Clinical Study Report Addendum 1 Synopsis	
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OPINION - A Phase IIIb, Single-arm, Open-label Multicentre Study of Olaparib Maintenance Monotherapy in Platinum Sensitive Relapsed non-Germline *BRCA* Mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum-based Chemotherapy

Study dates: First patient enrolled: 06 February 2018
Last subject last visit: 10 March 2022
Clinical database lock: 04 February 2022
The analyses presented in this report are based on a cut-off date of 17 September 2021

Phase of development: Therapeutic confirmatory (IIIb)

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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

This Clinical Study Report (CSR) Addendum reports the final analyses of the secondary endpoints of overall survival (OS), time to first subsequent therapy or death (TFST), chemotherapy-free interval (CT-FI), time to treatment discontinuation or death (TDT), the exploratory endpoint of assessing the impact of tumour protein p53 (TP53) disruption status on OS, and updated safety data, based on a data cut-off (DCO) of 17 September 2021.

The results of the primary objective i.e., progression-free survival (PFS) analysis (data maturity of 75.3%) were based on a DCO of 02 October 2020 and were reported along with the data for the secondary efficacy endpoints, exploratory efficacy endpoints, health-related quality of life (HRQoL), and safety data in the CSR for the OPINION primary analysis (OPINION Primary Analysis CSR), dated 21 May 2021.

Study centre(s)

The study enrolled 279 patients with platinum-sensitive high-grade serous ovarian cancer (HGSOC) (including patients with primary peritoneal and/or fallopian tube cancer) or high-grade endometrioid ovarian cancer who were in complete or partial response (CR or PR) following platinum-based chemotherapy and who were germline breast cancer susceptibility gene 1 (*BRCA*1) and/or *BRCA*2 negative. The study was conducted in 17 countries worldwide: Belgium, Bulgaria, Canada, Czech Republic, Denmark, Finland, Israel, Italy, Netherlands, Norway, Poland, Portugal, Slovenia, Spain, Sweden, Switzerland and the United Kingdom.

Publications

Poveda AM, Davidson R, Milner A. OPINION: A single-arm, open-label, Phase IIIb study of olaparib maintenance monotherapy in patients with platinum-sensitive relapsed ovarian cancer and without germline *BRCA* mutations. European Society for Medical Oncology (ESMO) Annual Meeting, 19-23 October 2018, Munich, Germany (Poster #: 1000TiP).

Poveda A, Davidson R, Blakeley C, Milner A. Olaparib maintenance monotherapy in platinum-sensitive, relapsed ovarian cancer without germline *BRCA* mutations: OPINION Phase IIIb study design. Future Oncology. 2019; 15 (32). Clinical Trial Protocol. Published online: 25 September 2019.

Poveda A, Lheureux S, Colombo N, Cibula D, Lindemann K, Weberpals J, et al. Olaparib maintenance monotherapy for patients with non-germline *BRCA*1/2-mutated platinum-sensitive relapsed ovarian cancer: Phase IIIb OPINION interim analysis. Poster presented at the 56th American Society of Clinical Oncology (ASCO) Annual Meeting, held virtually on May 29-31, 2020. (Abstract #: 6507. Poster #: 228).
With Supplementary Material.

Poveda A, Lheureux S, Colombo N, Cibula D, Lindemann K, Weberpals J, et al. Olaparib maintenance monotherapy for non-germline BRCA1/2-mutated (non-gBRCAm) platinum-

sensitive relapsed ovarian cancer (PSR OC) patients (pts): Phase IIIb OPINION primary analysis. Abstract presented at the 57th American Society of Clinical Oncology (ASCO) Annual Meeting, held virtually on June 4-8, 2021 (Abstract #: 5545).

Lindemann K, Skof E, Colombo N, Gonzalez-Martin A, Davidson R, Blakeley C, et al. Olaparib maintenance monotherapy for non-germline BRCA1/2-mutated (non gBRCAm) platinum-sensitive relapsed ovarian cancer (PSR OC): Exploratory biomarker analyses of the phase IIIb OPINION study. Abstract presented at the European Society of Medical Oncology (ESMO) 2021 Annual Meeting. September 16-21, 2021 (Poster #: 740P). Ann Oncol 2021; 32 (Suppl.5): S738-39.

Skof E, Bjurberg M, Rubio Pérez MJ, Davidson D, Blakeley C, Bennett J, Poveda A. Efficacy and safety of maintenance olaparib by patient age in non-germline BRCA-mutated platinum-sensitive relapsed ovarian cancer. Abstract presented at the 22nd European Society of Gynaecological Oncology (ESGO) Annual Meeting. October 23-25, 2021, Prague, Czech Republic (Abstract #: 172, Poster #: P315). Int J Gynecol Cancer 2021; 31 (Suppl.3): A202-203.

Poveda A, Lheureux S, Columbo N, Cibula D, Lindemann K, Weberpals J, et al. Olaparib maintenance monotherapy in platinum-sensitive relapsed ovarian cancer patients without a germline *BRCA*1/*BRCA2* mutation: OPINION primary analysis. Gynecologic Oncology 2022; 164: 498–504.

Lheureux S, Oaknin A, Sikorska M, et al. Clinical and molecular characteristics of patients with short- and long-term progression-free survival in the phase IIIb OPINION study of maintenance olaparib for patients with non-germline BRCA1/BRCA2-mutated platinum-sensitive relapsed ovarian cancer. Poster presented at: 2022 Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer. March 18-21, 2022. Phoenix, Arizona (Poster #: 306).

Colombo N, Madry R, Skof E, Weberpals J, Blakeley C, Marshall H, et al. Maintenance olaparib monotherapy for platinum-sensitive relapsed ovarian cancer in patients without a germline BRCA1/BRCA2 mutation: secondary safety results from the Phase IIIb OPINION study. 2022 Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer. March 18-21, 2022. Phoenix, Arizona (Oral presentation, Abstract #: 128).

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Estimand description/Endpoints
Primary	
• To determine the efficacy by progression free survival (PFS) (investigator-recorded assessments according to modified Response Evaluation Criteria In Solid Tumours [RECIST v1.1]) of olaparib maintenance monotherapy in non-germline breast cancer susceptibility gene mutated (non-gBRCAm) platinum-sensitive relapsed (PSR) ovarian cancer	• PFS: Time from date of first dose until the date of objective radiological disease progression according to modified RECIST 1.1 or death (by any cause in the absence of progression)
Secondary	
• To determine the efficacy of olaparib maintenance monotherapy in non gBRCAm PSR ovarian cancer by assessment of time to first subsequent therapy or death (TFST)	• TFST: Time from date of first dose to date of first subsequent treatment commencement or death due to any cause if this occurs before commencement of first subsequent treatment
• To determine the efficacy of olaparib maintenance monotherapy in non gBRCAm PSR ovarian cancer by assessment of time to treatment discontinuation or death (TDT)	• TDT: Time from date of first dose to date of study drug discontinuation or death due to any cause if this occurs before study drug discontinuation
• To determine the efficacy by PFS (investigator-recorded assessments according to modified RECIST v1.1) of olaparib maintenance monotherapy in non-gBRCAm PSR ovarian cancer according to tumour homologous recombination deficiency (HRD) status using the Myriad myChoice® HRD Plus test [a]	• PFS in the following subgroups: – Somatic BRCA mutated (sBRCAm) and HRD scar positive; – HRD scar positive, non-BRCA mutated; – HRD scar negative, non-BRCA mutated
• To determine the efficacy of olaparib maintenance monotherapy in non gBRCAm PSR ovarian cancer by assessment of chemotherapy-free interval (CT-FI)	• CT-FI: Time from the date of the last dose of platinum chemotherapy prior to olaparib maintenance therapy until the date of initiation of the next anticancer therapy
• To determine the overall survival (OS) of non gBRCAm PSR ovarian cancer patients treated with olaparib maintenance monotherapy	• OS: Time from the date of first dose of olaparib to the date of death from any cause
• To investigate the Health-Related Quality of Life (HRQoL) of non-gBRCAm PSR ovarian cancer patients treated with olaparib maintenance monotherapy as assessed by the trial outcome index (TOI) of the Functional Assessment of Cancer Therapy Ovarian (FACT-O) [a]	• Proportion of patients with any improvement from baseline in TOI score at any point during the treatment period • Proportion of patients with a 10 point deterioration from baseline in TOI score at any point during the treatment period

Safety	
• To assess the safety and tolerability of olaparib maintenance monotherapy in patients with non-gBRCAm PSR ovarian cancer	• Adverse events (AE)/serious adverse events (SAE) • Collection of clinical chemistry/haematology parameters
Exploratory	
• To explore the efficacy by PFS (investigator-recorded assessments according to modified RECIST version 1.1) of olaparib maintenance monotherapy in non-gBRCAm PSR ovarian cancer patients stratified into a range of molecular subgroups including mutations in homologous recombination repair (HRR) genes, microsatellite instability (MSI) status, and tumour mutation load score [a]	• PFS by molecular measures of HRR and genomic instability
• To explore the impact of tumour protein p53 (TP53) disruption status on both PFS [a] and OS	• OS and PFS by TP53 disruption status
• To explore the impact of treatment and disease state on health state utility by EuroQol five dimensions, five-level (EQ-5D-5L) [a]	• EQ-5D (EuroQol five dimensions) index score and the EQ-VAS (EuroQol visual analogue scale) score including the change from baseline for both scores
• To explore the feasibility of reliably identifying mutations in HRR genes from circulating tumour deoxyribonucleic acid (ctDNA) and to enable future diagnostic development [b]	• Correlation between HRD status from tumour and ctDNA in matched patient samples

a) Results for this analysis are presented in the OPINION Primary Analysis Clinical Study Report (CSR) (DCO: 02 October 2020).
b) This exploratory analysis was not performed for this CSR Addendum, it will be reported separately.
AE: Adverse event; ctDNA: Circulating tumour deoxyribonucleic acid; CT-FI: Chemotherapy-free interval; EQ-5D-5L: EuroQol five dimensions, five-level; EQ-VAS: EuroQol visual analogue scale; FACT-O: Functional Assessment of Cancer Therapy-Ovarian; gBRCAm: Germline breast cancer susceptibility gene mutations; HRD: Homologous recombination deficiency; HRQoL: Health-related quality of life; HRR: Homologous recombination repair; MSI: Microsatellite instability; OS: Overall survival; PFS: Progression-free survival; PSR: Platinum-sensitive relapsed; RECIST: Response Evaluation Criteria In Solid Tumours; SAE: Serious adverse event; sBRCAm: Somatic BRCA mutated; TDT: Time to treatment discontinuation or death; TFST: Time to first subsequent therapy or death; TOI: Trial outcome index; TP53: Tumour protein p53.

Study design

This was a Phase IIIb, single arm, open label, multicentre study to assess the efficacy and safety of single agent olaparib as a maintenance treatment in patients with platinum sensitive relapsed (PSR) HGSOC (including patients with primary peritoneal and/or fallopian tube cancer) or high-grade endometrioid ovarian cancer without known deleterious or suspected deleterious germline BRCA mutations (non gBRCAm), who were in CR or PR following platinum-based chemotherapy. Patients had clinic visits every 4 weeks (alternating safety and tumour evaluation) during the first 12 months. Tumour assessments were conducted every 8 weeks for the first 12 months, and thereafter every 12 weeks, up to disease progression.

Safety assessments were conducted every 4 weeks for the first 12 months and thereafter every 12 weeks, up to discontinuation of the study treatment.

Target subject population and sample size

The target population was comprised of patients with relapsed HGSOC (including patients with primary peritoneal and/or fallopian tube cancer) or high-grade endometrioid ovarian cancer who did not have known deleterious or suspected deleterious g*BRCA*m (non-g*BRCA*m) and who were in CR or PR following platinum-based chemotherapy.

A sample size of approximately 250 patients was proposed for this study in order to provide an adequate level of precision around the primary endpoint in the whole patient population.

In 2 randomised placebo-controlled studies (Study 19, NOVA) where non-g*BRCA* patients were treated with a Poly (ADP-ribose) polymerase (PARP) inhibitor (PARPi), the median PFS for patients treated with a PARPi ranged from 8 to 9 months compared to 4 to 5.5 months for those treated with placebo. Clinical trial simulations were performed assuming 250 patients enrolled over a 12-month period with 50% of patients enrolled after 8 months, a median PFS of 8.5 months and a piecewise exponential model for PFS. Across 500 simulations, it was estimated that the expected number of PFS events would be approximately 135 at 18 months (54% maturity) and 180 at 30 months (72% maturity), with a corresponding mean 95% confidence interval (CI) width of 3.87 and 3.27 months, respectively. The primary analysis was planned at approximately 30 months after the first patient was enrolled, with an interim analysis after approximately 18 months, in order to observe approximately 180 and 135 events, respectively.

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

Olaparib (100 mg and 150 mg tablets); the starting dose was 300 mg administered orally twice daily (bid). Individual batch numbers and further information are included in the CSR.

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 could continue to receive treatment beyond progression if, in the investigator's opinion, they were benefiting from treatment, and they did not meet any other study treatment discontinuation criteria. Once patients had been discontinued from study treatment, subsequent treatment options were at the discretion of the Investigator.

Statistical methods

The primary endpoint was investigator-assessed PFS using modified Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1.

All efficacy analyses were based on the full analysis set (FAS; all enrolled patients assigned to olaparib) with safety data summarised from the safety analysis set (all enrolled patients who received at least 1 dose of olaparib). Kaplan-Meier (KM) plots of time-to-event endpoints were presented for all non-g*BRCA*m patients and for subgroups determined by the tumour homologous recombination deficiency (HRD) status. Summaries of the number and percentage of patients experiencing an event, and the type of event (where relevant) were provided along with median estimates and 95% CI.

Adverse events (AE) were described by System Organ Class (SOC), preferred term (PT) and Common Terminology Criteria for Adverse Event (CTCAE, version 5.0) Grade.

The analyses presented in this report are based on the DCO of 17 September 2021.

Study population

Overall, 371 patients were screened for enrolment in the study; 279 patients from 17 countries were enrolled. Over half the patients were enrolled from 4 countries, including Spain (n=52, 18.6%), Canada (n=37, 13.3%), Italy (n=30, 10.8%), and Czech Republic (n=22, 7.9%). All 279 patients enrolled received treatment by olaparib and were included in the FAS and the Safety Analysis Set.

The final analyses presented in this CSR Addendum are based on the DCO of 17 September 2021, which was 43 months after the first patient was enrolled into the study, and 30 months after the last patient was enrolled into the study.

At the Final OS analysis DCO (17 September 2021), 46 patients (16.5%) were still undergoing study treatment and 233 patients (83.5%) had discontinued study treatment. The most common reason for discontinuation of olaparib was objective disease progression (n=196; 70.3%).

In total, 151 patients (54.1%) had terminated the study; the most common reason was death (n=146, 52.3%); 3 patients (1.1%) had withdrawn consent and 2 patients (0.7%) were lost to follow-up.

Thirty-nine patients (14.0%) presented an important protocol deviation, all these patients presented a deviation of eligibility criteria, mostly related to pre-treatment cancer antigen-125 (CA-125) measurements and documentation of platinum sensitivity. Important protocol deviations were not determined to have meaningfully impacted the overall quality of the study, including the conduct, data, and interpretation of results.

Twenty-seven patients (9.7%) had some disruption of the planned visits and assessments due to the COVID-19 pandemic, mostly visits performed remotely (phone or video) and missed PRO assessments, however there was minimal impact on the tumour assessments. The

COVID-19 pandemic is not determined to have meaningfully impacted the overall quality of the study, including the conduct, data, and interpretation of results.

Summary of efficacy results

At the Final OS analysis DCO (17 September 2021), the OS data were 52.3% mature (146 events / 279 patients); median OS was 32.7 months (95% CI: 29.5-35.3). Kaplan-Meier OS rates were 91.3%, 65.8% and 54.9% at 12, 24 and 30 months, respectively. Sensitivity analyses of OS were consistent with the primary analysis results, the median OS was 31.3 months (95% CI: 28.0-37.4) in Myriad-confirmed non-g*BRCA*m patients (n=253).

In ad-hoc analyses based on somatic *BRCA* mutated (s*BRCA*m) and/or HRD status, olaparib activity for OS tended towards a longer survival in HRD status positive and/or s*BRCA*m patients (n=121; maturity 41.3% [50 events / 121 patients]; median OS: 40.1 months; 95% CI: 33.3-NE), or HRD status positive non-*BRCA*m patients (n=94; maturity 43.6% [41 events / 94 patients]; median OS: 37.4 months; 95% CI: 32.8-NE), than in HRD status negative patients (n=115; maturity 67.0% [77 events / 115 patients]; median OS: 25.8 months; 95% CI: 22.2-28.9). Kaplan-Meier OS rates at 12, 24 and 30 months were 94.2%, 74.2% and 66.7% for HRD status positive and/or s*BRCA*m patients, and 85.9%, 55.8% and 38.9% in HRD status negative patients.

Kaplan-Meier OS rates by TP53 in patients with disruptive status (n=131), non-disruptive status (n=117), and wild-type patients (n=19) were 50.7%, 59.1% and 52.6% at 30 months respectively.

Ad-hoc analyses by other patient clinical characteristics showed a trend towards higher OS rates in patients with HRRm (including or excluding tumour *BRCA*m [t*BRCA*m]), as well as in patients with CR to last platinum-based regimen, no evidence of disease (NED) at baseline, or full sensitivity to the penultimate platinum regimen, relative to patients without these respective characteristics.

The TFST data were 69.9% mature (195 events / 279 patients); median TFST was 13.9 months (95% CI: 11.5-16.6); KM TFST estimates were 54.2%, 35.9% and 31.5% at 12, 24 and 30 months, respectively.

The CT-FI data were 55.9% mature (156 events / 279 patients); median CT-FI was 17.9 months (95% CI: 13.8-23.3); KM CT-FI estimates were 62.2%, 43.7% and 41.5% at 12, 24 and 30 months, respectively.

The TDT data were 83.5% mature (233 events / 279 patients); median TDT was 9.6 months (95% CI: 7.8-11.1).

Summary of safety results

At the Final OS analysis DCO (17 September 2021) the median (range) total treatment duration was 9.56 months (0.0-43.4).

The nature, incidence, and severity of the AEs were consistent with the established safety profile of olaparib.

The majority of patients (96.1%) reported at least 1 AE. Adverse events of CTCAE Grade 3 or higher were observed in 29.4% of the patients, serious adverse events (SAEs) in 20.8%, and AEs leading to treatment discontinuation in 8.2% of patients, respectively.

The majority of AEs were of CTCAE Grades 1 or 2. The most frequent AEs included nausea (n=136, 48.7%), anaemia (n=109, 39.1%), and fatigue (n=82, 29.4%). Anaemia was the most frequent AE of CTCAE Grade 3 or higher (n=38, 13.6%) and the most common SAE (n=22, 7.9%); discontinuation of the treatment due to anaemia was required for 6 patients (2.2%).

Two patients (0.7%) had an AE with fatal outcome (COVID-19 and aspiration pneumonia).

The overall incidence of the reported AESIs of pneumonitis (grouped term), MDS/AML and NPM was 1.4%, 0.7% and 1.1%, respectively. Nine adverse events of special interest (AESIs) were reported in 8 patients, including pneumonitis (n=2), lung infiltration (n=2), breast cancer (n=2), rectal adenocarcinoma (n=1), and myelodysplastic syndrome (MDS; n=2). One patient reported 2 AESIs (breast cancer and pneumonitis). Seven AESIs were already present at DCO for the primary analysis (02 October 2020), and 2 new AESIs (breast cancer and lung infiltration) were reported at the Final OS analysis DCO (17 September 2021). Additionally, during the final survival status update, acute myeloid leukaemia (AML) was identified as the cause of death of 1 patient in long-term follow-up, therefore resulting in 10 AESIs in 9 patients. The incidence of MDS/AML with the inclusion of this patient would be 1.1%.

Changes in laboratory parameters during the treatment period were evidenced for haemoglobin and the platelet count, which decreased in the first weeks of the treatment (through Week 8) and slowly improved afterwards, erythrocyte mean corpuscular volume (increasing from Week 8 throughout the treatment period), creatinine and bilirubin (both slightly increased). The erythrocyte mean corpuscular volume had not returned to the baseline level 30 days after discontinuation of olaparib.

Two patients met the criteria of potential Hy's law cases. In both cases, an alternative cause was identified and therefore these were not considered to be drug induced liver injury. These cases were already present at the DCO for the primary analysis (02 October 2020).

Conclusion(s)

- At the Final OS analysis DCO (17 September 2021), efficacy analyses showed that maintenance olaparib demonstrated activity in non-g*BRCA*m PSR ovarian cancer patients, irrespective of *BRCA*m or HRD status:
    - The OS data were 52.3% mature (146 events / 279 patients); median OS was 32.7 months (95% CI: 29.5-35.3) and KM OS rates were 91.3%, 65.8% and 54.9% at 12, 24 and 30 months, respectively
    - In ad-hoc analyses based on s*BRCA*m and/or HRD status, olaparib activity for OS tended towards a longer survival in HRD status positive and/or s*BRCA*m patients (n=121; maturity 41.3% [50 events / 121 patients]; median OS: 40.1 months; 95% CI: 33.3-NE), than in HRD status negative patients (n=115; maturity 67.0% [77 events/ 115 patients]; median OS: 25.8 months; 95% CI: 22.2-28.9).
    - Kaplan-Meier OS rates by TP53 in patients with disruptive status (n=131), non-disruptive status (n=117), and wild-type patients (n=19) were 50.7%, 59.1% and 52.6% at 30 months, respectively
    - The TFST data were 69.9% mature (195 events / 279 patients); median TFST was 13.9 months (95% CI: 11.5-16.6); KM TFST estimates were 54.2%, 35.9% and 31.5% at 12, 24 and 30 months, respectively
    - The CT-FI data were 55.9% mature (156 events / 279 patients); median CT-FI was 17.9 months (95% CI: 13.8-23.3); KM CT-FI estimates were 62.2%, 43.7% and 41.5% at 12, 24 and 30 months, respectively
    - The TDT data were 83.5% mature (233 events / 279 patients); median TDT was 9.6 months (95% CI: 7.8-11.1)
- The safety and tolerability of olaparib observed in this study was in line with the known safety and tolerability profile of the drug; no new safety findings were observed.