Breast Cancer Aotearoa Coalition Inc

Olaparib in Breast Cancer

July 2024

Olaparib in BRCA-mutated Breast Cancer

- A report by the New Zealand Breast Cancer Foundation in 2018 found that median survival after a diagnosis of metastatic/advanced breast cancer in New Zealand is 16 months, considerably worse than overseas. Survival varies greatly by subtype, from 27.3 months for Luminal A patients down to 6.6 months for triple negative breast cancer. Five-year survival after metastatic diagnosis is only 5% in Māori populations, compared to 15% in non-Māori populations (Breast Cancer Foundation New Zealand 2018).
- Approximately 5% of patients with breast cancer carry a germline BRCA mutation. Such mutations are more likely in patients who have a strong family history of breast cancer, younger patients, patients who have triple-negative breast cancer, and patients who are members of an ethnic group with known founder mutations in the BRCA genes. Patients with a BRCA1 mutation are predisposed to triple-negative breast cancer, whereas patients with a BRCA2 mutation most often have tumours that express oestrogen receptors.
- BRCA1 and BRCA2 are tumour-suppressor genes that encode proteins involved in the repair of DNA double-strand breaks by way of the homologous recombination repair pathway. Members of the poly(adenosine diphosphate‐ribose) polymerase (PARP) family of enzymes are central to the repair of DNA single-strand breaks.
- Genetic Health Service New Zealand (GHSNZ) currently offer testing for BRCA mutations when there is an estimated >10% chance of identifying a germline abnormality, based on age of diagnosis, tumour pathology, and family history (GHSNZ 2024).
- Olaparib (LYNPARZA®) is a PARP inhibitor approved by MEDSAFE for breast cancer:
    - As monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline BRCA1/2-mutations who have HER2-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy
    - As monotherapy for the treatment of adult patients with germline BRCA-mutated HER2 negative metastatic breast cancer who have previously been

treated with chemotherapy. These patients could have received chemotherapy in the neoadjuvant, adjuvant or metastatic setting.(AstraZeneca 2024).

- The approval for adjuvant treatment of patients with germline BRCA1/2 mutations with HER2-negative early breast cancer is based on the OlympiA trial, published initially in the New England Journal of Medicine in 2021, with update survival data published in Annals of Oncology in 2022 (Tutt, Garber et al. 2021, Geyer, Garber et al. 2022). A further update included subgroup analyses (Senkus, Delaloge et al. 2023).
- The approval for patients with germline BRCA-mutated HER2 negative metastatic breast cancer was based on the OlympiaAD trial. This trial was initially published in NEJM in 2017, followed by subsequent publications on further follow up, the Aian subgroup and Health-Related Quality of Life (Robson, Im et al. 2017, Robson, Ruddy et al. 2019, Robson, Tung et al. 2019, Im, Xu et al. 2020, Robson, Im et al. 2023).
- BCAC is proposing the listing of olaparib on the Pharmaceutical Schedule for breast cancer, consistent with the MEDSAFE approval (AstraZeneca 2024). This would bring the availability of the treatment here into line with local and international guidelines (Burstein, Somerfield et al. 2021, Gennari, André et al. 2021, Breast Cancer Special Interest Group (Breast SIG) New Zealand 2022, NCCN 2023).

Summary of Published Clinical Data for Olaparib in Breast Cancer

Proposed Indications for Olaparib

LYNPARZA is indicated as

- monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline BRCA1/2-mutations who have HER2-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy.
- monotherapy for the treatment of adult patients with germline BRCA-mutated HER2negative metastatic breast cancer who have previously been treated with chemotherapy. These patients could have received chemotherapy in the neoadjuvant, adjuvant or metastatic setting.(AstraZeneca 2024)

Pivotal Clinical Trials

High Risk Early Breast Cancer (OlympiA)

Tutt, A. N. J., et al. (2021). "Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer." N Engl J Med **384**(25): 2394-2405.

Geyer, C. E., Jr., et al. (2022). "Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in BRCA1/2 and high-risk, early breast cancer." Ann Oncol **33**(12): 1250-1268.

Metastatic Breast Cancer (OlympiAD)

Robson, M., et al. (2017). "Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation." N Engl J Med **377**(6): 523-533.

Robson, M., et al. (2019). "Patient-reported outcomes in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer receiving olaparib versus chemotherapy in the OlympiAD trial." Eur J Cancer **120**: 20-30.

Robson, M. E., et al. (2019). "OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer." Ann Oncol **30**(4): 558-566.

Im, S. A., et al. (2020). "Olaparib monotherapy for Asian patients with a germline BRCA mutation and HER2-negative metastatic breast cancer: OlympiAD randomized trial subgroup analysis." Sci Rep **10**(1): 8753.

Robson, M. E., et al. (2023). "OlympiAD extended follow-up for overall survival and safety: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer." Eur J Cancer **184**: 39-47.

Senkus, E., et al. (2023). "Olaparib efficacy in patients with germline BRCA-mutated, HER2-negative metastatic breast cancer: Subgroup analyses from the phase III OlympiAD trial." Int J Cancer **153**(4): 803-814.

Supportive Trials and Meta-Analyses

Gelmon, K. A., et al. (2021). "Clinical effectiveness of olaparib monotherapy in germline BRCA-mutated, HER2-negative metastatic breast cancer in a real-world setting: phase IIIb LUCY interim analysis." Eur J Cancer **152**: 68-77.

Miglietta, F., et al. (2022). "PARP-inhibitors for BRCA1/2-related advanced HER2-negative breast cancer: A meta-analysis and GRADE recommendations by the Italian Association of Medical Oncology." Breast **66**: 293-304.

Kunwor, R., et al. (2023). "PARP Inhibitors for the Treatment of BRCA1/2-Mutated Metastatic Breast Cancer: A Systematic Review and Meta-analysis." Hematol Oncol Stem Cell Ther **16**(3): 186-196.

Zhou, Y., et al. (2022). "Comparison of Adverse Reactions Caused by Olaparib for Different Indications." Front Pharmacol **13**: 968163.

High Early Risk Breast Cancer

Citations

Tutt, A. N. J., et al. (2021). "Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer." N Engl J Med **384**(25): 2394-2405.

Geyer, C. E., Jr., et al. (2022). "Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in BRCA1/2 and high-risk, early breast cancer." Ann Oncol **33**(12): 1250-1268.

Methods

OlympiA was a prospective, multicentre, multinational, double-blind clinical trial with eligible patients randomly assigned to receive either olaparib or placebo for 1 year, after the completion of standard adjuvant or neoadjuvant chemotherapy and local therapy. Patients were recruited patients in 420 centres across 23 countries (Tutt, Garber et al. 2021).

- Patients who were eligible had a germline $BRCA1$ or $BRCA2$ pathogenic or likely pathogenic variant defined by local or central testing and had high risk, HER2-negative primary breast cancer after definitive local treatment and neoadjuvant or adjuvant chemotherapy. If a local laboratory had reported an eligible variant, this was used for establishing eligibility.
- Patients had completed at least six cycles of neoadjuvant or adjuvant chemotherapy containing anthracyclines, taxanes, or both agents. Platinum chemotherapy was allowed.
- Adjuvant bisphosphonates and adjuvant endocrine therapy in patients with hormone-receptor‑positive disease were given according to institutional guidelines.
- No chemotherapy after surgery was allowed in patients who received neoadjuvant chemotherapy.
- Patients with triple-negative breast cancer who were treated with adjuvant chemotherapy were required to have axillary node‑positive disease or an invasive primary tumour measuring at least 2 cm on pathological analysis.
- Patients who were treated with neoadjuvant chemotherapy were required to have residual invasive breast cancer in the breast or resected lymph nodes (i.e., no pathological complete response from neoadjuvant therapy).
- Patients who were treated with adjuvant chemotherapy for hormone-receptor‑positive, HER2-negative breast cancer were required to have at least four pathologically confirmed positive lymph nodes.
- Those who were treated with neoadjuvant chemotherapy were required to have not had a pathological complete response with a CPS+EG score of 3 or higher. The CPS+EG scoring system estimates relapse probability on the basis of clinical and pathological stage (CPS) and oestrogen-receptor status and histologic grade (EG); scores range from 0 to 6, with higher scores indicating worse prognosis.

Patients were randomly assigned in a 1:1 ratio to receive olaparib (300 mg) or matching placebo tablets taken orally twice daily for 52 weeks. Patients were stratified according to hormone receptor status (positive or negative), timing of previous chemotherapy (neoadjuvant or adjuvant),and use of platinum chemotherapy for current breast cancer (yes or no).

Assessments

After randomization, medical history taking and physical examination were performed every 4 weeks for 24 weeks and then every 3 months through year 2, every 6 months in years 3 to 5, and annually thereafter. Imaging to assess the development of metastatic disease was obtained at investigator discretion when symptoms, physical examination findings, or laboratory results suggested the possibility of disease recurrence. Patients underwent mammography, breast magnetic resonance imaging, or both on an annual basis. After a first event, patients were followed for first distant relapse (if not the first event), central nervous system metastases, locoregional relapses, contralateral breast cancer, second primary cancers, and survival status

End Points

The primary end point of invasive disease‑free survival was defined as the time from randomization until the date of first occurrence of one of the following events: ipsilateral invasive breast tumour, locoregional invasive disease, distant recurrence, contralateral invasive breast cancer, second primary invasive cancer, or death from any cause. Data for patients without a documented event of invasive disease or death were censored at the date they were last known to be disease free. Secondary end points included distant disease‑free survival, overall survival, and safety.

Statistical Analysis

The trial was designed with a sample size of 1800 patients such that the primary analysis would be triggered by 330 events of invasive disease or death in the ITT population. These conditions would provide the trial with 90% power to detect a HR of 0.7 under the assumption of a two-sided 5% significance level. A single interim analysis of the ITT population was planned when 165 events of invasive disease or death had been observed in the first 900 patients enrolled (termed the mature cohort).

At the interim analysis, an analysis of the mature cohort was also prespecified and required a HR of similar magnitude to provide confidence in the sustainability of the ITT result. To control the type I error rate at the interim analysis, superiority boundaries that were based on a hierarchical multiple-testing procedure were a P value of less than 0.005 for invasive disease‑free survival, followed by a P value of less than 0.005 for distant disease‑free survival and a P value of less than 0.01 for overall survival, with confidence intervals for HR s selected to match the required significance levels for each end point at the interim analysis.

Efficacy analyses were based on the ITT population, which included all the patients who had undergone randomization. Survival functions were estimated by means of the Kaplan‑Meier method. The stratified Cox proportional hazards model was used to estimate the HR and confidence intervals, and the comparison of survival between trial groups was tested by stratified log-rank testing. Because of the early period when the HR was very low, the Cox assumption was not confirmed. According to the statistical analysis plan, restricted mean survival time was calculated, and the results supported those obtained from the Cox model analysis.

Safety was assessed in the population of patients who received at least one dose of olaparib or placebo.

Table 1. **Demographic and Disease Characteristics of the Patients at Baseline.***

Characteristic	Olaparib (N = 921)	Placebo (N = 915)
Median age (interquartile range) — yr	42 (36–49)	43 (36–50)
Germline *BRCA* mutation — no. (%)†		
BRCA1	657 (71.3)	670 (73.2)
BRCA2	261 (28.3)	239 (26.1)
BRCA1 and *BRCA2*	2 (0.2)	5 (0.5)
Missing data	1 (0.1)	1 (0.1)
Previous adjuvant or neoadjuvant chemotherapy — no. (%)		
Adjuvant	461 (50.1)	455 (49.7)
Neoadjuvant	460 (49.9)	460 (50.3)
Regimen with both anthracycline and taxane	871 (94.6)	849 (92.8)
Anthracycline regimen, without taxane	7 (0.8)	13 (1.4)
Taxane regimen, without anthracycline	43 (4.7)	52 (5.7)
Regimen not reported	0	1 (0.1)
<6 Cycles of neoadjuvant or adjuvant chemotherapy	7 (0.8)	15 (1.6)
Platinum-based neoadjuvant or adjuvant therapy		
No	674 (73.2)	676 (73.9)
Yes	247 (26.8)	239 (26.1)
Concurrent hormone therapy (hormone-receptor–positive patients only) — no./total no. (%)	146/168 (86.9)	142/157 (90.4)
Hormone-receptor status — no. (%)‡		
Hormone-receptor positive and HER2 negative§	168 (18.2)	157 (17.2)
Triple-negative breast cancer¶	751 (81.5)	758 (82.8)
Menopausal status (women only) — no./total no. (%)		
Premenopausal	572/919 (62.2)	553/911 (60.7)
Postmenopausal	347/919 (37.8)	358/911 (39.3)
Surgery for primary breast cancer — no. (%)		
Mastectomy	698 (75.8)	673 (73.6)
Conservative surgery only	223 (24.2)	240 (26.2)
Missing data	0	2 (0.2)

Results (Tutt et al. 2021)

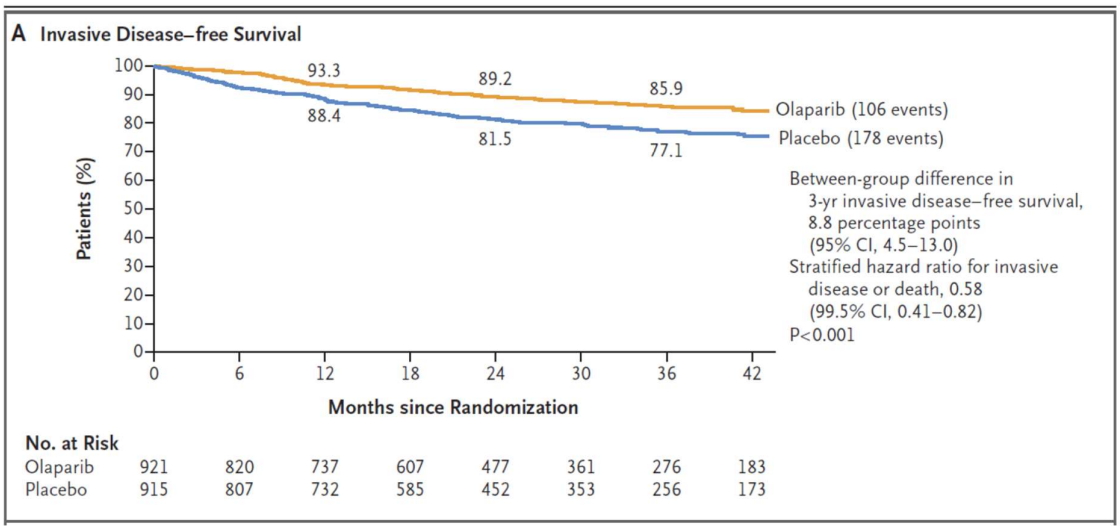
From June 2014 through May 2019, a total of 1836 patients (including 6 men) were randomly assigned to receive olaparib or placebo. At the time of data cutoff on March 27, 2020, a total of 284 events of invasive disease or death (86% of the primary-analysis target of 330 such events) had been observed, with a median follow-up of 2.5 years (IQR, 1.5 to 3.5) in the ITT population and 3.5 years (IQR, 2.9 to 4.1) in the mature cohort. After randomization, 10 patients in the olaparib group and 11 patients in the placebo group did not receive the assigned regimen.

Baseline characteristics of the patients were balanced between the two trial groups. A total of 82.2% of the patients had triple-negative breast cancer (hormone-receptor negative and HER2 negative). Half the patients had received adjuvant chemotherapy and half neoadjuvant chemotherapy, with the majority (93.7%) receiving a regimen that included both an anthracycline and a taxane. A platinum agent was received by 26.5% of the patients, primarily as neoadjuvant therapy. Germline mutations were present in *BRCA1* in 72.3% of the patients, in *BRCA2* in 27.2% of the patients, and in both *BRCA1* and *BRCA2* in 0.4% of the patients, with an even distribution between the trial groups.

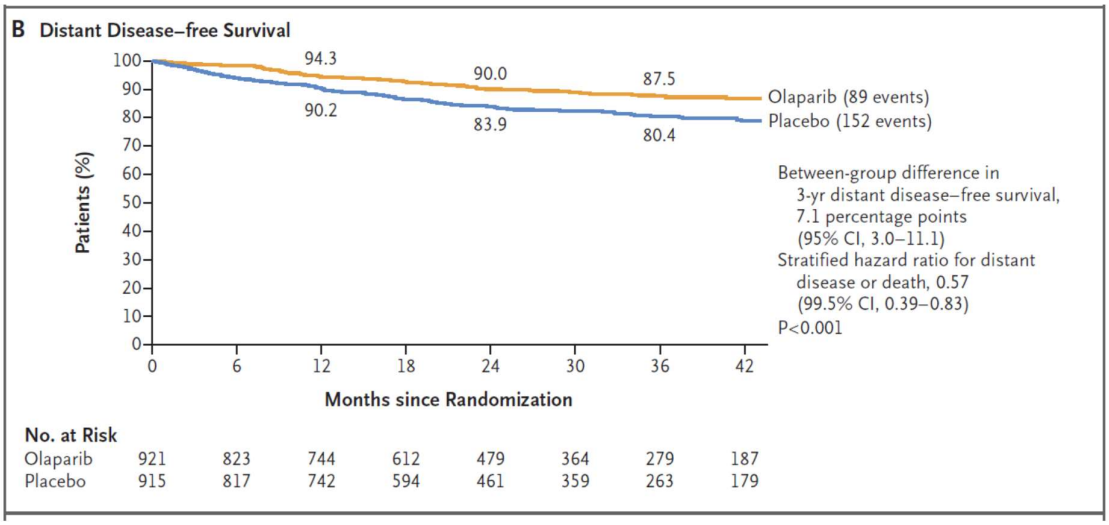
Efficacy

The early-reporting efficacy boundary was crossed at the prespecified interim analysis. The percentage of patients alive and free of invasive disease at 3 years was 85.9% in the olaparib group

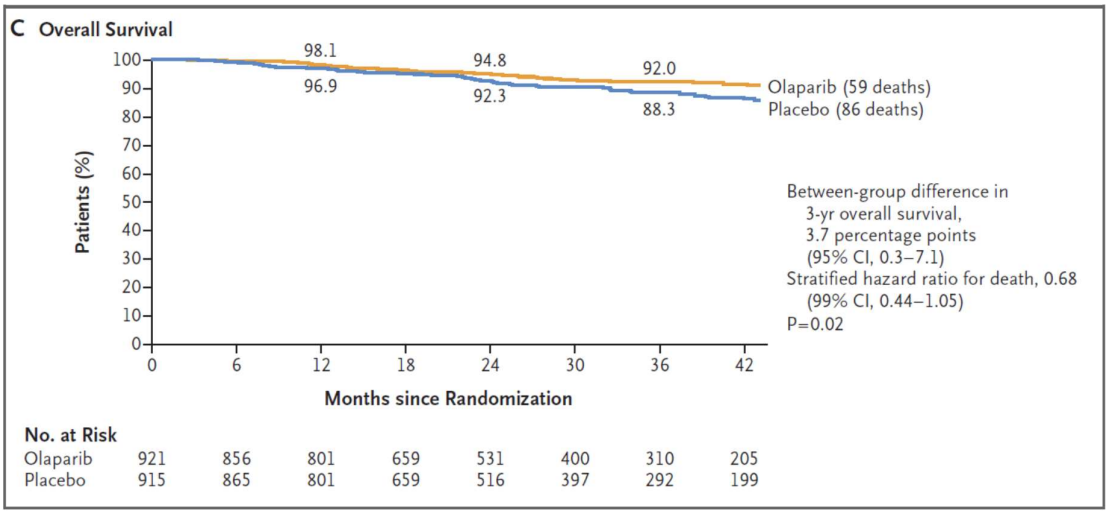
and 77.1% in the placebo group (difference, 8.8 percentage points; 95% CI 4.5 to 13.0). Invasive disease‑free survival was significantly longer among patients assigned to receive olaparib than among those assigned to receive placebo (HR, 0.58; 99.5% CI, 0.41 to 0.82; P<0.001) (Fig. 1A).



Events of invasive disease or death were reported in 106 patients in the olaparib group and 178 patients in the placebo group. The frequency of each type of event was lower with olaparib than with placebo. Distant disease‑free survival at 3 years was 87.5% in the olaparib group and 80.4% in the placebo group (difference, 7.1 percentage points; 95% CI, 3.0 to 11.1). Distant disease‑free survival was significantly longer among patients assigned to receive olaparib than among those assigned to receive placebo (HR, 0.57; 99.5% CI, 0.39 to 0.83; P<0.001) (Fig. 1B).



Fewer deaths were reported in the olaparib group (59) than in the placebo group (86), with a HR of 0.68 (99% CI, 0.44 to 1.05; P = 0.02) (Fig. 1C). However, the between-group difference did not cross the prespecified multiple-testing procedure boundary for significance of P<0.01.



The primary cause of death was breast cancer in 55 of 59 patients (93%) in the olaparib group and in 82 of 86 patients (95%) in the placebo group (Table S8). Death without a previous event of invasive disease was reported in 2 patients, both in the olaparib group (the cause was cardiac arrest in 1 patient and was unknown in 1 patient) (Table S7). None of the prespecified sensitivity analyses changed the conclusions.

Subgroup analysis of invasive disease‑free survival revealed point estimates of treatment effect for olaparib over placebo that were consistent with those in the overall analysis population across all the stratification groups and prespecified subgroups (Fig. 2 and Table S10). The benefit of adjuvant olaparib relative to placebo was observed for invasive disease‑free survival irrespective of the germline *BRCA* mutation (*BRCA1* vs. *BRCA2*), the hormone-receptor status, or the timing of previous chemotherapy (neoadjuvant vs. adjuvant), with confidence intervals that crossed the point estimate of the HR for invasive disease‑free survival in the overall population. No evidence suggested statistical heterogeneity in the treatment effect across subgroups (Tutt, Garber et al. 2021).

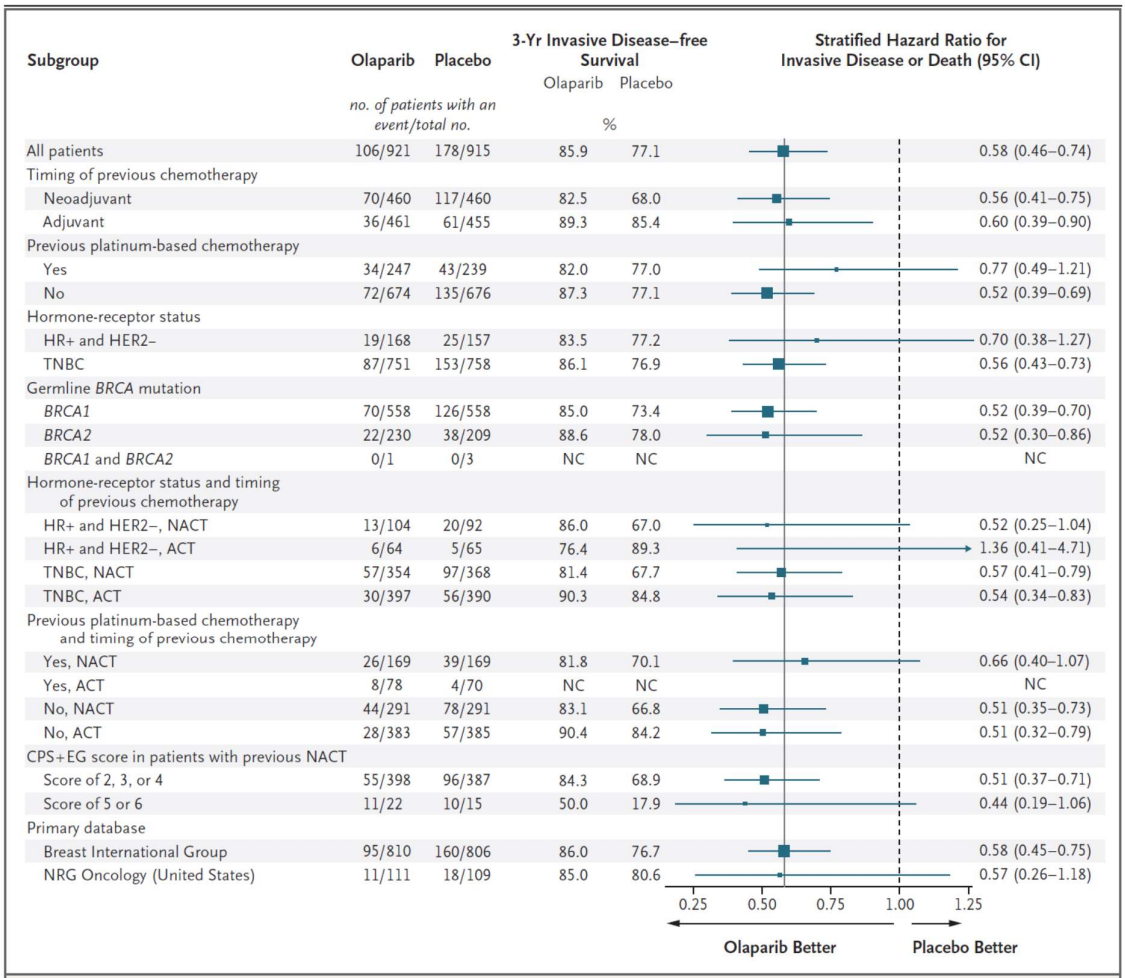


Figure 2. Subgroup Analysis of Invasive Disease–free Survival.

The solid vertical line indicates the overall hazard-ratio estimate, and the dashed vertical line indicates a hazard ratio of 1.00, as recommended by Cuzick.[23] The size of the blue squares corresponds to the number of events contributing to the estimate of the treatment effect. Even without correcting for multiple comparisons, none of the tests for heterogeneity reached statistical significance. *BRCA* mutation data reflect central Myriad testing results only. The CPS+EG score is a staging system for disease-specific survival among patients with breast cancer treated with neoadjuvant chemotherapy (NACT).[20] This incorporates pretreatment clinical stage, estrogen-receptor status, nuclear grade, and postneoadjuvant chemotherapy pathological stage. Patients who were enrolled had scores ranging from 2 to 6, with higher scores indicating worse prognosis. The prespecified subgroup analysis of the CPS+EG score in patients with previous NACT was performed in all the patients who had received NACT, whether they had hormone-receptor–positive (HR+) disease or triple-negative breast cancer (TNBC). ACT denotes adjuvant chemotherapy, HER2 human epidermal growth factor receptor 2, and NC not calculated.

Results of Second Interim Analysis (Geyer et al. 2022)

With a median follow-up of 3.5 years, the second IA of OS demonstrated significant improvement in the olaparib group relative to the placebo group [HR 0.68; 98.5% confidence interval (CI) 0.47–0.97; P = 0.009]. Four-year OS was 89.8% in the olaparib group and 86.4% in the placebo group (D 3.4%, 95% CI −0.1% to 6.8%). Four-year IDFS for the olaparib group versus placebo group was 82.7% versus 75.4% (D 7.3%, 95% CI 3.0% to 11.5%) and 4-year DDFS was 86.5% versus 79.1% (D 7.4%, 95% CI 3.6% to 11.3%), respectively. Subset analyses for OS, IDFS, and DDFS demonstrated benefit across major subgroups. No new safety signals were identified including no new cases of acute myeloid leukaemia or myelodysplastic syndrome (Geyer, Garber et al. 2022).

Safety

A total of 1815 patients (911 in the olaparib group and 904 in the placebo group) were included in the safety analysis. The median number of days at the protocol dose of 300 mg twice daily was 338 in the olaparib group and 358 in the placebo group; the median percentage of the intended dose that was received was 94.8% and 98.9%, respectively. Early discontinuations of the trial regimen, including discontinuations due to recurrence, occurred in 236 patients (25.9%) in the olaparib group and 187 (20.7%) in the placebo group.

Table 3. Summary of Adverse Events in the Safety Analysis Set.*

Adverse Event	Olaparib (N = 911)	Placebo (N = 904)
	no. of patients (%)	
Any adverse event	835 (91.7)	753 (83.3)
Serious adverse event	79 (8.7)	76 (8.4)
Adverse event of special interest†	30 (3.3)	46 (5.1)
MDS or AML	2 (0.2)	3 (0.3)
Pneumonitis‡	9 (1.0)	11 (1.2)
New primary cancer§	19 (2.1)	32 (3.5)
Grade ≥3 adverse event	221 (24.3)	102 (11.3)
Grade 4 adverse event¶	17 (1.9)	4 (0.4)
Adverse event leading to permanent discontinuation of olaparib or placeboll	90 (9.9)	38 (4.2)
Adverse event leading to death**	1 (0.1)	2 (0.2)

Table 2. Adverse Events According to Grade.*

Adverse Event	Olaparib (N = 911)				Placebo (N = 904)			
	Any Grade	Grade 1	Grade 2	Grade ≥3†	Any Grade	Grade 1	Grade 2	Grade ≥3†
	number of patients (percent)							
Nausea	518 (56.9)	390 (42.8)	121 (13.3)	7 (0.8)	211 (23.3)	185 (20.5)	26 (2.9)	0
Fatigue	365 (40.1)	240 (26.3)	109 (12.0)	16 (1.8)	245 (27.1)	188 (20.8)	53 (5.9)	4 (0.4)
Anemia	214 (23.5)	68 (7.5)	67 (7.4)	79 (8.7)	35 (3.9)	19 (2.1)	13 (1.4)	3 (0.3)
Vomiting	206 (22.6)	160 (17.6)	40 (4.4)	6 (0.7)	74 (8.2)	64 (7.1)	10 (1.1)	0
Headache	180 (19.8)	145 (15.9)	33 (3.6)	2 (0.2)	152 (16.8)	120 (13.3)	31 (3.4)	1 (0.1)
Diarrhea	160 (17.6)	125 (13.7)	32 (3.5)	3 (0.3)	124 (13.7)	96 (10.6)	25 (2.8)	3 (0.3)
Decreased neutrophil count	146 (16.0)	36 (4.0)	66 (7.2)	44 (4.8)	59 (6.5)	17 (1.9)	35 (3.9)	7 (0.8)
Decreased white-cell count	143 (15.7)	41 (4.5)	75 (8.2)	27 (3.0)	52 (5.8)	27 (3.0)	22 (2.4)	3 (0.3)
Decreased appetite	119 (13.1)	101 (11.1)	16 (1.8)	2 (0.2)	53 (5.9)	45 (5.0)	8 (0.9)	0
Dysgeusia	107 (11.7)	101 (11.1)	6 (0.7)	0	38 (4.2)	36 (4.0)	2 (0.2)	0
Dizziness	104 (11.4)	91 (10.0)	12 (1.3)	1 (0.1)	67 (7.4)	61 (6.7)	5 (0.6)	1 (0.1)
Arthralgia	84 (9.2)	60 (6.6)	22 (2.4)	2 (0.2)	107 (11.8)	85 (9.4)	20 (2.2)	2 (0.2)

* Shown are adverse events of any grade with an incidence of at least 10% in either trial group in the safety analysis set.
† All listed adverse events are grade 3 except for 10 grade 4 events in the olaparib group: 5 events involving decreased neutrophil count, 4 involving anemia, and 1 involving fatigue.

Adverse events that occurred in at least 10% of the patients in either group are shown in Table 2 from the published paper (reproduced below), and the events in the olaparib group were consistent with the product label. Important adverse events are summarized in Table 3. Adverse events of grade 3 or higher that occurred in more than 1% of the patients in the olaparib group were anaemia (8.7%),

decreased neutrophil count (4.8%), decreased white-cell count (3.0%), fatigue (1.8%), and lymphopenia (1.2%). No adverse events of grade 3 or higher occurred in more than 1% of the patients in the placebo group. Blood transfusion was infrequent, with 53 patients (5.8%) in the olaparib group and 8 patients (0.9%) in the placebo group having at least one transfusion.

Serious adverse events occurred in 79 patients (8.7%) who received olaparib and 76 patients (8.4%) who received placebo. Adverse events leading to death were cardiac arrest in 1 patient in the olaparib group and acute myeloid leukaemia (AML) and ovarian cancer in 1 patient each in the placebo group. Adverse events of special interest included pneumonitis, radiation pneumonitis, myelodysplastic syndrome (MDS) or AML, and new primary cancer other than MDS or AML. None occurred at a higher frequency in the olaparib group than in the placebo group.

In the olaparib group, 228 patients (25.0%) had a dose reduction, as compared with 47 (5.2%) in the placebo group. Adverse events that led to permanent discontinuation of the trial regimen occurred in 90 patients (9.9%) in the olaparib group and 38 patients (4.2%) in the placebo group. The most common reasons for discontinuation of olaparib were nausea (2.0%), anaemia (1.8%), fatigue (1.3%), and decreased neutrophil count (1.0%) (Tutt, Garber et al. 2021).

Patient Reported Outcomes

The results of the European Organization for Research and Treatment of Cancer QLQ-C30 Global Health Status and Quality of Life scale indicated that global health quality did not decline during the 12 months of treatment with either olaparib or placebo. Any differences between the trial groups were not considered to be clinically significant (Tutt, Garber et al. 2021).

Conclusion

The OlympiA trial showed that 1 year of adjuvant olaparib can meaningfully reduce recurrence risk and prevent progression to metastatic disease among patients with high-risk early breast cancer and germline *BRCA1* or *BRCA2* pathogenic or likely pathogenic variants, with high adherence rates and primarily a low-grade toxicity profile. Patients with these variants are increasingly identified in patients with early breast cancer as a result of greater acceptance of the influence of germline *BRCA1* or *BRCA2* pathogenic or likely pathogenic variant status on treatment choices. The trial provides evidence that germline *BRCA1* and *BRCA2* sequencing is an important biomarker for the selection of systemic therapy in early breast cancer.

Metastatic Breast Cancer

Citations

Robson, M., et al. (2017). "Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation." N Engl J Med **377**(6): 523-533.

Robson, M., et al. (2019). "Patient-reported outcomes in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer receiving olaparib versus chemotherapy in the OlympiAD trial." Eur J Cancer **120**: 20-30.

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Methods

OlympiAD was a randomised, open-label, phase 3 trial in which olaparib monotherapy was compared with standard therapy in patients with a germline *BRCA* mutation and human epidermal growth factor receptor type 2 (HER2)‑negative metastatic breast cancer who had received no more than two previous chemotherapy regimens for metastatic disease.

Patients were randomly assigned, in a 2:1 ratio, to receive olaparib tablets (300 mg twice daily) or standard therapy with single-agent chemotherapy of the physician’s choice (capecitabine, eribulin, or vinorelbine in 21-day cycles). Randomization was stratified according to previous use of chemotherapy for metastatic disease), hormone-receptor status (hormone receptor positive vs. triple negative), and previous use of platinum-based therapy (yes vs. no). Patients were randomly assigned, in a 2:1 ratio, to receive olaparib tab lets (300 mg twice daily) or standard therapy with one of the following three prespecified chemotherapy regimens: capecitabine administered orally at a dose of 2500 mg/m2 (divided into two doses) for 14 days, repeated every 21 days; eribulin mesylate administered intravenously at a dose of 1.4 mg/m2 on day 1 and day 8, repeated every 21 days; or vinorelbine administered intravenously at a dose of 30 mg/m2 on day 1 and day 8, repeated every 21 days. The assigned treatment was continued until disease progression or unacceptable toxic effects occurred. After disease progression occurred, treatment was at the discretion of the investigator. Crossover to olaparib was not permitted in this trial.

Assessments

CT or MRI was performed every 6 weeks until week 24 and then every 12 weeks thereafter. Overall survival and the time to a second progression event or death after a first progression event were assessed every 8 weeks after the first progression event. Adverse events were graded with the use of

the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Health-related quality of life was assessed with the QLQ-C30, which was completed by the patient at baseline and then every 6 weeks until disease progression. Scores on the QLQ-C30 range from 0 to 100, with higher scores indicating better quality of life; an increase or decrease of at least 10 points was considered to be a clinically meaningful change.

End Points

The primary end point was progression-free survival, which was defined as the time from randomization to objective radiologic disease progression (according to modified RECIST, version 1.1) or death from any cause. The primary analysis was based on BICR. A prespecified sensitivity analysis was based on investigator assessment. At the time of data cutoff for the primary end point (after at least 230 events had occurred), additional data were collected for the following prespecified secondary end points: safety outcomes, overall survival, time from randomization to a second progression event or death after a first progression event (based on investigator assessment), objective response rate and scores for health-related quality of life.

Statistical Analysis

A total of 230 progression free survival events would give the trial 90% power (at a two-sided significance level of 5%) to show a statistically significant difference in progression-free survival between the olaparib group and the standard-therapy group, with a corresponding HR for disease progression or death of 0.635. Efficacy data were analysed on an ITT basis, and safety was assessed in all patients who received at least one dose of the assigned treatment. The primary analysis of progression-free survival was based on BICR and was performed with the use of a stratified log-rank test. The Kaplan‑Meier method was used to generate time-to-event curves, from which medians were calculated. For the primary end point, a logrank test (stratified according to hormone-receptor status and previous use of chemotherapy) was used to compare the Kaplan‑Meier curves in the two treatment groups, and the P value derived from this comparison was reported. HR s and confidence intervals were estimated from the log-rank test statistics. Progression-free survival event rates at 12 months were calculated with the use of Kaplan‑Meier curves.

Results (Robson, Im et al. 2017)

A total of 302 patients underwent randomization; 205 were assigned to the olaparib group and received the assigned treatment, and 97 were assigned to the standard-therapy group, of whom 91 received the assigned treatment. The median age was 44 years, and baseline demographic characteristics were well balanced between the two treatment groups (Table 1 = below).

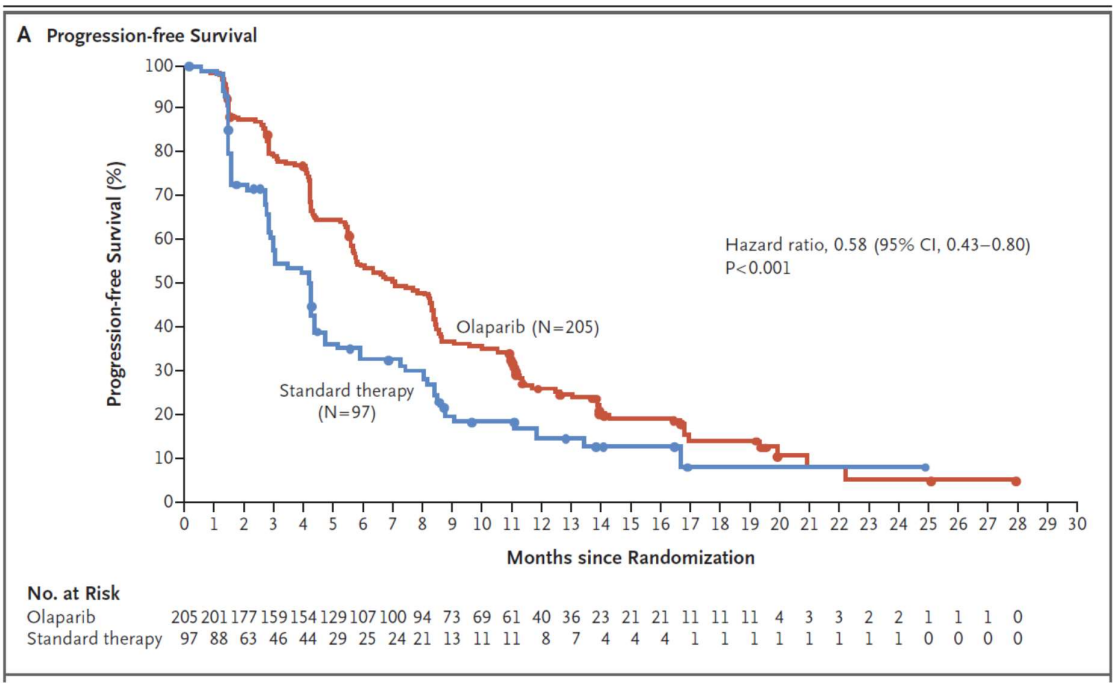
The median duration of follow-up was 14.5 months (range, 2.1 to 29.5) in the olaparib group and 14.1 months (range, 0 to 28.2) in the standard-therapy group.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Olaparib Group (N=205)	Standard-Therapy Group (N=97)
Age — yr		
Median	44	45
Range	22–76	24–68
Male sex — no. (%)	5 (2.4)	2 (2.1)
Race or ethnic group — no. (%)†		
White	134 (65.4)	63 (64.9)
Asian	66 (32.2)	28 (28.9)
Other	5 (2.4)	6 (6.2)
ECOG performance status — no. (%)‡		
0	148 (72.2)	62 (63.9)
1	57 (27.8)	35 (36.1)
BRCA mutation type — no. (%)§		
BRCA1	117 (57.1)	51 (52.6)
BRCA2	84 (41.0)	46 (47.4)
BRCA1 and *BRCA2*	4 (2.0)	0
Hormone-receptor status — no. (%)¶		
Hormone-receptor positive	103 (50.2)	49 (50.5)
Triple negative	102 (49.8)	48 (49.5)
New metastatic breast cancer — no. (%)	26 (12.7)	12 (12.4)
Previous chemotherapy for metastatic breast cancer — no. (%)	146 (71.2)	69 (71.1)
Previous platinum-based therapy for breast cancer — no. (%)	60 (29.3)	26 (26.8)
≥2 Metastatic sites — no. (%)	159 (77.6)	72 (74.2)
Location of the metastasis — no. (%)		
Bone only	16 (7.8)	6 (6.2)
Other‖	189 (92.2)	91 (93.8)
Measurable disease — no. (%)	167 (81.5)	66 (68.0)

Primary Endpoint (PFS)

The primary end point was assessed after 234 of the 302 patients (77.5%) had had disease progression (assessed by blinded independent central review) or had died. At the time of this analysis, median progression-free survival was significantly longer in the olaparib group than in the standard-therapy group (7.0 months vs. 4.2 months; HR for disease progression or death, 0.58; 95% CI, 0.43 to 0.80; P<0.001) (Fig. 2A).



Progression-free survival results that were based on investigator assessment were consistent with results based on blinded independent central review; on the basis of investigator assessment, median progression-free survival was 7.8 months in the olaparib group and 3.8 months in the standard-therapy group (HR for disease progression or death, 0.50; 95% CI, 0.36 to 0.68; P<0.001). At 12 months, 25.9% of the patients in the olaparib group and 15.0% of the patients in the standard-therapy group were free of progression or death.

Other Endpoints (Robson, Im et al. 2017)

- At the time of the initial analysis, 157 of the 302 patients (52.0%) had had a second progression event or had died after a first progression event. The median time from randomization to a second progression event or death after a first progression event was 13.2 months in the olaparib group and 9.3 months in the standard-therapy group (HR, 0.57; 95% CI, 0.40 to 0.83; P = 0.003).
- A total of 94 patients (45.9%) in the olaparib group and 46 patients (47.4%) in the standard therapy group had died at the time of the primary analysis. The median time to death was 19.3 months in the olaparib group and 19.6 months in the standard-therapy group. Overall survival did not differ significantly between groups (HR for death, 0.90; 95% CI, 0.63 to 1.29; P = 0.57). More patients in the standard-therapy group than in the olaparib group received treatment with PARP inhibitors, platinum-based therapy, or other cytotoxic chemotherapy after the first progression event. Analysis of overall survival is therefore likely to be confounded by subsequent treatment.
- Response to treatment occurred in 100 of the 167 patients who had measurable disease in the olaparib group (59.9%; 95% CI, 52.0 to 67.4) and in 19 of the 66 patients in the standard-therapy group (28.8%; 95% CI, 18.3 to 41.3).
- A complete response was seen in 9.0% of the patients who had measurable disease in the olaparib group and in 1.5% in the standard-therapy group.

- The median duration of response was 6.4 months (interquartile range, 2.8 to 9.7) in the olaparib group and 7.1 months (interquartile range, 3.2 to 12.2) in the standard-therapy group.
- Median time to the onset of a response was 47 days and 45 days, respectively.

Safety

The median total treatment duration was 8.2 months (range, 0.5 to 28.7) in the olaparib group and 3.4 months (range, 0.7 to 23.0) in the standard-therapy group. Table 2 shows data on adverse events of any grade that occurred in at least 15% of patients in either treatment group. Anaemia, nausea, vomiting, fatigue, headache, and cough occurred more frequently in the olaparib group than in the standard-therapy group; neutropenia, palmar‐plantar erythrodysesthesia, and an increase in liver-function enzymes were more common in the standard-therapy group than in the olaparib group

Table 2. Summary of Adverse Events.*

Variable	Olaparib Group (N=205)		Standard-Therapy Group (N=91)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number (percent)			
Adverse event				
Any	199 (97.1)	75 (36.6)	88 (96.7)	46 (50.5)
Anemia†	82 (40.0)	33 (16.1)	24 (26.4)	4 (4.4)
Neutropenia‡	56 (27.3)	19 (9.3)	45 (49.5)	24 (26.4)
Decreased white-cell count	33 (16.1)	7 (3.4)	19 (20.9)	9 (9.9)
Nausea	119 (58.0)	0	32 (35.2)	1 (1.1)
Vomiting	61 (29.8)	0	14 (15.4)	1 (1.1)
Diarrhea	42 (20.5)	1 (0.5)	20 (22.0)	0
Decreased appetite	33 (16.1)	0	11 (12.1)	0
Fatigue	59 (28.8)	6 (2.9)	21 (23.1)	1 (1.1)
Headache	41 (20.0)	2 (1.0)	14 (15.4)	2 (2.2)
Pyrexia	29 (14.1)	0	16 (17.6)	0
Cough	35 (17.1)	0	6 (6.6)	0
Increased alanine aminotransferase level	23 (11.2)	3 (1.5)	16 (17.6)	1 (1.1)
Increased aspartate aminotransferase level	19 (9.3)	5 (2.4)	15 (16.5)	0
Palmar–plantar erythrodysesthesia	1 (0.5)	0	19 (20.9)	2 (2.2)
Dose reduction owing to adverse event	52 (25.4)	NA	28 (30.8)	NA
Treatment interruption or delay owing to adverse event	72 (35.1)	NA	25 (27.5)	NA
Treatment discontinuation owing to adverse event	10 (4.9)	NA	7 (7.7)	NA

Results – Other Publications

Subsequent publications reported on final follow up results for this trial.

Robson et al. (2019) reported that at 64% data maturity, median OS was 19.3 months with olaparib versus 17.1 months with TPC (HR 0.90, 95% CI 0.66–1.23; P¼0.513); median follow-up was 25.3 and 26.3 months, respectively. HR for OS with olaparib versus TPC in prespecified subgroups were prior chemotherapy for mBC [no (first-line setting): 0.51, 95% CI 0.29–0.90; yes (second/third-line): 1.13,

0.79–1.64]; receptor status (triple negative: 0.93, 0.62–1.43; hormone receptor positive: 0.86, 0.55–1.36); prior platinum (yes: 0.83, 0.49–1.45; no: 0.91, 0.64–1.33). Adverse events during olaparib treatment were generally low grade and manageable by supportive treatment or dose modification. There was a low rate of treatment discontinuation (4.9%), and the risk of developing anaemia did not increase with extended olaparib exposure. Although there was no statistically significant improvement in OS with olaparib compared to TPC, there was the possibility of meaningful OS benefit among patients who had not received chemotherapy for metastatic disease. Olaparib was generally well-tolerated, with no evidence of cumulative toxicity during extended exposure (Robson, Tung et al. 2019).

Robson et al. (2019) reported in more details on Health-Related Quality of Life measured in this trial. Overall questionnaire compliance rates were 93.2% for olaparib and 76.3% for TPC. Between-treatment global health status/QoL comparison showed a significant improvement in the olaparib arm versus the TPC arm, with mean change 3.9 (SD 1.2) versus −3.6 (2.2), a difference of 7.5 points (95% CI 2.48, 12.44; P=0.0035). A higher proportion of patients in the olaparib arm showed a best overall response of 'improvement' in global health status/QoL (33.7% vs 13.4%). Median time to global health status/QoL deterioration was not reached in olaparib patients and was 15.3 months for TPC patients (hazard ratio 0.44 [95% CI 0.25, 0.77]; P=0.004). For QLQ-C30 symptoms and functioning subscales, only nausea/vomiting symptom score was worse in the olaparib arm compared with TPC (across all visits compared with baseline). It was concluded that HRQoL was consistently improved for patients treated with olaparib, compared with chemotherapy TPC (Robson, Ruddy et al. 2019).

Robson et al. (2023) reported on post-hoc extended follow-up, 25.7 months longer than previously reported for OS. During extended follow-up, OS was analysed every 6 months using the stratified log-rank test (overall population) and Cox proportional hazards model (pre-specified subgroups). In the overall population (302 patients; 76.8% maturity), median OS was 19.3 months for olaparib and 17.1 months for TPC (hazard ratio 0.89, 95% confidence interval 0.67-1.18); median follow-up was 18.9 and 15.5 months, respectively. Three-year survival was 27.9% for olaparib versus 21.2% for TPC. With olaparib, 8.8% of patients received study treatment for >3 years versus none with TPC. In first-line mBC, median OS was longer for olaparib than TPC (22.6 versus 14.7 months; HR 0.55, 95% CI 0.33-0.95) and 3-year survival was 40.8% for olaparib versus 12.8% for TPC. No new serious adverse events related to olaparib were observed. It was concluded that OS was consistent with previous analyses from OlympiAD. These findings supported the possibility of meaningful long-term survival benefit with olaparib, particularly in first-line mBC (Robson, Im et al. 2023).

Conclusion

Although the trial met the primary endpoint of improved progression-free survival in the olaparib group, there was an improvement in overall survival only in the group who received this treatment in first line treatment of MBC. However, it should be noted that there was greater use of subsequent treatment in the standard treatment group, that may have confounded analysis of OS.

Fewer grade 3 or higher adverse events and adverse events leading to discontinuation occurred with olaparib than with standard therapy. In the olaparib group, the most common adverse event was grade 1 or 2 nausea, and the most common grade 3 or higher adverse event was anaemia. The safety profile of olaparib was similar to that reported in other studies of olaparib monotherapy.

Analysis of HR-QoL showed that this was consistently improved for patients treated with olaparib, compared with chemotherapy TPC.

Supportive Trials and Meta-Analyses

Gelmon, K. A., et al. (2021). "Clinical effectiveness of olaparib monotherapy in germline BRCA-mutated, HER2-negative metastatic breast cancer in a real-world setting: phase IIIb LUCY interim analysis." Eur J Cancer **152**: 68-77.

This open-label, single-arm trial of olaparib (300 mg, twice daily) enrolled patients with BRCAm, HER2-negative mBC who had received taxane and/or anthracycline in the (neo)adjuvant/metastatic setting and not more than two lines of prior chemotherapy for mBC. Patients with hormone receptor-positive mBC had progressed on at least one line of endocrine therapy in an adjuvant/metastatic setting and were unsuitable for further endocrine treatment. This interim analysis was planned after 160 PFS events. Of 563 patients screened, 252 patients with gBRCAm were enrolled and received at least one dose of olaparib. The median investigator-assessed PFS was 8.11 months (95% confidence interval [CI], 6.93e8.67; 166/252 events [65.9% maturity]). The investigator-assessed clinical response rate was 48.6%, and median time to first subsequent treatment or death was 9.66 months (95% CI, 8.67e11.14). The most common treatment-emergent adverse events (TEAEs; >20% patients) were nausea, anaemia, asthenia, vomiting and fatigue. Eleven patients (4.4%) discontinued treatment because of a TEAE. Grade 3 or higher TEAEs occurred in 64 patients (25.4%), including anaemia (33 patients; 13.1%). It was concluded that olaparib was clinically effective in patients with gBRCAm, HER2-negative mBC with safety outcomes consistent with previous findings.

Miglietta, F., et al. (2022). "PARP-inhibitors for BRCA1/2-related advanced HER2-negative breast cancer: A meta-analysis and GRADE recommendations by the Italian Association of Medical Oncology." Breast **66**: 293-304.

The panel of the Italian Association of Medical Oncology (AIOM) Clinical Practice Guidelines on Breast Cancer addressed two critical clinical questions, adopting the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach and the Evidence to Decision framework (EtD), to develop recommendations on the use of PARP-inhibitors, with respect to single-agent chemotherapy, in patients with BRCA-related triple-negative (clinical question 1) and hormone receptor-positive (HR+)/HER2- (clinical question 2) advanced BC. RESULTS: Two studies were eligible (OlympiAD and EMBRACA). For both clinical questions, the Panel judged the benefit/harm balance probably in favour of the intervention, given the favourable impact in terms of PFS, ORR, and QoL at an acceptable cost in terms of toxicity; the overall certainty of the evidence was low. The panel's final recommendations were conditional in favour of PARP-inhibitors over single-agent chemotherapy in both HR+/HER2-and triple-negative BC. Finally, the Panel identified and discussed areas of uncertainty calling for further exploration. The Panel of AIOM BC Clinical Practice Guideline provided clinical recommendations on the use of PARP-inhibitors, with respect to single-agent chemotherapy, in patients with BRCA-related HER2-advanced BC by adopting the GRADE methodology.

Kunwor, R., et al. (2023). "PARP Inhibitors for the Treatment of BRCA1/2-Mutated Metastatic Breast Cancer: A Systematic Review and Meta-analysis." Hematol Oncol Stem Cell Ther **16**(3): 186-196.

This analysis used systematic review methods up to March 2021. Only phase II and III RCTs evaluating PFS and OS for PARPis alone or in combination with chemotherapy (CT) and comparing the findings with standard CT were included in this meta-analysis. Pooled analysis of the hazard ratio (HR) was performed with RevMan v5.4 using a random effects method. Five RCTs with a total of 1563 BRCA-mutated MBC patients were included in this meta-analysis. A statistically significant increase in PFS was observed in the PARPi group compared to the standard CT group (HR, 0.64; 95% CI, 0.56-0.74; P

< 0.00001). However, the differences in OS did not reach statistical significance (HR, 0.89; 95% CI, 0.77-1.02; P = 0.09). Moreover, differences were not observed in the adverse event profile between the two groups (odds ratio, 1.18; 95% CI, 0.84-1.64; P = 0.33). It was concluded that results of confirmed the previously reported PFS benefit of PARPis over standard CT. PARPis lead to superior PFS in gBRCA + MBC when used alone or in combination with standard CT. The OS benefit is similar between PARPis and standard CT.

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