LUCY - Lynparza Breast Cancer Real-World Utility, Clinical Effectiveness and Safety Study

A Phase IIIb, Single-arm, Open-label Multicentre Study of Olaparib Monotherapy in the Treatment of HER2-ve Metastatic Breast Cancer Patients with Germline or Somatic BRCA1/2 Mutations

ClinicalTrials.gov Identifier: NCT03286842

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2. SYNOPSIS

Study Centres

This is an international multicentre study conducted at 125 sites in 15 countries (comprising 2 sites in the United States and 123 sites in the rest of world).

Publications

Gelmon KA, Fasching PA, Couch F, Gelpi JB, Delaloge S, Labidi-Galy I, et al. Real-world clinical effectiveness and safety of olaparib monotherapy in HER2-negative gBRCA-mutated metastatic breast cancer: Phase IIIb LUCY interim analysis. J Clin Oncol. 2020;38(15_suppl):1087-.

Gelmon KA, Fasching PA, Couch FJ, Balmana J, Delaloge S, Labidi-Galy I, et al. 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. 2021;152:68-77.

Objectives and Criteria for Evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the clinical effectiveness of olaparib treatment in HER2-ve metastatic breast cancer patients in a real-world setting through assessment of progression-free survival in germline *BRCA* mutated patients	• Progression-free survival, defined as the time from first dose of olaparib to the date of progression as determined by the Investigator (physician-defined progression *) or death from any cause (in the absence of progression)
Secondary	
• To determine the clinical effectiveness of olaparib treatment in HER2-ve metastatic breast cancer patients in a real-world setting by assessment of overall survival in germline *BRCA* mutated patients	• Overall survival, defined as the time from first dose of olaparib to the date of death from any cause
• To determine the clinical effectiveness of olaparib treatment in HER2-ve metastatic breast cancer patients in a real-world setting by assessment of time to use of subsequent therapies, second progression, and study treatment discontinuation in germline *BRCA* mutated patients	• Time to first subsequent treatment or death, defined as the time from first dose of olaparib to first subsequent treatment commencement or death if this occurs before commencement of first subsequent treatment • Time to second subsequent treatment or death, defined as the time from first dose of olaparib to second subsequent treatment commencement or death if this occurs before commencement of second subsequent treatment • Time to study treatment discontinuation or death, defined as the time from first dose of olaparib to study treatment discontinuation or death if this occurs before discontinuation of study treatment

Objectives	Endpoints
	• Time to second progression or death, defined as the time from first dose of olaparib to the earliest progression event subsequent to that used for the primary variable PFS or death from any cause
• To determine the clinical effectiveness of olaparib treatment in HER2-ve metastatic breast cancer patients in a real-world setting by assessment of clinical response rate and duration of clinical response in germline *BRCA* mutated patients	• Clinical response rate, defined as the proportion of patients assessed by the Investigator as responding (physician-defined clinical response, radiological [eg, RECIST] or symptomatic) • Duration of clinical response, defined as the time from the date the Investigator first assessed the patient as responding to the date the Investigator assessed the patient as progressing or the date of death from any cause (in the absence of progression)
Safety	
• To evaluate the safety and tolerability of olaparib treatment in HER2-ve metastatic breast cancer patients in a real-word setting	• Adverse events/serious adverse events • Collection of clinical chemistry/haematology parameters
Exploratory	
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]

* Physician-defined progression can be radiological (eg, RECIST) progression, symptomatic progression, or clear progression of non-measurable disease, as long as progression can be documented.

BRCA = breast cancer susceptibility gene; CT = computed tomography; HER2-ve = human epidermal growth factor receptor 2 negative; MRI = magnetic resonance imaging; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours.

Study Design

This was a Phase IIIb, single-arm, open-label, multicentre study to assess the clinical effectiveness in a real-world setting of single-agent olaparib treatment in HER2-ve metastatic breast cancer patients with germline or somatic *BRCA1/2* mutations. The target population was patients with HER2-ve metastatic breast cancer who have previously progressed after treatment with anthracycline- or taxane-based chemotherapy. All patients were to have a confirmed germline or somatic mutation status for *BRCA1*, *BRCA2*.

Target Population and Sample Size

Patients were eligible if they had either triple-negative breast cancer or oestrogen-receptor or progesterone-receptor positive HER2-ve breast cancer. All patients enrolled (enrolled patients were patients who fulfilled eligibility criteria for receiving study treatment) in the study were selected based on the following 3 principles:

- Genetic selection: All patients were to have a confirmed germline or somatic mutation status for *BRCA1*, *BRCA2.* If the patient had a known positive *gBRCAm*, no retesting was needed. No blood or tumour tissue sample was needed.
  - If the patient had a known positive *sBRCAm*:
    - If the *sBRCAm* testing was done by a validated method (eg, results from a CLIA-certified laboratory or CE-IVD device), no retesting is needed.
    - If *sBRCAm* testing was done in an unaccredited laboratory, then blood sample and tumour sample (if consented) would have been sent to Myriad for testing.
  - In the absence of a known *BRCA* mutation, blood (mandatory) and tumour sample (optional) would have been collected:
    - Where a tumour sample was available (and consented to), this sample should have been sent to Myriad for *tBRCAm* testing first. If a tumour sample could not be obtained and shipped within 10 days, the Investigator may have proceeded with sending the blood sample for *gBRCAm* testing, to mitigate the risk of delaying trial entry for a potentially positive *gBRCAm* patient. In this case, *gBRCAm* test may have been performed locally.
    - Positive *tBRCAm* results would have enable trial entry and dosing for that patient. This would have been followed by a confirmatory *gBRCAm* test performed by Myriad. To ensure a high quality *gBRCAm* sample is sent for testing, this sample should have been taken once a positive *tBRCAm* result was obtained, ie, Visit 1b or Visit 2. Test result must have been known prior to the next scheduled tumour assessment for *sBRCAm* patients (Visit 3). As long as a patient has positive *tBRCAm* result they may receive their first dose of olaparib without delay even as they were awaiting confirmatory test results.

  - Documented germline or somatic mutation in *BRCA1* or *BRCA2* that was predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function; see Section 3.1). Patients with *BRCA1* and/or *BRCA2* mutations that were considered to be non-detrimental (eg, "variants of uncertain clinical significance" or "variant of unknown significance" or "variant, favour polymorphism" or "benign polymorphism," etc.) could be reviewed by a diagnostics committee to determine whether or not the patient was eligible for the study.

- Treatment setting: All patients were to have metastatic breast cancer and had to have received treatment with anthracycline or taxane in either an adjuvant (could include neoadjuvant) or a metastatic setting. Patients were to have received no more than 2 prior cytotoxic chemotherapy regimens in the metastatic setting.
- Phenotypic tumour selection: Patients could have either triple-negative breast cancer (defined as oestrogen-receptor and progesterone-receptor negative [immunohistochemistry nuclear staining < 1%] and HER2-ve [immunohistochemistry 0, 1+ or 2+ and/or in situ hybridisation non-amplified with ratio less than 2.0]) or oestrogen-receptor/progesterone-receptor positive breast cancer, as long as they were HER2-ve. Patients with oestrogen-receptor and/or progesterone-receptor positive breast cancer were to have received and progressed on at least one line of endocrine therapy in either an adjuvant or a metastatic setting, including endocrine therapy in combination with a targeted agent such as a CDK4/6 or mTOR inhibitor. Patients were not considered suitable for further endocrine therapy.

Based on the prevalence of *BRCA1/2* mutations in HER2-ve breast cancer patients, it was estimated that up to 1400 patients would have required screening for enrolment into this study. In contrast to oestrogen-receptor and/or progesterone-receptor positive breast cancer patients, it was anticipated that a significant proportion of patients with triple-negative breast cancer would already have had their *BRCA1/2* status documented, especially in the USA. There was no requirement for a repeat germline *BRCA1/2* genetic diagnostic test amongst this population.

Recruitment of 250 patients with germline *BRCA* mutated tumours was expected to provide a sufficiently precise estimate of median PFS. If the median PFS observed was 7 months and analysed after 160 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). Similarly, at the OS follow up analysis, if the median OS observed was 19 months and data were analysed after 130 events, the 95% CI for the median was predicted to extend from 16.0 to 22.6 months.

Investigational Product: Dosage, Mode of Administration and Batch Numbers

Olaparib film-coated tablets were manufactured by AstraZeneca's Pharmaceutical Development, Research and Development Supply Chain and supplied to the Investigator.

Patients were administered olaparib orally, twice daily at 300 mg. Fourteen batches of olaparib film-coated tablets were used in the study. Individual batch numbers and further information are included in the CSR.

Duration of Treatment

Tumour assessments were conducted as per local practice at each patient visit, up to first disease progression. Tumour assessments were defined at a minimum as being clinical assessments as done in accordance with local practice, with documentation of the results on the eCRF; RECIST 1.1 was to be used to assess tumour progression in patients with somatic *BRCA* mutated tumours. After first progression, assessments had to be conducted in accordance with local practice and standard of care.

Patients could continue to receive study treatment until documented physician-defined disease progression (see note below) as assessed by the Investigator or unacceptable toxicity, or for as long as they did not meet any other discontinuation criteria. Note: Patients could continue to receive olaparib beyond Investigator-assessed progression as long as, in the Investigator's opinion, they were benefiting from treatment, and they did not meet any other discontinuation criteria.

Once patients had been discontinued from study treatment, patients were to be moved on to other treatment options or standard of care, as determined by their physician.

Statistical methods

Table S2 summarises the formal statistical analyses for this study, all of which are presented in this CSR.

Table S2 Formal Statistical Analyses

Endpoints Analysed	Notes
PFS	Primary analysis based on assessment of disease progression using the FAS
	Kaplan-Meier methodology: A graph depicting the survival curve and estimates of median progression-free survival and associated 95% CI
	CI for the median calculated using the Brookmeyer-Crowley method
OS	Kaplan-Meier methodology: A graph depicting the survival curve and estimates of median survival and associated 95% CI were provided together with OS rates at 6-monthly intervals

Table S2 Formal Statistical Analyses

Endpoints Analysed	Notes
DoCR, DoR, TFST, TSST, TDT and PFS2	Kaplan-Meier methodology: A graph depicting the survival curve and estimates of median time to event and associated 95% CI were provided together with rates at 6-monthly intervals
CRR and ORR	Exact binomial (Clopper-Pearson) 95% CIs
DCR at Week 24	Exact binomial (Clopper-Pearson) 95% CIs

CI = confidence interval; CRR = clinical response rate; DCR = disease control rate; DoCR = duration of clinical response; DoR = duration of response; FAS = full analysis set; *gBRCAm* = germline breast cancer susceptibility gene mutation; OS = overall survival; ORR = objective response rate; PFS = progression-free survival; PFS2 = time to second progression or death; TDT = time to study treatment discontinuation or death; TFST = time to first subsequent treatment or death; TSST = time to second subsequent treatment or death.

The primary endpoint was progression-free survival. The statistical analyses were performed at a minimum of 2 time points:

- The first when approximately 160 patients with germline *BRCA* mutated tumours have had a progression-free survival event (the DCO for this interim analysis was 23 September 2019) and the results were published [Gelmon et al 2020; Gelmon et al 2021]).
- The second after approximately 130 patients with germline *BRCA* mutated tumours have had a death event, at which point the progression-free survival analysis was updated. The DCO for this analysis was 1 September 2021 and this CSR reports all data collected up to this final DCO.

The somatic *BRCA* mutated tumour patient cohort was also to be assessed at these time points.

In this study, disease progression in patients with germline *BRCA* mutated tumours was based on Investigator assessment; RECIST 1.1 was to be used to determine disease progression in patients with somatic *BRCA* mutated tumours. Tumour assessments were conducted as per local practice at each patient visit, until first progression, then in accordance with local practice and standard of care. For patients with germline *BRCA* mutations, tumour assessments were defined at a minimum as being clinical assessments as done in accordance with local practice, with documentation of the results on the eCRF; for patients with somatic *BRCA* mutations, RECIST 1.1 was to be used to assess tumour progression with documentation of results on the eCRF. Progression-free survival was defined as the time (days) from the first dose of olaparib until the date of disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdrew from therapy or received another anti-cancer therapy prior to progression. The case report forms captured each time a patient was assessed for progression regardless of the outcome of the assessment. 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.

Progression-free survival was summarised using a Kaplan-Meier plot together with the median and its 95% CI and the estimated progression rates and 95% CIs at clinically important landmarks (such as 1 year), calculated using Kaplan-Meier methodology.

Data from the germline and somatic *BRCA* mutated tumour patient cohorts were presented separately and combined.

Study Population

A total of 563 patients were screened, of these 307 were screening failures, 256 patients were enrolled in the study, and 255 patients (252 patients in the *gBRCAm* cohort and 3 patients in the *sBRCAm* cohort) received at least one dose of study treatment. One patient enrolled in the *gBRCAm* did not receive study treatment.

At the final DCO date (01 September 2021), 80 (31.4%) patients were still ongoing in the study and 29 (11.4%) patients were still receiving study treatment. The majority of patients who discontinued study treatment did so because of disease progression (192 [75.3%] patients). Remaining reasons for discontinuation were AEs (15 [5.9%] patients) and patient's decision (7 [2.7%] patients). In the of majority cases, termination of study participation was due to death (142 [55.7%] patients) and withdrawal by the patient (28 [11.0%] patients).

In the *sBRCAm* cohort, all 3 (100%) patients discontinued study treatment, and 1 (33.3%) patient was still ongoing in survival follow-up in the study.

Demographic and Key Baseline Characteristics

Of the 255 patients included in the FAS, 4 (1.6%) patients were male. The mean (SD) age was 46.3 (11.34) years, and the majority of the patients were < 65 years (232 [91.0%] patients). The majority of the patients were White (177 [69.4%] patients), with the remainder predominantly Asian (23 [9.0%] patients). Only 2 (0.8%) patients were Black or African American. The race of 52 (20.4%) patients were not recorded.

Baseline Patient and Disease Characteristics

The key disease characteristics at baseline were as follows:

- The majority of the patients (185 [72.5%] patients), had an ECOG performance status of 0, 65 (25.5%) patients had an ECOG performance status 1, and the remaining 2 (0.8%) patients had an ECOG performance status 2. For 3 (1.2%) patients the ECOG performance status was not recorded.
- The cancer stage (at the time of initial diagnosis) according to American Joint Committee on Cancer (AJCC) was predominantly Stage II (II: 18 [7.1%] patients; IIA: 45 [17.6%] patients; and IIB: 35 [13.7%] patients). The remaining patients were Stage I (37 [14.5%] patients), Stage III (68 [26.7%] patients), and Stage IV (43 [16.9%] patients). The cancer stage (at the time of initial diagnosis) was missing for 9 (3.5%) patients.

- The *BRCA* status was *BRCA1* for 138 (54.1%) patients, *BRCA2* for 109 (42.7%) patients, both *BRCA1* and *BRCA2* for 5 (2.0%) patients and 3 (1.2%) patients had a missing status.
- The tumour grade was Grade 3 (poorly differentiated) for the majority of patients, 131 (51.4%) patients.
- The histology type was predominantly invasive ductal, 148 (58.0%) patients.
- The median (range) time from original diagnosis to enrolment was 46.3 (4 to 500) months.
- The median (range) time from first diagnosis of metastatic disease to enrolment was 9.4 (0 to 279) months.

Summary of Efficacy Results

The efficacy endpoints are provided in Table S1. Based on Investigator tumour assessment in a real-world setting, there were 208 PFS events reported in 255 HER2-ve metastatic breast cancer patients (81.6% maturity). Median PFS was 8.18 months with a 95% CI from 6.97 to 9.17 months on olaparib treatment. The estimated PFS rate at 24 months, was 18.6 % with a 95% CI from 14.0% to 23.8%. The estimated PFS rate at 30 months, was 15.0% with a 95% CI from 10.8% to 19.9%.

- There were 142 deaths events (n = 255, 55.7% maturity). The median overall survival (OS) was 24.94 months with a 95% CI from 21.09 to 27.93 months. The estimated OS rate at 24 months was 51.3% with a 95% CI of 44.6% to 57.7%. The estimated OS rate at 30 months was 41.7% with a 95% CI of 35.2% to 48.1%.
- There were 196 first subsequent treatment or death (FST) events (n = 255, 76.9% maturity). The median time to first subsequent treatment or death (TFST) was 9.33 months with a 95% CI from 8.64 to 10.64 months in patients. At 24 months (95% CI) 23.3% (18.1, 29.0) patients overall did not experience a TFST event. At 30 months (95% CI) 19.1% (14.3, 24.5) patients overall did not experience a TFST event.
- There were 173 second subsequent treatment or death (SST) events (n = 255, 67.8% maturity). The median time to second subsequent treatment or death (TSST) was 14.65 months with a 95% CI from 13.50 to 17.12 months. At 24 months (95% CI) 32.8% (26.7, 39.1) patients overall did not experience a TSST event. At 30 months (95% CI) 26.2% (20.6, 32.2) patients overall did not experience a TSST event.
- There were 226 study treatment discontinuation or death (TD) events (n = 255, 88.6% maturity). The median time to study treatment discontinuation or death (TDT) was 7.98 months with a 95% CI from 6.90 to 8.51 months. At 24 months (95% CI) 17.6% (13.3, 22.6) patients overall did not experience a TDT event. At 30 months (95% CI) 14.5% (10.5, 19.1) patients overall did not experience a TDT event.
- There were 170 PFS2 events (n = 255, 66.7% maturity). The median PFS2 was 14.49 months with a 95% CI from 13.17 to 16.62 months. At 24 months (95% CI) 32.6% (26.4, 38.9) patients overall did not experience a PFS2 event.

- A total of 125 of the 252 *gBRCAm* patients showed a clinical response to olaparib treatment resulting in a clinical response rate (CRR) of 49.6% with a 95% CI of 43.3% to 55.9%.
- There were 99 of the 125 responders (79.2%) in the *gBRCAm* cohort who subsequently progressed or died and the median duration of clinical response (DoCR) was 8.0 months.
- Treatment outcomes were generally consistent across the key subgroups (line of therapy, hormone receptor status etc.).

Summary of Safety Results

The majority of patients (246 [96.5%] patients) experienced one or more AEs during the study. Around a quarter of the patients (71 [27.8%] patients) had AEs of Grade 3 or higher. A total of 33 (12.9%) patients experienced SAEs.

A total of 16 (6.3%) patients experienced an AE leading to treatment discontinuation (irrespective of relationship), 111 (43.5%) patients experienced an AE leading to any dose modification (irrespective of relationship), (dose reduction in 49 [19.2%] patients and dose interruption in 99 [38.8%] patients).

There were no deaths associated with AEs reported during study treatment or during the 30-day safety follow-up period.

At the SOC level, AEs most frequently reported (in > 40% of patients) were as follows: gastrointestinal disorders (187 [73.3%] patients), general disorders and administration site conditions (155 [60.8%] patients), and blood and lymphatic system disorders (120 [47.1%] patients).

The most common AEs occurring in ≥ 20% of patients receiving olaparib treatment were nausea (141 [55.3%] patients), anaemia (100 [39.2%] patients), asthenia (71 [27.8%] patients), vomiting (68 [26.7%] patients), fatigue (59 [23.1%] patients) and diarrhoea (53 [20.8%] patients), which were generally mild or moderate in severity.

The olaparib safety and tolerability profile in this study was consistent with previous studies of olaparib.

Conclusions

- Based on Investigator tumour assessment in a real-world setting, treatment with olaparib in 255 breast cancer patients provided a median PFS of 8.18 months after 208 events (81.6% maturity) with a 95% CI from 6.97 to 9.17 months:
  - The estimated PFS rate at 24 months, was 18.6 % with a 95% CI from 14.0% to 23.8%.
  - The estimated PFS rate at 30 months, was 15.0% with a 95% CI from 10.8% to 19.9%.
- In this study the median OS in 255 breast cancer patients was 24.94 months after 142 deaths events (55.7% maturity) with a 95% CI from 21.09 to 27.93 months.
- Treatment outcomes were generally consistent across the subgroups including lines of treatment and hormone receptor status.
- The olaparib safety and tolerability profile in this study was consistent with that observed in previous studies of olaparib.