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Original Research

Clinical effectiveness of olaparib monotherapy in germline BRCA-mutated, HER2-negative metastatic breast cancer in a real-world setting: phase IIIb LUCY interim analysis

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Abstract ***Background:*** In the phase III OlympiAD trial, olaparib significantly increased progression-free survival (PFS) compared with chemotherapy of physician's choice in patients with germline BRCA-mutated (gBRCAm), human epidermal growth factor 2 (HER2)-negative metastatic breast cancer (mBC). The phase IIIb LUCY trial assessed the clinical effectiveness of olaparib in similar patients, in a setting reflecting clinical practice.
Methods: 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

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Progression-free survival;
Treatment outcome

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.

Results: 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], 6.93–8.67; 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, 8.67–11.14). 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%).

Conclusion: Olaparib was clinically effective in patients with gBRCAm, HER2-negative mBC with safety outcomes consistent with previous findings. ClinicalTrials.gov identifier: NCT03286842.

1. Introduction

Germline *BRCA1* and *BRCA2* mutations (gBRCAm) account for approximately 5% of all breast cancers [1–5], with a higher prevalence occurring in certain patient populations, including those with a family history of breast cancer [6]. *BRCA1* mutations are often associated with triple-negative breast cancer (TNBC); patients with *BRCA2* mutations are more likely to develop hormone receptor (HR)-positive tumours [7–9]. Although patients with gBRCAm are generally younger at breast cancer diagnosis and have aggressive tumour characteristics [8,10], the impact of gBRCAm on prognosis compared with the general breast cancer population remains unclear [11–13].

Poly(ADP-ribose) polymerase (PARP) inhibitors are a targeted treatment for patients with gBRCAm, human epidermal growth factor receptor 2 (HER2)-negative advanced/metastatic breast cancer. In the randomized phase III OlympiAD trial (ClinicalTrials.gov: NCT02000622), olaparib monotherapy significantly increased progression-free survival (PFS) compared with chemotherapy treatment of physician's choice in patients with gBRCAm, HER2-negative metastatic breast cancer [14]. Similarly, talazoparib showed significant benefits over standard chemotherapy in patients with gBRCAm locally advanced or metastatic breast cancer [15].

Randomized clinical trials performed in tightly defined settings deliver robust evidence demonstrating the clinical efficacy and safety of treatments. However, their findings may have limited applicability to routine clinical practice. Clinical effectiveness data generated in real-world settings can address evidence gaps and strengthen understanding of treatment benefits and challenges [16,17]. The phase IIIb LUCY trial (ClinicalTrials.gov: NCT03286842) [18] assessed the clinical effectiveness of olaparib monotherapy in patients with BRCAm, HER2-negative metastatic breast cancer in a setting designed to closely reflect real-world clinical practice.

2. Methods

2.1. Trial design and oversight

This open-label, single-arm, multicentre, international trial was performed in accordance with the Declaration of Helsinki, International Conference on Harmonisation of Good Clinical Practice guidelines, applicable regulatory requirements, and the AstraZeneca Global Policy on Bioethics [19]. The trial protocol was approved by ethics review committees at all participating institutions/countries. Patients provided written informed consent before commencing study-related procedures. Data underlying the findings described in this article may be obtained in accordance with AstraZeneca's data-sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

2.2. Patients

Eligible patients were at least 18 years of age and had histologically or cytologically confirmed HER2-negative breast cancer, regardless of HR status, with evidence of metastatic disease (Fig. 1). Patients had a documented deleterious or suspected deleterious gBRCAm or somatic BRCAm (sBRCAm). Patients with an sBRCAm were included after a protocol amendment and will be evaluated in a separate exploratory analysis. Patients had received a maximum of two lines of prior chemotherapy for metastatic disease and a taxane and/or an anthracycline in either a neoadjuvant/adjuvant or metastatic breast cancer treatment setting. Previous treatment with platinum-based chemotherapy was permitted in early

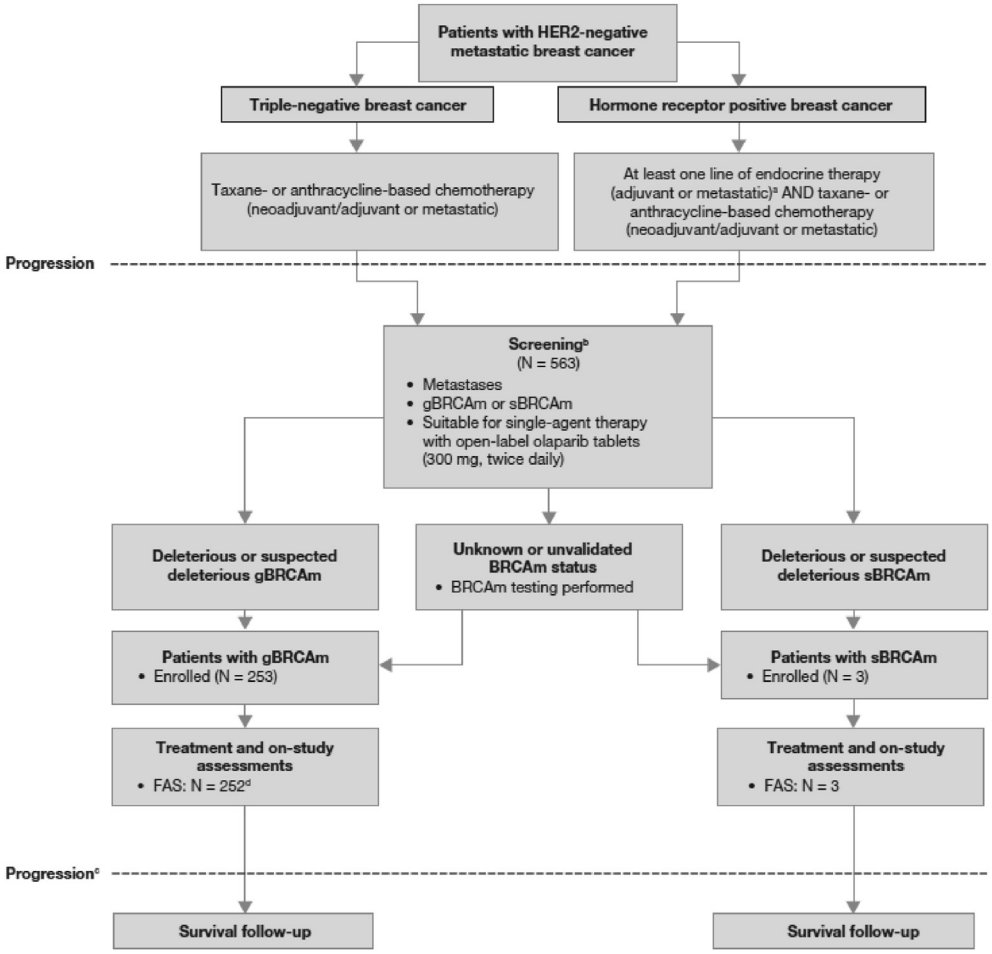

Fig. 1. Study flow chart. BRCAm, BRCA mutation; FAS, full analysis set; gBRCAm, germline BRCA mutation; HER2, human epidermal growth factor receptor 2; sBRCAm, somatic BRCA mutation. [a]Patients with hormone receptor–positive breast cancer had to have received and progressed with at least one line of endocrine therapy in either a neoadjuvant/adjuvant or a metastatic setting or, at the point of trial entry, have been considered unsuitable for endocrine therapy. [b]Reasons for screening failure were lack of documented *BRCA1* or *BRCA2* mutation, 251 (81.8%); treatment with systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks before study treatment, 15 (4.9%); lack of histologically or cytologically confirmed HER2-negative metastatic breast cancer, 8 (2.6%); abnormal organ and bone marrow function measured within 14 days before study treatment, 7 (2.3%); other, n = 27 (8.8%). Criteria were not mutually exclusive. [c]Patients who discontinued olaparib treatment in the absence of progression were followed up for progression. [d]One patient experienced progression before receiving olaparib and was excluded from the FAS.

neoadjuvant/adjuvant or metastatic disease regardless of the time of last administration. HR-positive status (i.e. oestrogen and/or progesterone receptor positive; immunohistochemistry nuclear staining $\geq$1%) was determined from primary tumour or metastatic sampling. Patients with HR-positive breast cancer had to have previously completed at least one line of endocrine therapy in either an adjuvant or metastatic setting or been considered inappropriate for further endocrine treatment at that time. Patients who had received systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks before study treatment could not enter the study. Exclusion criteria also included previous treatment with a PARP inhibitor and presence of symptomatic uncontrolled brain metastases; patients with adequately treated stable brain metastases were eligible.

2.3. BRCA mutation testing

Patients with a known deleterious or suspected deleterious gBRCAm at screening did not require further re-testing. Patients with an unknown BRCA mutation status but meeting certain eligibility criteria provided a blood sample (mandatory) and/or tumour sample (optional); tumour testing was performed centrally using BRACAnalysis® (Myriad Genetics), followed by confirmatory gBRCAm testing.

2.4. Treatment

Patients received olaparib tablets (300 mg, twice daily) until disease progression, unacceptable toxicity, or other protocol-specified discontinuation criteria were met [20]. Dose interruptions and reductions were permitted in

patients experiencing toxicities related to olaparib treatment; dose re-escalations were permitted at the discretion of the investigator after resolution. After disease progression, continued treatment with olaparib was at the discretion of the investigator. Patients who discontinued study treatment were followed up for progression (if treatment was discontinued in the absence of progression), subsequent therapies, time to second progression, and overall survival.

2.5. Endpoints and assessments

The primary endpoint was investigator-assessed PFS in the gBRCAm cohort, defined as the time from first dose of olaparib to progression or death from any cause (in the absence of progression). Progression could be radiological (e.g. Response Evaluation Criteria in Solid Tumours [RECIST]), symptomatic, or clear progression of non-measurable disease, as long as progression could be documented. Tumour assessments were conducted in accordance with local practice at each patient visit until documented disease progression, and then in accordance with local practice and standard of care.

Secondary endpoints evaluated in the gBRCAm cohort included clinical response rate (CRR; proportion of patients with at least one visit in which the investigator assessed the patient as responding [radiological or symptomatic]), duration of clinical response (DoCR; time from when the investigator first assessed the patient as responding to the date of progression or death from any cause, in the absence of progression), time to first subsequent treatment or death (TFST), time to study treatment discontinuation or death (TDT), and safety outcomes.

Adverse events (AEs) were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and coded to preferred terms using Medical Dictionary for Regulatory Activities version 22.1. Treatment-emergent AEs (TEAEs) were defined as an onset date or a pre-existing AE worsening after the first dose of study treatment through to 30 days after the last dose of study treatment. Prespecified AEs of special interest were myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML), new primary malignancy (other than MDS/AML), and pneumonitis. MDS/AML or new primary malignancy occurring after the 30-day follow-up period was to be reported for pharmacovigilance and characterization.

2.6. Statistical analysis

The interim analysis was planned after reaching approximately 160 PFS events in the gBRCAm cohort. If recruitment occurred over 12 months, it was estimated that 160 PFS events would have occurred by 19 months after enrolment of the first patient with a gBRCAm (assuming exponentially distributed PFS data with a median of 7 months and enrolment of 25% of patients after 6 months). Recruitment of 250 patients with a gBRCAm would provide a sufficiently precise estimate of median PFS; if median PFS was 7 months [14] and analysed after 160 PFS events, the 95% confidence interval (CI) for the median was predicted to extend from 6.0 to 8.2 months (based on the formula of Collett) [21]. An updated PFS analysis and assessment of overall survival will be performed after reaching approximately 160 deaths in the gBRCAm cohort.

For PFS, patients who had not progressed or died at the time of analysis were censored at the time of the latest date of assessment from their last evaluable progression assessment. Survival curves were generated using the Kaplan–Meier method, from which the median PFS and its associated 95% CI were calculated using the Brookmeyer–Crowley method. PFS was also assessed for the following predefined subgroups: HR status (HR-positive versus TNBC), line of therapy (first line versus second line or later), and previous exposure to platinum-based chemotherapy (yes versus no). PFS was also assessed in the subset of patients with HR-positive mBC by previous exposure to a CDK4/6 inhibitor (yes versus no; *post hoc*). No formal statistical comparisons were performed between subgroups.

Other time-to-event endpoints (DoCR, TFST and TDT) were also analysed using the Kaplan–Meier method. A 95% CI for CRR was calculated using the Clopper–Pearson exact method for binomial proportions.

Efficacy and safety analyses were performed in all patients who received at least one dose of olaparib, defined as the full analysis set.

3. Results

3.1. Patient disposition

From January 2018 to December 2018, 563 patients were screened at 125 sites in 15 countries (Fig. 1, Supplementary Table 1). A total of 307 patients did not fulfil all eligibility criteria and were not included in the study. Lack of a documented *BRCA1* or *BRCA2* mutation was the most common reason for screening failure (n = 251 patients [81.8%]). Of the 256 patients enrolled (gBRCAm, N = 253; sBRCAm, N = 3), one patient in the gBRCAm cohort experienced disease progression before receiving olaparib and was excluded from the full analysis set. At data cutoff (23 September 2019), 81 patients (32.1%) in the gBRCAm cohort remained on study treatment, and 171 (67.9%) had discontinued.

3.2. BRCA mutation status and baseline characteristics

Of the patients in the gBRCAm full analysis set (N = 252), 216 patients (85.7%) had a known deleterious or suspected deleterious gBRCAm at screening. Of the 36 patients

(14.3%) who had an unknown BRCAm status, a gBRCAm was confirmed by central testing (15 patients) or by local testing (21 patients).

Baseline characteristics of patients in the gBRCAm cohort are shown in Table 1. The median age was 45.0 years (range, 22–75 years), and most patients (n = 185; 73.4%) had an Eastern Cooperative Oncology Group-Performance Status score of 0 (normal activity). Similar proportions of patients had HR-positive breast cancer (n = 131; 52.0%) versus TNBC (n = 121; 48.0%). Approximately half of patients (n = 137; 54.4%) received olaparib as their first therapy in the metastatic setting (first-line), with prior chemotherapy in the neoadjuvant/adjuvant setting only. Most patients had previously received both taxane and anthracycline-based chemotherapy (n = 188; 74.6%). Of the 81 patients (32.1%) who had received prior platinum-based chemotherapy, 34 (42.0%) and 47 patients (58.0%) had received treatment in the early (neoadjuvant/adjuvant) or metastatic disease settings, respectively.

3.3. Effectiveness

At data cutoff, there were 166 PFS events in the gBRCAm cohort (65.9% maturity; Table 2), 6.8 months after the last enrolled gBRCAm patient received their first dose of olaparib. Of the 86 patients (34.1%) censored, 79 (31.3%) remained progression-free, and the remaining 7 patients (2.8%) were censored for other reasons. The investigator-assessed median PFS was 8.11 months (95% CI, 6.93–8.67) (Fig. 2). Descriptive Kaplan–Meier plots of PFS by HR status, line of therapy and previous platinum-based chemotherapy are shown in Fig. 3. In patients who had received previous platinum-based chemotherapy (n = 81), the median PFS was 6.70 months (95% CI, 5.22–8.38, n = 34) and 5.19 months (95% CI, 3.15–8.18, n = 47) in those who had received treatment in the early (neoadjuvant/adjuvant) and metastatic disease settings, respectively. In patients with HR-positive mBC (n = 131), the median PFS was 7.95 months (95% CI, 6.21–14.46, n = 25) and 8.34 months (95% CI, 7.49–10.15, n = 106) in those with and without prior exposure to a CDK4/6 inhibitor, respectively.

Almost half of the evaluable patients (n = 119; 48.6%) had a clinical response as per the investigator assessment (Table 2). In these patients, the median DoCR was 6.6 months (interquartile range, 4.2–10.8). The median TFST and TDT were 9.66 months (95% CI, 8.67–11.14) and 6.90 months (95% CI, 6.21–7.79), respectively (Table 2).

3.4. Safety

The median total treatment duration was 7.90 months (range, 0.2 to 20.0). Most patients (n = 240; 95.2%) had a TEAE. Most TEAEs were CTCAE grade 1 or 2 in severity, with a maximum reported grade of grade 1 in 69 patients (27.4%); grade 2 in 107 patients (42.5%); grade 3 in 61 patients (24.2%) and grade 4 in 3 patients (1.2%). The most common TEAEs of any grade (occurring in >20% of patients) were nausea, anaemia, asthenia, vomiting and fatigue (Fig. 4). Grade 2 or higher anaemia TEAEs were reported in 71 patients (28.2%); of these, 40 (56.3%) received a blood transfusion. None of the patients with a grade 1 anaemia TEAE (n = 26) required a blood transfusion.

Grade 3 or higher TEAEs were reported in 64 patients (25.4%). Grade 3 or higher TEAEs occurring in at least 2% of patients were anaemia (n = 33; 13.1%) and neutropenia (n = 11; 4.4%). Serious TEAEs of any

Table 1
Baseline characteristics (full analysis set).

Characteristic	gBRCAm[a] (N = 252)
Age, years, median (min, max)	45.0 (22, 75)
Female	248 (98.4)
Race	
White	176 (69.8)
Asian	21 (8.3)
Black or African American	2 (0.8)
ECOG performance status	
0	185 (73.4)
1	62 (24.6)
2	2 (0.8)
Missing	3 (1.2)
Hormone receptor status[b]	
HR-positive breast cancer	131 (52.0)
TNBC	121 (48.0)
Line of olaparib therapy[c]	
First line	137 (54.4)
Second line or later	115 (45.6)
Previous taxane-based chemotherapy	223 (88.5)
Previous anthracycline-based chemotherapy	217 (86.1)
Previous platinum-based chemotherapy	81 (32.1)
Previous CDK4/6 inhibitor therapy[d]	25 (19.1)
Menopausal status	
Premenopausal/perimenopausal	72 (28.6)
Postmenopausal	176 (69.8)
Not applicable	4 (1.6)
De novo metastatic breast cancer	
Yes	43 (17.1)
No	191 (75.8)
Unknown	18 (7.1)

Data are presented as n (%) unless otherwise stated.
CDK4/6, cyclin-dependent kinase 4 and 6; ECOG, Eastern Cooperative Oncology Group; gBRCAm, germline BRCA mutation; HR, hormone receptor; TNBC, triple-negative breast cancer.
[a] The LUCY trial also enrolled three patients with a somatic BRCA mutation (data not presented).
[b] HR-positive includes positive oestrogen receptor expression, positive progesterone receptor expression and both. TNBC is HER2-negative, oestrogen receptor negative and progesterone receptor negative.
[c] First line = no prior chemotherapy for advanced/metastatic disease, but received in the neoadjuvant/adjuvant setting; second line or later = received at least one prior chemotherapy in the metastatic setting (not including prior chemotherapy in the neoadjuvant/adjuvant setting).
[d] Based on patients with HR-positive breast cancer (N = 131).

Table 2
Primary and secondary endpoints (full analysis set).

Outcome	gBRCAm (N = 252)
Investigator-assessed PFS[a]	
Events	166 (65.9)
Progression	159 (63.1)
Death in the absence of progression	7 (2.8)
Censored patients[b]	86 (34.1)
Time to event, months, median (95% CI)	8.11 (6.93, 8.67)
Patients who were progression free at 6 months, % (95% CI)	63.8 (57.4, 69.5)
Investigator-assessed CRR, % (95% CI)[c]	48.6 (42.2, 55.0)
DoCR from onset of response	
Responders, n	119
Responders who subsequently progressed or died	69 (58.0)
DoCR, months, median (Q1–Q3)	6.6 (4.2–10.8)
TFST	
Events	135 (53.6)
Censored patients	117 (46.4)
Time to event, months, median (95% CI)	9.66 (8.67, 11.14)
Patients with no event at 6 months, % (95% CI)	73.8 (67.8, 78.9)
TDT	
Events	171 (67.9)
Censored patients	81 (32.1)
Time to event, months, median (95% CI)	6.90 (6.21, 7.79)
Patients with no event at 6 months, % (95% CI)	57.9 (51.1, 64.1)

Data are presented as n (%) unless otherwise stated.
CI, confidence interval; CRR, clinical response rate; DoCR, duration of clinical response; gBRCAm, germline BRCA mutation; PFS, progression-free survival; TDT, time to study treatment discontinuation or death; TFST, time to first subsequent treatment or death.

[a] Investigator-assessed disease progression could be radiological (e.g. RECIST) or symptomatic, or clear progression of non-measurable disease, as long as progression could be documented.

[b] Reasons for censoring: progression-free at time of analysis (n = 79; 31.3%); withdrawn consent (n = 3; 1.2%); terminated study for other reasons (n = 3; 1.2%); lost to follow-up (n = 1; 0.4%).

[c] N = 245; 7 patients were not included due to a missing post-baseline tumour assessment.

grade occurred in 28 patients (11.1%). The serious TEAEs occurring in more than one patient were anaemia (n = 7; 2.8%), febrile neutropenia (n = 2; 0.8%) and vomiting (n = 2; 0.8%). No TEAEs resulted in death. Eleven patients (4.4%) discontinued treatment due to a TEAE.

Seven patients (2.8%) had AEs of special interest: bladder cancer *in situ* (stage 0; n = 1), neoplasm of the appendix (n = 1), pancreatic carcinoma (n = 1) and pneumonitis (n = 4). All pneumonitis AEs were grade 2 or less; one case led to discontinuation of olaparib. No cases of MDS or AML were reported.

4. Discussion

Findings from the phase IIIb LUCY trial support the clinical effectiveness of olaparib in patients with gBRCAm, HER2-negative metastatic breast cancer in a setting that closely reflects real-life clinical practice. Overall, olaparib was well tolerated, providing a clinically effective and targeted treatment option for these patients with high unmet need.

The clinical efficacy of olaparib was consistent with previous findings from the phase III OlympiAD trial [14]. At data cutoff, it was encouraging to see that the median PFS in the LUCY trial (8.1 months) was similar to that for the olaparib arm in OlympiAD (7.0 months) [14]. In LUCY, a consistent benefit of olaparib was observed irrespective of HR status, line of therapy or previous platinum-based chemotherapy. In the subset of patients with HR-positive mBC, PFS was similar in those with or without previous exposure to a CDK4/6 inhibitor. However, no formal statistical comparisons were performed between subgroups in this single-arm study.

The pragmatic LUCY trial was designed to more closely reflect clinical practice compared with the OlympiAD trial [14,17,22]. The clinical effectiveness of olaparib was evaluated across a wide range of outcomes in a patient population highly relevant to that encountered in clinical practice. Specifically, LUCY enrolled patients with gBRCAm, HR-positive breast cancer or TNBC, two patient populations with high unmet needs. The eligibility criteria were limited but ensured that the patient population was broadly in line with the label criteria [20]. Overall, a higher proportion of patients received olaparib in the first-line metastatic disease setting in LUCY (~55%) than OlympiAD (~30%) [23]. Most patients had previously received treatment with both a taxane- and an anthracycline-based chemotherapy before enrolment, even though this was not mandated by the inclusion criteria. This was unsurprising given that BRCA-related disease is generally

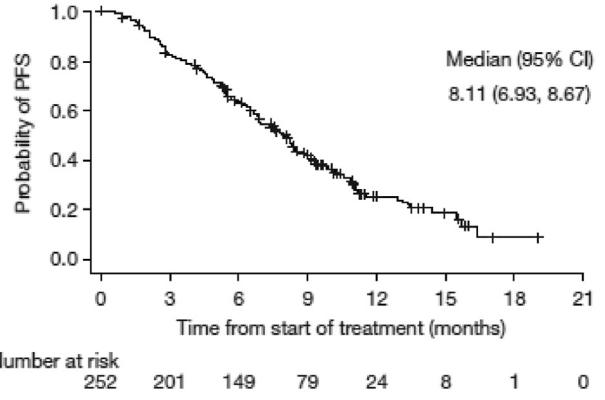

Fig. 2. Kaplan–Meier analysis of PFS (full analysis set). CI, confidence interval; PFS, progression-free survival.

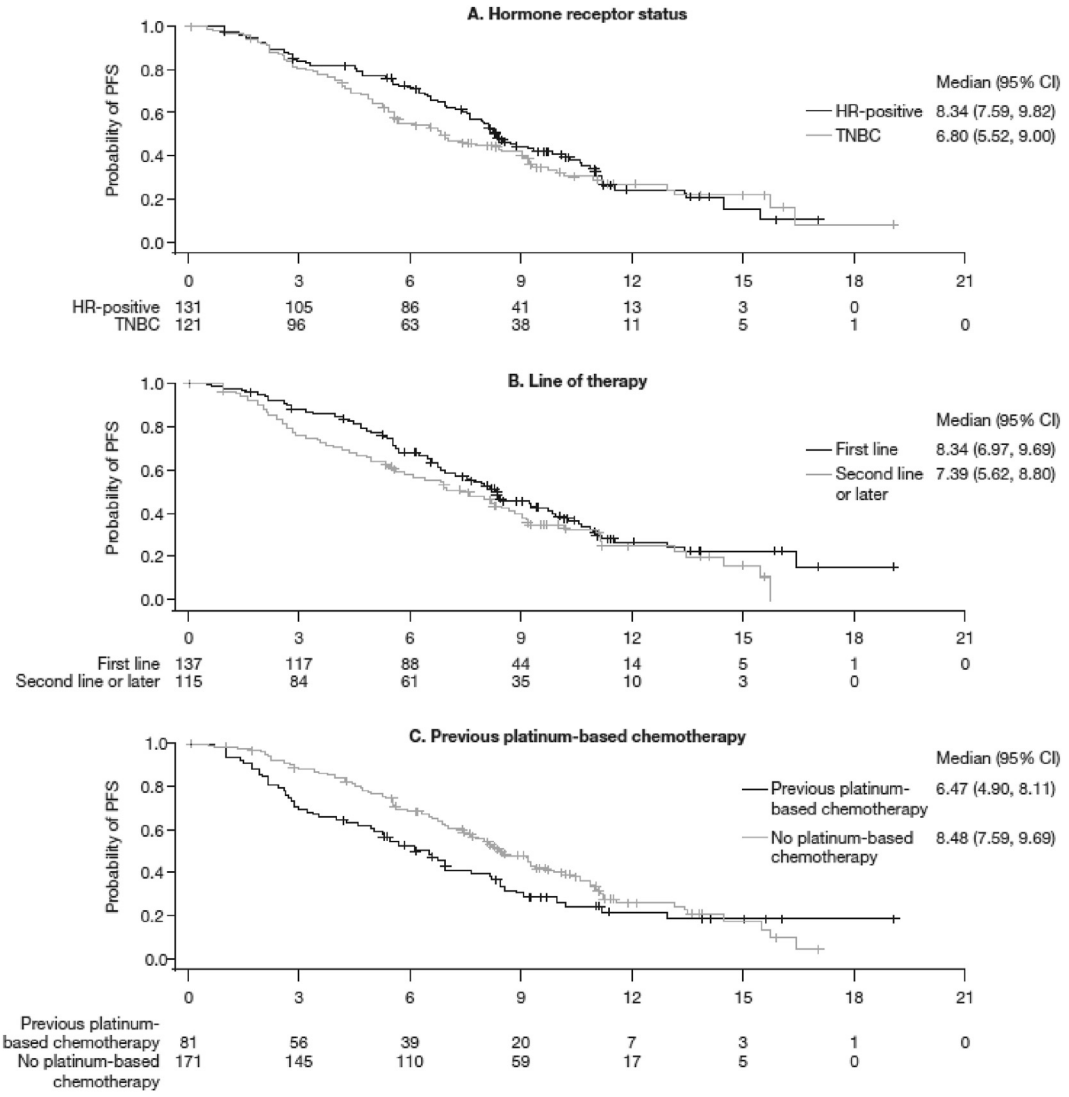

Fig. 3. Descriptive analysis of PFS by subgroups (full analysis set). CI, confidence interval; HR, hormone receptor; PFS, progression-free survival; TNBC, triple-negative breast cancer.

aggressive, such that most patients receive both treatments in the early disease setting. In OlympiAD, previous neoadjuvant/adjuvant treatment with platinum-based chemotherapy was allowed if at least 12 months had elapsed since the last dose. Previous treatment with platinum-based chemotherapy for metastatic disease was allowed if disease progression had not occurred during treatment [14]. In contrast, the LUCY trial permitted prior platinum-based chemotherapy in early or advanced disease, regardless of the time of last administration. Further studies are required to assess the relative efficacy of olaparib according to these prior treatment options.

There were also cross-trial differences in tumour assessments between the LUCY and OlympiAD trial. In OlympiAD, tumour response evaluation was based on RECIST criteria and assessed by blinded independent central review (BICR) in patients who had measurable disease as their primary assessment. In LUCY, evaluation of tumour response was pragmatic and based on investigator assessment. Progression could be radiological (e.g. RECIST) or symptomatic, or clear progression of non-measurable disease, as long as progression could be documented. The frequency of patient follow-up for tumour evaluation was not mandated and was carried out per local practice and standard of care. Overall, the investigator-assessed CRR in LUCY (48.6%) was more comparable to the investigator-assessed objective response rate (49.3%) in OlympiAD than to the BICR objective response rate (59.9%) [14].

Olaparib had a well-tolerated and manageable safety profile consistent with previous findings [14,23,24]. The low incidence of CTCAE grade 3 or higher TEAEs (25.4%) was consistent with that seen for the olaparib arm in OlympiAD (36.6%) [14]. The median total treatment duration (7.9 months) at data cutoff was

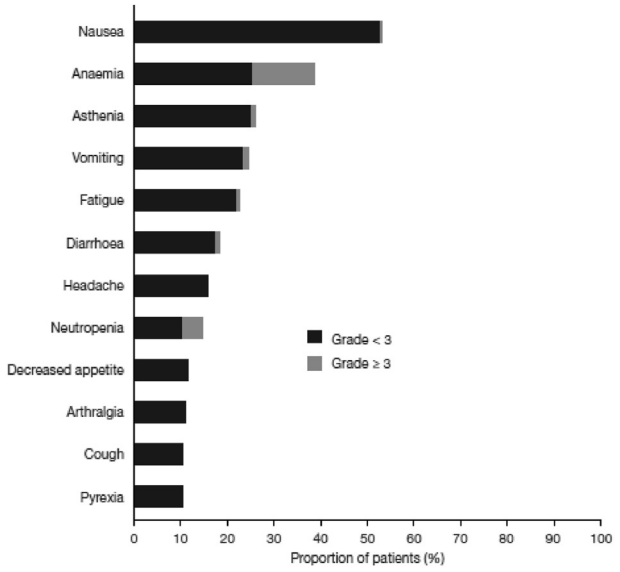

Fig. 4. Treatment-emergent adverse events occurring in >10% of patients (full analysis set).

similar to that observed at the time of the OlympiAD reporting (8.2 months), and the incidence of discontinuations due to TEAEs was low in LUCY (4.4%) and OlympiAD (4.9%). No new safety signals were observed, and there were no cases of MDS or AML.

Overall, the findings from the phase IIIb LUCY trial support the clinical effectiveness of olaparib in patients with gBRCAm, HER2-negative metastatic breast cancer and may help to guide and inform clinical practice. The planned final analysis of the LUCY trial will include an assessment of overall survival, in addition to updates for all other endpoints.

Authors' contributions

K. Gelmon, S. Delaloge and S. McCutcheon contributed to conceptualization. K. Gelmon, S. McCutcheon and G. Walker framed the study methodology. K. Gelmon, F. J. Couch, S. Delaloge, G. Walker and J. O'Shaughnessy carried out investigation. K. Gelmon, P. A. Fasching, F. J. Couch, J. Balmaña and J. O'Shaughnessy provided resources related contributions. K. Gelmon performed data curation. All the authors contributed to writing the original draft and reviewing and editing the same. P. A. Fasching, F. J. Couch, J. Balmaña, J. Bennett and S. McCutcheon contributed to validation. P. A. Fasching, J. Bennett and G Walker carried out the formal analysis. I. Labidi-Galy contributed to TBC. J. Bennett and S. McCutcheon contributed to visualization. S. McCutcheon and G. Walker contributed to supervision and project administration. S. McCutcheon contributed to funding acquisition.

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Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests. S. McCutcheon is an employee and stockholder of AstraZeneca LP. J. Bennett and G. Walker are contractors for AstraZeneca LP. The following authors have received compensation for serving as consultants or speakers, or they or the institutions they work for have received research support, from the companies or organizations indicated: K. A. Gelmon (AstraZeneca, Bristol-Myers Squibb, Genentech, Genomic Health, Janssen Oncology, Lilly, Merck, Mylan, NanoString Technologies, Novartis, Pfizer, and Roche); P. A. Fasching (Amgen, AstraZeneca, BionTech AG, Celgene, Cepheid, Daiichi Sankyo, Eisai, Hexal, Lilly, Macrogenics, Merck Sharp & Dohme, Myelo Therapeutics GmbH, Novartis, Pfizer, Puma Biotechnology, Roche, and Seattle Genetics); F. J. Couch (Ambry Genetics, AstraZeneca, GRAIL, and Qiagen); J. Balmaña (AstraZeneca, PharmaMar, and Pfizer); S. Delaloge (AstraZeneca, Lilly, Novartis, Pfizer, Puma Biotechnology, Roche/Genentech, and Sanofi); I. Labidi-Galy (AstraZeneca, Bristol-Myers Squibb, MSD Brazil, Novimmune, and PharmaMar); J. O'Shaughnessy (Abbvie, Agendia, Amgen, AstraZeneca, Bristol-Myers Squibb, Celgene, Daiichi Sankyo, Eisai, Genentech, Genomic Health, GRAIL, HERON, Immunomedics, Ipsen, Jounce Therapeutics, Lilly, Merck Sharp & Dohme, Myriad Pharmaceuticals, Novartis, Ondonate, Pfizer, Puma Biotechnology, Roche, Samsung, Sanofi, Seattle Genetics, and Syndax). The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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Appendix

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Appendix A. Supplementary data

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