treatment lines. Patients receiving first-line therapy differ systematically from those receiving second- or third-line therapy in disease burden, performance status, organ function, treatment resistance, and opportunity to receive subsequent therapies. The first-line signal is therefore clinically compelling but remains a subgroup finding.

5.3 Early-phase and heavily pretreated metastatic evidence

Before the phase III trials, olaparib activity was observed in advanced breast cancer with germline BRCA mutations. In the breast cancer cohort of a multicancer phase II study, 62 patients had a median of approximately 4.6 previous chemotherapy regimens for metastatic disease. The overall tumor response rate was 12.9%, stable disease lasting at least eight weeks occurred in 46.8%, and median progression-free survival was 3.7 months [2]. Response was 12.0% among the 25 patients with BRCA2 mutations and 13.5% among the 37 patients with BRCA1 mutations. These results should not be

compared directly with OlympiAD without accounting for the much heavier pretreatment burden and the earlier olaparib formulation and dose.

The older findings remain useful because they demonstrate that activity can persist after extensive prior treatment, but they also show that treatment line matters. A drug that produces a response in a heavily pretreated population may still have a much larger effect when used before resistant clones and extensive organ dysfunction develop. Conversely, the lower response rate in the phase II study cautions against assuming that the results of first-line or limited-line trials will apply unchanged to all later-line patients.

6. Real-world effectiveness

Randomized trials provide the strongest causal evidence, but their eligibility criteria can exclude patients commonly seen in practice. The phase IIIb LUCY study was designed to assess olaparib effectiveness in a more clinically representative population of patients with germline or somatic BRCA-mutated, HER2-negative metastatic breast cancer [14], [15].

In the final LUCY analysis, 256 patients were enrolled, including 253 with germline BRCA mutations and three with somatic BRCA mutations. Within the germline cohort, 109 patients had a BRCA2 mutation alone and five had both BRCA1 and BRCA2 mutations. The median investigator-assessed progression-free survival was 8.18 months and median overall survival was 24.94 months. The clinical response rate was 49.6%, with a median clinical-response duration of 8.0 months [15].

LUCY is valuable for BRCA2-focused interpretation because it includes a substantial number of BRCA2 carriers. However, the published summary does not provide a separate BRCA2-specific progression-free survival or overall-survival estimate. The study therefore supports the effectiveness of olaparib in a population containing many BRCA2 carriers but does not quantify the BRCA2-specific treatment effect. The distinction is essential: a cohort's mutation composition can increase the relevance of a study to BRCA2 without producing a BRCA2 subgroup estimate.

The interim LUCY analysis reported a median progression-free survival of 8.11 months and a clinical response rate of 48.6%. Grade 3 or higher treatment-emergent adverse events occurred in 25.4% of patients, and grade 3 or higher anemia occurred in 13.1% [14]. The final analysis reported nausea in 55.3%, anemia in 39.2%, grade 3 or higher treatment-emergent adverse events in 27.8%, and treatment discontinuation because of an adverse event in 6.3% [15]. These results are broadly consistent with the known tolerability profile and show that olaparib can remain deliverable outside the narrower environment of a phase III randomized trial.

The prospective PRAEGNANT registry offers another real-world perspective, although it includes both olaparib and talazoparib. Among 152 patients with HER2-negative advanced breast cancer receiving a PARP inhibitor, 138 received olaparib. Among patients with a reported germline mutation, 62.9% had BRCA2 and 36.1% had BRCA1. Median real-world progression-free survival was 6.0 months and median real-world overall survival was 15.6 months in the olaparib group [16]. These results are lower than the LUCY estimates, likely reflecting differences in patient selection, treatment line, missing mutation data, outcome ascertainment, and registry follow-up. They should not be interpreted as evidence that olaparib is less effective in BRCA2 tumors; they demonstrate how effectiveness estimates change when treatment is delivered later and under routine-care conditions.

7. Somatic BRCA2 mutations

The evidence for somatic BRCA2 mutations is substantially weaker than the evidence for germline BRCA2 mutations. The distinction is not only methodological. Somatic testing may identify variants of uncertain pathogenicity, subclonal alterations, or mutations without confirmed biallelic loss. Tumor-only sequencing can also misclassify germline variants or fail to establish whether the mutation is functionally relevant.

TBCRC 048 was a phase II study of olaparib in metastatic breast cancer with mutations in homologous-recombination-related genes. Patients with somatic BRCA1 or BRCA2 mutations were enrolled in a cohort that excluded known germline BRCA1/2 mutations. In the initial report, ten patients had somatic BRCA2 mutations, but efficacy was generally reported for the pooled somatic BRCA1/2 group. The pooled objective response rate was 50%, the clinical benefit rate at 18 weeks was 66%, median progression-free survival was 6.3 months, and median duration of response was 6.3 months. Responses occurred exclusively in the somatic BRCA1/2 subgroup among the somatic cohorts [8].

The expansion analysis published in 2026 included 15 patients with somatic BRCA1 and 15 with somatic BRCA2 mutations. Because the primary analysis again reported the somatic BRCA group together, the most defensible estimate is pooled: objective response rate 36.7%, clinical benefit rate 53.3%, median progression-free survival 5.5 months, and median duration of response 11.2 months [9]. These data support biological activity in somatic BRCA-mutated metastatic breast cancer, but they do not establish a BRCA2-only response rate or prove equivalence with germline BRCA2 disease.

A small retrospective series also reported activity in somatic BRCA1/2-mutated cancers. All four patients treated off-label with olaparib for somatic BRCA1/2-mutated metastatic breast cancer responded, with a median progression-free survival of 6.5 months, whereas patients with non-BRCA homologous-recombination gene alterations did not respond [17]. The sample is too small for a reliable mutation-specific estimate and is vulnerable to selection bias, but it is directionally consistent with TBCRC 048.

Taken together, the somatic evidence justifies considering olaparib when a pathogenic somatic BRCA2 alteration is identified, particularly when the tumor has a compatible phenotype and no better-supported treatment option is available. It does not justify treating every somatic BRCA2 call as equivalent to a confirmed germline pathogenic variant. Clinical decisions should incorporate variant classification, allele status, testing platform, germline confirmation where appropriate, prior platinum sensitivity, and the quality of the evidence supporting the intended treatment.

8. Combination strategies and treatment intensification

Olaparib has also been studied in combination with chemotherapy and immune-checkpoint inhibitors. These approaches are relevant because combination treatment could theoretically increase tumor-cell killing, broaden activity, or overcome resistance. They also increase the risk of overlapping toxicity and make it harder to determine how much benefit is attributable to olaparib itself.

The MEDIOLA study evaluated olaparib followed by olaparib plus durvalumab in patients with germline BRCA-mutated, HER2-negative metastatic breast cancer. Thirty patients were eligible for activity analysis, and 80% had disease control at 12 weeks. The study was open-label, non-randomized, and included both BRCA1 and BRCA2 carriers. Its results support feasibility and antitumor activity, but they cannot establish that durvalumab improves outcomes beyond olaparib monotherapy [18].

A randomized phase II study compared olaparib alone with olaparib plus atezolizumab in advanced BRCA-mutated breast cancer. In the reported abstract, progression-free survival was 7.0 months with olaparib and 7.67 months with the combination, with P = 0.92. Median overall survival was 26.5 versus 22.4 months, with P = 0.3. The combination did not significantly improve efficacy and produced more adverse events [19]. Because this report was available as a conference abstract and did not provide a definitive BRCA2-specific analysis, it should be regarded as preliminary.

The combination evidence therefore does not currently justify replacing single-agent olaparib with routine immunotherapy combinations for BRCA2-mutated breast cancer. The same principle applies to chemotherapy combinations in the neoadjuvant setting: a plausible mechanism is not sufficient when randomized clinical results are small, mixed, or discordant across endpoints.

9. Safety, tolerability, and quality of life as components of efficacy

Efficacy should not be assessed separately from the ability to maintain treatment. The most consistent olaparib toxicities are gastrointestinal symptoms, fatigue, and hematologic adverse events, particularly anemia. In OlympiAD, common adverse events included nausea, anemia, and vomiting, while grade 3 or higher adverse events were less frequent with olaparib than with physician-choice chemotherapy overall. Treatment discontinuation because of adverse events was uncommon, and the risk of anemia did not appear to increase with longer exposure [6].

In OlympiA, olaparib produced more grade 3 or higher adverse events than placebo, including anemia, neutropenia, leukopenia, fatigue, and lymphopenia. Permanent discontinuation because of adverse events was higher with olaparib than with placebo, but serious adverse events were similar between groups in the initial report [4]. Longer follow-up did not identify new safety signals, and the observed incidence of myelodysplastic syndrome or acute myeloid leukemia remained low and similar between groups, although longer surveillance remains necessary [5].

The LUCY studies provide a practical perspective. Nausea and anemia were common, but only a small proportion of patients discontinued treatment because of toxicity [14], [15]. In real-world registries, adverse-event reporting may be less complete than in clinical trials, so lower observed toxicity rates should not be interpreted as proof that treatment is intrinsically safer in routine practice [16].

Quality of life favors olaparib over chemotherapy in the metastatic randomized evidence. The pooled single-agent PARP inhibitor analysis found a significant delay in time to clinically meaningful quality-of-life deterioration, with a hazard ratio of 0.40 [20]. This outcome is clinically important because the principal metastatic benefit of olaparib is often a longer period without progression rather than a proven overall-survival extension. A treatment that delays progression while preserving quality of life can be valuable even when the overall-survival curve is affected by subsequent therapy.

10. What the meta-analyses add

Meta-analyses help place the olaparib findings in the broader PARP inhibitor literature, but they must be interpreted cautiously because most pool different drugs, settings, and mutation populations.

The 2018 systematic review and meta-analysis of two randomized trials, OlympiAD and EMBRACA, included 733 patients. Single-agent PARP inhibition improved progression-free survival compared with physician-choice chemotherapy, with a pooled hazard ratio of 0.56, and improved objective response, with an odds ratio of 4.15. Overall survival was not significantly different, with a pooled hazard ratio of 0.82. The analysis also found a delay in quality-of-life deterioration and a higher risk of anemia with

PARP inhibitors [20]. Because only one of the included trials tested olaparib and the other tested talazoparib, these results support the class effect more directly than the olaparib-specific BRCA2 effect.

A broader meta-analysis of 43 studies and 2,409 patients found a weighted mean objective response rate of 45% across PARP inhibitor studies. Response was higher in studies combining PARP inhibition with platinum than in studies of PARP inhibitor monotherapy, but the included populations were heterogeneous. After sensitivity analysis, randomized evidence showed improved progression-free survival with a pooled hazard ratio of 0.64, while overall survival remained statistically nonsignificant with a hazard ratio of 0.87. Importantly, the analysis found no significant response difference between BRCA1 and BRCA2 mutations: pooled objective response was 43% for BRCA1 and 46% for BRCA2, and pooled clinical benefit was 68% and 74%, respectively [21].

The lack of a statistically significant BRCA1-versus-BRCA2 difference is reassuring, but it is not the same as proof of identical efficacy. The analysis pooled studies with different drugs, mutation definitions, treatment lines, and response assessments. It also reported substantial heterogeneity, with I^2 values of 91% for objective response and 88% for clinical benefit. Prior platinum exposure was associated with lower response, underscoring the importance of treatment sequence [21].

The Italian Association of Medical Oncology meta-analysis and GRADE assessment reached a similar practical conclusion. In pooled advanced HER2-negative germline BRCA1/2 populations, PARP inhibitors improved progression-free survival and objective response in both triple-negative and hormone-receptor-positive disease, but overall-survival differences were not statistically significant. The panel issued conditional recommendations in favor of PARP inhibitors over single-agent chemotherapy while rating the overall certainty of evidence as limited by imprecision, indirectness, and uncertainty about treatment sequencing [22].

Another systematic review of randomized trials found a pooled progression-free survival hazard ratio of 0.64 and an overall-survival hazard ratio of 0.89 for PARP inhibitors in BRCA-mutated metastatic breast cancer [23]. An earlier narrative review of olaparib in BRCA-mutated breast cancer concluded that the available studies suggested clinical benefit but were too heterogeneous for quantitative pooling and were generally low in certainty [24]. These reviews are useful for context, but they should not be used to replace the BRCA2-specific analyses from OlympiAD and OlympiA.

11. Evidence hierarchy and major limitations

The evidence is strongest for germline BRCA2-mutated, HER2-negative breast cancer in two situations: high-risk early disease after completion of standard local therapy and chemotherapy, and metastatic disease treated with olaparib instead of physician-choice single-agent chemotherapy. Even in these settings, the BRCA2-specific evidence is a subgroup of a pooled BRCA1/2 trial rather than a BRCA2-only randomized trial.

Several limitations recur across the literature.

- Limited BRCA2-specific reporting. Many publications report outcomes for all germline BRCA1/2 carriers. The absence of a separate BRCA2 estimate does not imply absence of benefit, but it limits precision.

- Small subgroup sizes. The uncertainty becomes greater in somatic BRCA2 studies, neoadjuvant trials, national subsets, and retrospective cohorts.

- Mutation heterogeneity. Germline pathogenic variants, somatic pathogenic variants, variants of uncertain significance, monoallelic loss, and biallelic loss are not equivalent biological categories.

- Treatment-line confounding. Response and survival are generally better when olaparib is used before extensive metastatic chemotherapy. Cross-study comparisons that ignore treatment line are unreliable.

- Prior platinum exposure. Platinum sensitivity and PARP inhibitor sensitivity may overlap, while platinum resistance may predict lower response to PARP inhibition. The available studies do not establish a universal sequencing rule.

- Post-progression therapy. Subsequent PARP inhibitor use and other active therapies can dilute an overall-survival difference between randomized groups.

- Mixed endpoints. Pathological complete response, invasive disease-free survival, progression-free survival, and overall survival measure different clinical events. A lack of improvement in one endpoint cannot automatically be used to reject benefit on another.

- Underrepresentation of routine-care populations. Trial participants are usually younger, fitter, and more closely monitored than patients treated in general practice. Real-world studies improve generalizability but introduce confounding and incomplete data.

- Incomplete full-text access for some records. Several highly relevant papers in the completed search did not have workspace PDFs. Their metadata and abstracts were used, but detailed claims from those records should be verified against the final published texts before journal submission.

12. Clinical interpretation for BRCA2-mutated breast cancer

The evidence supports several clinically defensible conclusions.

First, olaparib is effective in germline BRCA2-mutated, HER2-negative early breast cancer when the patient meets the high-risk criteria used in OlympiA. The benefit is demonstrated by improvements in invasive disease-free survival, distant disease-free survival, and overall survival in the pooled population, with favorable BRCA2 subgroup estimates. The strongest evidence is for one year of adjuvant therapy after chemotherapy and local treatment, not for replacing standard surgery, radiotherapy, or chemotherapy.

Second, olaparib is effective in germline BRCA2-mutated, HER2-negative metastatic breast cancer. The BRCA2 subgroup in OlympiAD had a progression-free survival hazard ratio of 0.49 versus physician-choice chemotherapy, and response was higher across subgroups. The overall-survival advantage was not statistically significant, but the first-line metastatic subgroup showed a clinically important signal. Therefore, treatment goals should be discussed explicitly: the most certain benefits are tumor response, progression control, and quality-of-life preservation, while the magnitude of overall-survival benefit remains less certain.

Third, the evidence is not strong enough to treat germline and somatic BRCA2 alterations as identical. Somatic BRCA2 data support activity, but estimates come mainly from small single-arm studies in which BRCA1 and BRCA2 outcomes are often pooled. Molecular confirmation and careful variant interpretation are especially important when treatment is being considered outside an approved germline indication.

Fourth, BRCA2 status should not be interpreted independently of breast-cancer subtype and treatment history. Olaparib activity is documented in both triple-negative and hormone-receptor-positive/HER2-negative disease. Prior platinum treatment, the number of metastatic treatment lines, endocrine sensitivity, and the presence of visceral or central-nervous-system disease may all affect expected benefit.

Fifth, the absence of a statistically significant overall-survival difference in OlympiAD should not be misread as evidence that olaparib lacks clinical value. Progression-free survival, objective response, treatment duration, and quality-of-life outcomes all favored olaparib, and overall survival is affected by later treatments. At the same time, it would be equally inappropriate to claim a proven large overall-survival benefit for all metastatic BRCA2 carriers.

13. Future research priorities

Future studies should be designed to answer questions that the current pooled evidence cannot resolve.

1. BRCA2-stratified randomized analyses. Trials should prespecify and adequately power analyses by BRCA1 versus BRCA2 mutation, rather than reporting only pooled estimates.

2. Germline versus somatic comparison. Studies should distinguish germline BRCA2, somatic BRCA2, biallelic loss, monoallelic loss, and reversion mutations.

3. Treatment sequencing. Prospective trials should compare olaparib before versus after platinum, endocrine therapy, antibody-drug conjugates, or immune-checkpoint therapy where clinically appropriate.

4. Mechanisms of resistance. Serial sampling could clarify the role of BRCA2 reversion mutations, restoration of homologous recombination, replication-fork protection, and clonal selection.

5. Early-disease optimization. Neoadjuvant studies should establish whether olaparib should be used alone, in a chemotherapy combination, or after surgery. Secondary survival endpoints should be interpreted cautiously when pCR is not a validated surrogate in the specific BRCA2 population.

6. Patient-reported outcomes and survivorship. Long-term fatigue, anemia, quality of life, fertility, second malignancy risk, and treatment adherence require continued follow-up, particularly in patients treated in the curative setting.

7. Representation and access. Trials and registries should include more diverse populations and report outcomes by ancestry, age, comorbidity, and access to genetic testing. The clinical effectiveness of a targeted therapy depends partly on whether eligible patients are identified and can receive it.

14. Conclusion

Olaparib has a strong clinical-efficacy rationale and a substantial evidence base in BRCA2-mutated breast cancer, but the evidence must be read at the correct level of specificity. In high-risk early HER2-negative breast cancer with a germline BRCA2 pathogenic variant, adjuvant olaparib improves invasive disease-free, distant disease-free, and overall survival in the context of the OlympiA trial. In HER2-negative metastatic disease, olaparib improves progression-free survival and objective response compared with physician-choice chemotherapy, with a favorable BRCA2-specific progression-free survival estimate in OlympiAD. Metastatic overall-survival benefit is less certain, although first-line use appears more promising than later-line use.

Neoadjuvant, somatic BRCA2, combination, and real-world evidence support biologic activity but remain less definitive. The main unresolved issue is not whether BRCA2-mutated breast cancer can respond to olaparib; it is how the magnitude and durability of benefit vary by mutation origin, disease stage, treatment sequence, and tumor context. The most accurate current conclusion is that olaparib is an effective targeted treatment for appropriately selected germline BRCA2-mutated breast cancer, while BRCA2-specific evidence should continue to be reported separately rather than inferred uncritically from pooled BRCA1/2 results.

Disclosure

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All authors have read and agreed to the submitted version of the manuscript.
Funding: This research received no external funding.
Institutional Review Board Statement: Not applicable.
Informed Consent Statement: Not applicable.
Data Availability Statement: No new data were created or analyzed in this narrative review. Data availability is therefore not applicable.
Conflicts of Interest: The authors declare no conflict of interest.
Use of generative artificial intelligence: ChatGPT (OpenAI) was used to support language refinement, structural editing, and formatting. The authors are responsible for verifying all scientific claims and references and take full responsibility for the final manuscript.

Disclosure

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All authors have read and agreed with published version of the manuscript.

Funding statement: No applicable.

Institutional review board statement: Not applicable.

Informed consent statement: Not applicable.

Data availability statement: The authors confirm that the data supporting this study are available in the article's references.

Conflict of interest: Authors declare no conflict of interest.

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