Clinical Study Report Synopsis	
Drug Substance	Olaparib
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An Open-Label, Single Arm, Multicentre Study to Assess the Clinical Effectiveness and Safety of Lynparza (Olaparib) Capsules Maintenance Monotherapy in Platinum Sensitive Relapsed somatic or germline *BRCA* Mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum-based Chemotherapy (ORZORA)

Addendum 2 (Overall survival and safety update)

Study dates: First subject enrolled: 28 September 2015
Last subject last visit: 17 December 2021
Database lock: 18 August 2021
The analyses presented in the report are based on a cut-off date of 25 June 2021

Phase of development: Therapeutic confirmatory (III)

International Co-ordinating Investigator:
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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

The Clinical Study Report (CSR) Addendum 2 reports the final analyses of the secondary endpoints of overall survival (OS), time to Investigator-assessed second progression (PFS2), time to first subsequent therapy or death (TFST), time to second subsequent therapy or death (TSST), time to olaparib discontinuation or death (TDT), CCI [redacted] and updated safety data, based on a data cut-off (DCO) of 25 June 2021.

The results of the primary objective i.e., progression-free survival (PFS) analysis (data maturity of 63.6% in the s*BRCA*m patients, 59.8% in the g*BRCA*m patients, and 60.7% in the *BRCA*m cohort) were based on a DCO of 17 April 2020 and were reported along with the data for the secondary efficacy endpoints, quality of life (QoL), and safety data in the CSR for the ORZORA primary analysis (ORZORA Primary Analysis CSR), dated 07 December 2020.

Study centre(s)

The study was conducted in 8 countries: Bulgaria, Canada, Czech Republic, Hungary, Italy, Poland, Spain and the United Kingdom (UK). Sixty-six centres were initiated to enrol up to 250 ovarian cancer patients with somatic or germline breast cancer susceptibility gene mutations (s*BRCA*m or g*BRCA*m).

Publications

Pignata S, Lewis J, Tchakov I, Robertson JD, Morris T, Jayawardene D, et al. ORZORA: Open-label phase IV trial of olaparib in patients with *BRCA*-mutated ovarian cancer. European Society of Gynaecological Oncology, 19th International Meeting, Nice, France, 24-27 October 2015. (Abstract #0933, Poster #EP08)

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Estimand description/Endpoints
Primary [a]	
To assess the real-world clinical effectiveness of olaparib maintenance monotherapy by Investigator-assessed progression-free survival (PFS) according to modified Response Evaluation Criteria In Solid Tumours (RECIST) v1.1 in patients with somatic breast cancer susceptibility gene mutated (s*BRCA*m) ovarian cancer. To assess the real-world clinical effectiveness of olaparib maintenance monotherapy by Investigator-assessed PFS according to RECIST v1.1 in patients with *BRCA*m ovarian cancer.	Time from study enrolment to disease progression (assessed according to RECIST v1.1 guidelines) or death.

Objectives	**Estimand description/Endpoints**
Secondary	
To assess the real-world clinical effectiveness of olaparib maintenance monotherapy in patients with *BRCA*m ovarian cancer and patients with s*BRCA*m ovarian cancer, by assessment of: a) overall survival (OS), b) time to Investigator-assessed second progression (PFS2), or death.	a) Time to death b) Time to second progression event or death if this occurs before second progression event.
To assess the real-world clinical effectiveness of olaparib maintenance monotherapy in patients with *BRCA*m ovarian cancer and patients with s*BRCA*m ovarian cancer, by assessment of: a) time to first subsequent therapy or death (TFST), b) time to second subsequent therapy or death (TSST) and, c) time to olaparib discontinuation or death (TDT).	a) Time to first subsequent treatment commencement or death if this occurs before commencement of first subsequent treatment b) Time to second subsequent treatment commencement or death if this occurs before commencement of second subsequent treatment c) Time to olaparib discontinuation or death if this occurs before discontinuation of olaparib maintenance therapy.
To assess and describe the quality of life (QoL) of patients with *BRCA*m ovarian cancer and patients with s*BRCA*m ovarian cancer. [a]	Functional Assessment of Cancer Therapy-Ovarian (FACT-O), Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue, and ORZORA QoL Additional Items Questionnaire.
To describe patterns of routine clinical use of olaparib, the nature and patterns of adverse events (AEs) of nausea and vomiting and their impact on QoL in patients with *BRCA*m ovarian cancer and patients with s*BRCA*m ovarian cancer. To describe nausea/vomiting toxicity management patterns used in routine clinical practice. [a]	Safety summary tables, Functional Living Index- Emesis (FLIE) Questionnaire, and concomitant medication (CM) use.
Safety	
To assess the safety and tolerability of olaparib maintenance monotherapy in patients with *BRCA*m ovarian cancer and patients with s*BRCA*m ovarian cancer.	• AEs/serious adverse events (SAEs)/AEs of special interest (AESI).
Exploratory	
CCI [redacted]	[redacted]

Objectives	Estimand description/Endpoints
CCI	

[a] Results for this analysis are presented in the ORZORA primary analysis Clinical Study Report (CSR) dated 07 December 2020.

CCI

PFS: Progression-free survival; RECIST: Response Evaluation Criteria In Solid Tumours; *BRCA*m: Breast cancer susceptibility gene mutation (mutated); s*BRCA*m: Somatic *BRCA*m; AE: Adverse event; OS: Overall survival; PFS2: Time to Investigator-assessed second progression; TFST: Time to first subsequent therapy or death; TSST: Time to second subsequent therapy or death; TDT: Time to olaparib discontinuation or death; QoL: Quality of Life; FACT-O: Functional Assessment of Cancer Therapy-Ovarian; FACIT: Functional Assessment of Chronic Illness Therapy; FLIE: Functional Living Index-Emesis;

SAE: Serious adverse event; AESI: Adverse event of special interest; AML: Acute myeloid leukaemia; CA-125: Cancer antigen-125; CM: Concomitant medication; ctDNA: Circulating tumour DNA; DNA: Deoxyribonucleic acid; HRR: Homologous recombination repair; HRRm^: Qualifying mutation in the tumour of any of 13 genes involved in homologous recombination repair (excluding *BRCA*1 and *BRCA*2 mutations); MDS: Myelodysplastic syndrome; NPM: New primary malignancy; PFS: Progression-free survival; PFI: Progression-free interval; GCIG: Gynaecological Cancer InterGroup; LOH: Loss of heterozygosity

Study design

This was a prospective, open-label, single arm, multicentre study to assess the real-world clinical effectiveness and safety of olaparib maintenance monotherapy. The study was conducted in patients with platinum sensitive relapsed (PSR) g*BRCA*m or s*BRCA*m high grade epithelial ovarian (including fallopian tube or primary peritoneal) cancer, who were in complete response (CR) or partial response (PR) to platinum-based chemotherapy. From Protocol edition 2 onwards, *BRCA* mutation status was determined through central tumour and blood testing performed by Myriad Genetics (patients enrolled under Protocol edition 1 were enrolled based on a local test). An additional, HRRm^ exploratory cohort was enrolled into the study. The investigational clinical trial assay developed as the Lynparza HRR Assay and now called the Foundation One CDx, from Foundation Medicine Inc. (FMI) was used for this testing.

Patients were assigned olaparib capsules p.o. 400 mg twice daily. They initiated olaparib treatment within 8 weeks after their last dose of platinum-containing chemotherapy (last dose is the day of the last infusion). All patients had clinical and objective radiological tumour assessments according to modified Response Evaluation Criteria In Solid Tumours (RECIST) v1.1 at baseline and every 12 weeks relative to date of enrolment, until objective radiological disease progression as determined by the Investigator.

Once a patient progressed, the patient was followed for PFS2 and then for survival status every 12 weeks until the final analysis. Patients were contacted by the site personnel in the 7 calendar days following the DCO for each analysis to provide complete survival data (survival sweep). Where the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient was obtained by site personnel from publicly available resources where possible under applicable local laws.

Target subject population and sample size

Eligible patients had PSR high grade epithelial ovarian cancer, primary peritoneal and/or fallopian tube cancer, who were found to carry a g*BRCA* or s*BRCA* mutation, known or suspected to be deleterious. Patients had to have completed at least 2 previous lines of platinum-based therapy (eg containing carboplatin or cisplatin) before entry into the study, be considered platinum sensitive, and be in PR or CR after the penultimate platinum-based chemotherapy.

Patients with unknown g*BRCA*m status or patients found to carry wild type g*BRCA* (g*BRCA*wt) disease or patients previously identified as having *BRCA*m disease based on a tumour test (with unknown g*BRCA* mutation status or with previously identified g*BRCA*wt status) were considered for screening. Patients previously diagnosed with g*BRCA*m disease were not included in this study.

No formal sample size calculation was performed for this study. A total sample size of approximately 250 patients was anticipated, driven by the need to have at least 50 patients with s*BRCA*m disease, and to help understand patterns of olaparib use in routine clinical practice with the capsule formulation, and across various subgroups. Assuming that approximately 5% of patients with *BRCA*wt disease screened in the study carried a qualifying genetic alteration in any of the 13 genes involved in the HRR pathway (excluding *BRCA*1 and *BRCA*2 mutations), approximately 25 patients were to be included in the HRRm^ cohort.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Olaparib 400 mg bid (50 mg capsules; orally administered).

Duration of treatment

Patients continued with olaparib until documented disease progression as assessed by the Investigator or unacceptable toxicity or for as long as they did not meet any other discontinuation criteria. Patients continued to receive treatment beyond 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, subsequent treatment options were at the discretion of the Investigator.

Statistical methods

Descriptive and efficacy analyses were summarised for all patients who were assigned to olaparib and safety analyses were summarised for all patients who had received at least one dose of olaparib.

All time to event endpoints were presented as Kaplan-Meier (KM) estimates of median or event rate at appropriate timepoints with 95% Confidence Interval (CI), with no formal statistical comparison between patients with s*BRCA*m or g*BRCA*m disease. A summary of OS, PFS2, TFST, TSST, and TDT was produced.

The analyses of OS and safety data were repeated for the exploratory cohort of patients with *BRCA*-independent HRRm^ ovarian cancer.

Study population

Disposition

The 181 enrolled patients were comprised of 145 patients with *BRCA*m status (87 g*BRCA*m, 55 s*BRCA*m, and 3 patients with germline or somatic mutation status undetermined), 33 patients with HRRm^ disease, and 3 patients enrolled in error (unassigned).

From these 181 patients, 177 were treated with olaparib and were part of the Safety Analysis Set (4 patients withdrew from the study before treatment start). Few patients had important protocol deviations.

At the time of DCO for the final analysis (25 June 2021), the mean total follow-up time was 2.83 years (range: 0.0-5.7) overall; 2.84 years (range: 0.0-5.7) in the *BRCA*m cohort and 2.82 years (range: 0.1-4.4) in the HRRm^ cohort.

Thirty-four patients (18.8%) were still receiving study treatment, 4 patients (2.2%) had never been treated with olaparib, and 143 patients (79.0%) had discontinued study treatment; 65 patients (35.9%) in total were still ongoing in the study. The majority of patients who discontinued study treatment did so due to worsening of the condition under investigation (n=102/143, 71.3%).

Overall, 64.1% of patients (n=116/181) had discontinued the study. The main reason for study discontinuation was death (n=57, 49.1%), followed by patient decision (n=45, 38.8%); 11 patients (9.5%) were lost to follow-up. Among them, 41 patients withdrew from the study or were lost to follow-up within 40 days of their date of discontinuation of olaparib. Noting, early censoring in these patients may have affected the maturity of data, and the capacity to evaluate accurately the secondary endpoints of TFST, TSST, and PFS2 and, to a lesser extent, the OS (as the survival sweep permitted to obtain data for a part of the patients who withdrew from the study).

The proportion of patients with protocol deviations related to the COVID-19 pandemic was low. Altogether, the outbreak of the COVID-19 pandemic before the DCO for this addendum (25 June 2021) is not judged to have meaningfully impacted the study conduct and the overall quality of the data.

Summary of efficacy results

Maintenance therapy with olaparib capsules demonstrated consistent clinical activity in *BRCA*m and s*BRCA*m PSR ovarian cancer patients.

At the final analysis DCO (25 June 2021) the OS data in the *BRCA*m cohort were 46.9% mature (68 events/145 patients). The median OS was 46.8 months (95% CI: 37.9-54.4) in the *BRCA*m cohort; and 43.2 months and 47.4 months for s*BRC*Am and g*BRCA*m patients, respectively. The KM OS estimates for the *BRCA*m cohort were 95.0%, 78.8% and 60.4% at

12, 24 and 36 months, respectively, and were similar in the overall *BRCA*m cohort, s*BRC*Am and g*BRCA*m patients.

At the final analysis DCO (25 June 2021), in the *BRCA*m cohort, TFST data were 50.3% mature (73 events/145 patients), PFS2 data were 42.8% mature (62 events/145 patients), and TSST data were 41.4% mature (60 events/145 patients). The KM estimates at 6, 12, 18, 24 and 30 months were generally similar in the overall *BRCA*m cohort, s*BRCA*m and g*BRCA*m patients for these endpoints.

The median TDT was 19.8 months (95% CI: 14.3-22.9) and 19.0 months (95% CI: 13.5-22.8), in the *BRCA*m cohort and the s*BRCA*m patients, respectively. In g*BRCA*m patients, results were generally consistent with the *BRCA*m cohort and s*BRCA*m patients.

Overall survival data in the HRRm^ cohort was 42.4% mature (14 events/33 patients) at DCO; KM estimates at 6, 12, 18, 24 and 30 months were generally similar to those of the *BRCA*m cohort.

Summary of safety results

The safety profile of olaparib was generally consistent in all groups (*BRCA*m cohort, s*BRCA*m and g*BRCA*m patients, HRRm^ cohort, and total safety population).

At the time of DCO for the final analysis (25 June 2021), the median total treatment duration was 17.71 months for the total safety population (n=177), and 19.42 months in the *BRCA*m cohort (20.24 months and 17.87 months, respectively, in the g*BRCA*m and s*BRCA*m patients).

The median relative dose intensity (RDI) was over 95% in all groups (*BRCA*m cohort, s*BRCA*m and g*BRCA*m patients, HRRm^ cohort, and total patient population).

The nature, incidence, and severity of the adverse events (AEs) were consistent with the established/known safety profile of olaparib; the majority of AEs were Grade 1 or Grade 2 events.

In the total safety population, the most frequent AEs (presented for ≥20% of the patients) were known adverse drug reactions (ADRs) of olaparib and included nausea (54.8%), anaemia (44.1%), fatigue (42.9%), and vomiting (28.2%). Those events were typically Grade 1 or Grade 2 and were similarly distributed across all patient groups.

The frequency distribution of AEs of Common Terminology Criteria for Adverse Event (CTCAE) Grade 3 or higher, serious adverse events (SAEs), AEs leading to dose interruption, and AEs leading to permanent treatment discontinuation was similar in the total patient population and across all patient groups.

In the total safety population, AEs of CTCAE Grade 3 or higher were observed in 37.9% of the patients, SAEs in 27.1%, and AEs leading to treatment interruption in 51.4%, and to permanent treatment discontinuation in 6.2% of patients, respectively. Grade 4 AEs were reported by 7 patients in the total safety population, including anaemia, nausea, small intestinal obstruction, platelet count decreased and myelodysplastic syndrome (MDS) in the *BRCA*m cohort, myocardial infarction, and pulmonary embolism in the HRRm^ cohort.

Anaemia was the most frequent AE of CTCAE Grade 3 or higher (n=29, 16.4%) and the most common SAE (n=13 patients, 7.3%); discontinuation of the treatment due to anaemia was required for 1 patient only (0.6%).

There were 9 adverse events of special interest (AESIs) in 9 patients, all in the *BRCA*m cohort, including 2 cases of acute myeloid leukaemia (AML), 4 cases of MDS, and 3 cases of new primary malignancy (NPM; Burkitt's lymphoma, non-Hodgkin's lymphoma, and papillary thyroid cancer); there were no events of pneumonitis. A 10th patient had brain metastases from ovarian cancer, which are not considered an NPM. Therefore, this event was adjudicated as not being an AESI.

Four AEs (all in g*BRCA*m patients and reported in the Primary Analysis CSR) had an outcome of death, including AML (n=2), Burkitt's lymphoma, and sudden death.

The most common AE leading to dose interruption was anaemia (n=34, 19.2%), followed by vomiting (n=12, 6.8%) and nausea (n=10, 5.6%).

Eleven patients (6.2%) in total experienced 14 AEs leading to permanent treatment discontinuation, including 2 events each of diarrhoea, AML, MDS, neutropenia, and 1 event each of non-Hodgkin's lymphoma, anaemia, thrombocytopenia, fatigue, anxiety, and small intestinal obstruction.

Changes in laboratory parameters during the treatment period were evidenced for haemoglobin and platelet count, which decreased over time; erythrocyte mean corpuscular volume (increasing throughout the treatment period), creatinine and bilirubin (both slightly increased). The erythrocyte mean corpuscular volume and blood creatinine had not completely returned to the baseline level 30 days after discontinuation of the treatment by olaparib.

No hepatobiliary or renal safety concerns were identified from review of the laboratory and AE data. No potential Hy's law case was identified in this study.

Conclusion(s)

- Maintenance therapy with olaparib capsules demonstrated consistent clinical activity in *BRCA*m and s*BRCA*m PSR ovarian cancer patients.

- At the final analysis DCO (25 June 2021) the OS data in the *BRCA*m cohort were 46.9% mature (68 events/145 patients). Kaplan-Meier OS estimates for the *BRCA*m cohort were 95.0%, 78.8% and 60.4% at 12, 24 and 36 months, respectively, and were similar in the overall *BRCA*m cohort, s*BRCA*m and g*BRCA*m patients.

- In the *BRCA*m cohort, TFST data were 50.3% mature (73 events/145 patients), PFS2 data were 42.8% mature (62 events/145 patients), and TSST data were 41.4% mature (60 events/145 patients). Kaplan-Meier curves overlapped in the overall *BRCA*m cohort, s*BRCA*m and g*BRCA*m patients for these endpoints.

- The TDT data in the *BRCA*m cohort were 79.3% mature (115 events/145 patients). The median TDT (95% CI) in the overall *BRCA*m cohort was 19.8 months (95% CI: 14.3-22.9); the median TDT (95% CI) was 19.0 months (95% CI: 13.5-22.8) in the s*BRCA*m patients (n=55, 78.2% maturity), and 20.3 months (95% CI: 14.0-26.3) in the g*BRCA*m patients (n=87, 81.6% maturity).

- Overall survival data in the HRRm^ cohort was 42.4% mature (14 events/33 patients) at DCO; KM estimates at 6, 12, 18, 24 and 30 months were generally similar to those of the *BRCA*m cohort.

- The safety and tolerability of olaparib observed in this study was in line with the known safety profile of olaparib used in monotherapy.