Clinical Study Report Synopsis (Primary Analysis)	
Drug Substance	Olaparib
Study Code	D0816C00020
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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 patient last visit: Not applicable (ongoing study)
The primary analyses presented in this report are based on the data cut-off of 02 October 2020

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.

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 accepted to be presented at the 57th American Society of Clinical Oncology (ASCO) Annual Meeting, held virtually on June 4-8 2021 (Abstract #: 5545).

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objectives		Outcome Variable
Priority	**Description**	**Description**
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-g*BRCA*m) 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-g*BRCA*m 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-g*BRCA*m 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 in non-g*BRCA*m PSR ovarian cancer according to tumour homologous recombination deficiency (HRD) status using the Myriad myChoice® HRD Plus test	PFS in the following subgroups: • Somatic *BRCA* mutated (s*BRCA*m) 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-g*BRCA*m 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-g*BRCA*m 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

Objectives		Outcome Variable
Priority	**Description**	**Description**
	To investigate the Health-Related Quality of Life (HRQoL) of non-g*BRCA*m 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)	• 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-g*BRCA*m 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-g*BRCA*m 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	PFS by molecular measures of HRR and genomic instability
	To explore the impact of tumour protein p53 (TP53) disruption status on both OS and PFS	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)	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 [a]	Correlation between HRD status from tumour and ctDNA in matched patient samples

a) This exploratory analysis was not conducted at the time of this primary analysis.

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; g*BRCA*m: 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; s*BRCA*m: 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-g*BRCA*m), 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 two 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 progression-free survival (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).

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, other 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 analyses set (all enrolled patients who received at least 1 dose of olaparib). Kaplan-Meier (KM) plots of PFS 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 a PFS event, and the type of event (progression or death) were provided along with median PFS and 95% CI. Other time-to-events endpoints were summarised in a similar manner.

Adverse events (AE) were described by System Organ Class (SOC), preferred term (PT) and Common Terminology Criteria for Adverse Event (CTCAE, version 4.0) Grade.

The primary analyses presented in this report are based on the data cut-off (DCO) of 02 October 2020.

Subject 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 mean age (standard deviation [SD]) of the patients was 64 years (9.19). The majority of the patients were in the ≥50 to <65 (n=110, 39.4%) and ≥65 to <75 (n=113, 40.5%) age categories. Race and ethnicity were available for 278 patients; the majority of patients were White (n=273; 97.8%) and not Hispanic or Latino (n=271; 97.1%).

Overall (n=279), the median time from original diagnosis was 3.04 years. The primary tumour location was the ovary (n=219; 78.5%), followed by the fallopian tube (n=41; 14.7%) and the

peritoneum (n=19; 6.8%). The majority of the patients (n=198; 71.0%) were Federation of Gynaecology and Obstetrics (FIGO) Stage III at original diagnosis. Histologically, the majority of the tumours were serous (n=260; 93.2%), followed by endometrioid (n=12; 4.3%), mixed epithelial (n=4; 1.4%), other histology (n=2; 0.7%, including adenocarcinoma and carcinosarcoma of the ovary), and primary peritoneal (n=1; 0.4%).

Full platinum sensitivity (disease progression ≥12 months after completion of penultimate platinum chemotherapy) was reported for 185 patients (66.3%), and partial platinum sensitivity (disease progression >6 to <12 months after completion of penultimate platinum chemotherapy) for 88 patients (31.5%). Six patients (2.2%) had missing data. The majority of patients reported a PR (n=184, 65.9%) to the latest platinum chemotherapy, one-third had a CR (n=91, 32.6%). One hundred and thirty-four patients (48.0%) had metastatic disease at screening/baseline, followed by no evidence of disease (NED) (n=91; 32.6%), locally advanced tumours (n=34; 12.2%), and both metastatic and locally advanced tumours (n=19; 6.8%). One patient (0.4%) had missing data.

The Eastern Cooperative Oncology Group (ECOG) performance status at baseline was rated 0 for 191 patients (68.5%) and 1 for 88 patients (31.5%).

The mean (SD) number of previous platinum chemotherapy regimens at baseline was 2.5 (0.79). The majority of patients (n=165; 59.1%) received 2 prior regimens, followed by 3 regimens (n=84; 30.1%), and >3 regimens (n=30; 10.8%).

The majority of patients (n=241, 86.4%) were enrolled in this study based on a local g*BRCA* test, and the remainder (n=38, 13.6%) based on a central test performed by Myriad Genetics. Overall, 264 patients (94.6%), enrolled based on a blood or saliva test, which did not contain a deleterious or a suspected deleterious germline mutation; 15 patients (5.4%) had unconfirmed non-g*BRCA*m status. For patients enrolled based on a local or prior germline test, a blood sample was provided to Myriad to confirm the patients' non-g*BRCA*m status retrospectively, using the Myriad BRACAnalysis CDx® assay. Results of central determination of *BRCA* status were as follows: non-g*BRCA*m: n=253 (90.7%); g*BRCA*m: n=6 (2.2%); no confirmatory result (test failed/cancelled or sample not available): n=20 (7.2%).

Central tumour testing was performed at Myriad, using the Myriad myChoice® HRD Plus assay to determine the somatic *BRCA*m (s*BRCA*m, determined as g*BRCA* wild type [g*BRCA*wt] patients with a tumour *BRCA*m [t*BRCA*m] result) and HRD status (formerly labelled HRD scar positive or negative) for each patient enrolled. Two patient classifications were therefore available, one based on the screening *BRCA* blood/saliva test and the Myriad tumour test ('screening status', by which the interim analysis was performed), and one based on the Myriad confirmatory blood test and tumour test ('Myriad-confirmed status', by which the primary analysis by HRD/*BRCA*m subgroups was prioritized).

Out of the total 279 patients in the FAS, the Myriad t*BRCA*m status was available for 269 patients (96.4%) based on central tumour testing. The majority of patients were non-t*BRCA*m (n=232; 83.2%). A proportion of patients did harbour t*BRCA*m tumours (n=37, 13.3%); 24 patients (8.6%) were t*BRCA*1m and 13 patients (4.7%) were t*BRCA*2m. There were no cases where t*BRCA*1m and t*BRCA*2m co-occurred in the tumour. Of the 37 patients with t*BRCA*m tumours, 27 patients (9.7%) were determined to be s*BRCA*m (based on the central blood and tumour tests), 6 patients (2.2%) were found to be g*BRCA*m, and 4 patients (1.4%) had their s*BRCA*m/g*BRCA*m status not defined (confirmatory blood test failed or not performed).

Results of HRD/*BRCA*m status based on the central blood and tumour assessments by Myriad Genetics were as follows: s*BRCA*m: n=27 (9.7%); HRD status positive, non-*BRCA*m: n=94 (33.7%); HRD status positive and/or s*BRCA*m: n=121 (43.4%); HRD status negative: n=115 (41.2%); g*BRCA*m: n=6 (2.2%). The HRD test failed for 23 patients (8.2%) and overall, the HRD/*BRCA*m status was unknown for 37 patients (13.3%) in the FAS.

Thirty-nine patients (14.0%) presented an important protocol deviation, all these patients presented a deviation of eligibility criteria, mostly related to pre-treatment CA-125 measurements and documentation of platinum sensitivity.

Twenty-one patients (7.5%) had some deviation of their visit schedule (mostly by performing phone visits) or assessments planned related to the COVID-19 pandemic, 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

Maintenance olaparib therapy demonstrated clinical activity on Investigator-assessed PFS by modified RECIST version 1.1 in non-g*BRCA*m PSR ovarian cancer patients.

The PFS results are provided with 75.3% maturity (n=210 events). The median PFS was 9.2 months (95% CI: 7.6-10.9) in the overall study population. Based on the KM estimates of PFS, 65.3%, 38.5%, and 24.3% of patients remained alive and progression-free at 6, 12, and 18 months, respectively. Sensitivity analyses of PFS were consistent with the primary analysis results, the median PFS was 9.1 months (95% CI: 7.4-10.3) in a sensitivity analysis of Myriad-confirmed non-g*BRCA*m patients.

The PFS by pre-defined biomarker analyses demonstrated that olaparib activity was seen across all patient subgroups. Results displayed by the Myriad tumour HRD status and s*BRCA*m status showed a longer PFS in the 121 patients with HRD status positive and/or s*BRCA*m status (median PFS: 11.1 months; 95% CI: 9.2-14.6) and in the 94 patients with non-*BRCA*m HRD status positive (median PFS: 9.7 months; 95% CI: 8.1-13.6), than in the

115 patients with HRD status negative (median PFS: 7.3 months; 95% CI: 5.5-9.0). Median PFS in the 27 patients with s*BRCA*m was 16.4 months (95% CI: 12.8-not evaluable [NE]).

Time to treatment discontinuation or death (TDT) (with 74.6% maturity; n=208 events) had a median of 9.6 months (95% CI: 7.8-11.1).

Time to first subsequent therapy or death (TFST) (with 61.3% maturity; n=171 events) had a median of 13.9 months (95% CI: 11.5-16.4); 53.0% of patients initiated a subsequent therapy; the most common agents were platinum compounds and anthracyclines.

The CT-FI (with 53.0% maturity; n=148 events) had a median of 17.3 months (95% CI: 13.9-23.3).

Data for the secondary endpoint of OS was immature (30.5% maturity; n=85 deaths).

Summary of patient-reported outcomes/health-related quality of life results

Health-related quality of life (HRQoL) of patients was preserved during the treatment period. Overall, 64.3% patients had a FACT-O Trial Outcome Index (TOI) response of "any improvement" at any timepoint. Across all visits, the majority of patients reported either any improvement or no change in TOI score while on treatment. Overall, 42.6% of patients reported experiencing a 10-point deterioration at any time point.

Mean FACT-O TOI scores remained stable, with no clinically meaningful deterioration observed across visits.

Summary of pharmacogenetic results

Not applicable.

Summary of safety results

At the DCO the median total treatment duration was 9.40 months.

The median relative dose intensity (RDI) was 98.7%, and the median proportion of the intended dose (PID) delivered was 97.3%.

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

The majority of patients (95.7%) presented at least 1 AE. The AEs of CTCAE Grade 3 or higher were observed in 29.0% of the patients, serious adverse events (SAEs) in 19.7%, and AEs leading to treatment discontinuation in 7.5%, respectively.

The majority of AEs were of mild or moderate severity (CTCAE Grades 1 or 2). The most frequent AEs of olaparib included nausea (n=135, 48.4%), anaemia (n=105, 37.6%), and fatigue (n=80, 28.7%). 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 5 patients only (1.8%).

There were 7 AESIs in 6 patients, including pneumonitis (n=2), lung infiltration (n=1), breast cancer (n=1), rectal adenocarcinoma (n=1), and myelodysplastic syndrome (MDS) (n=2). One patient reported 2 AESIs (breast cancer and pneumonitis).

One AE of aspiration pneumonia with fatal outcome (n=1, 0.4%) was reported at DCO.

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 from Day 29 throughout the treatment period). 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.

Conclusions

- The patient population enrolled in the OPINION study was representative of the target patient population with non-g*BRCA*m PSR high-grade ovarian tumours.
- Olaparib used as maintenance therapy demonstrated clinical activity on Investigator-assessed PFS by modified RECIST version 1.1 in patients with PSR high-grade ovarian cancer (including patients with primary peritoneal and/or fallopian tube cancer) not harbouring a g*BRCA*m.
- Data from secondary endpoints (TDT, TFST, CT-FI) support clinical activity observed for the primary endpoint.

- The effect of olaparib maintenance therapy on PFS was demonstrated in the overall study population and in all pre-defined subgroups based on s*BRCA*m and HRD status, with a trend toward a greater magnitude of effect in HRD status positive and/or s*BRCA*m patients than in HRD status negative patients.

- The HRQoL of patients was preserved during the treatment period.

- The safety and tolerability of olaparib observed in this study was in line with the known safety profile of the drug, and consistent with that observed in previous studies of olaparib monotherapy.