Clinical Study Report Addendum 2 Synopsis	
Drug Substance	Olaparib
Study Code	D081FC00001
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A Phase III, Randomised, Double-Blind, Placebo-Controlled, Multicentre Study of Maintenance Olaparib Monotherapy in Patients with *gBRCA* Mutated Metastatic Pancreatic Cancer whose Disease Has Not Progressed on First-Line Platinum-Based Chemotherapy

Exploratory CCI [redacted] Analysis and Safety Update

Study dates:
First subject enrolled: 16 December 2014
Data cut-off date: 21 July 2021
The analyses presented in this report are based on a database lock date of 01 September 2021

Phase of development:
Therapeutic confirmatory (III)

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

SYNOPSIS

This is the second clinical study report (CSR) addendum to the CSR for Study D081FC00001 (hereafter referred to as the POLO study). The results of the progression-free survival (PFS) analysis by blinded independent central review (BICR) were based on a data cut-off (DCO) date of 15 January 2019 and were reported along with the data for the secondary efficacy endpoints, global health status/quality of life (QoL), pharmacokinetics, and safety data in the CSR for the POLO PFS analysis, dated 04 June 2019. The first CSR addendum reported the final analysis of overall survival (OS), as well as updated data for the following:

- Sensitivity analysis of PFS by investigator assessment
- Time from randomisation to second progression or death (PFS2)
- Time to first subsequent therapy or death (TFST)
- Time to second subsequent therapy or death (TSST)
- Time to study treatment discontinuation or death (TDT)
- Safety data
- Global health status/QoL

The data in CSR addendum 1 were based on a DCO of 21 July 2020, for the overall study population, and for the subset of patients who had their germline breast cancer susceptibility gene (*gBRCA*) mutation (*gBRCAm*) status confirmed by the Myriad test.

This second CSR addendum reports the CCI [redacted], as well as updated data for the following:

- Sensitivity analysis of PFS by investigator assessment
- CCI [redacted]
- Safety data (including exposure and adverse events [AEs])

The data in this second CSR addendum are based on a DCO of 21 July 2021, for the overall study population.

Study Centres

This was an international multicentre study that randomised patients at a total of 59 study centres in 12 countries.

Publications

Golan T, Hammel P, Reni M, Van Cutsem E, Macarulla T, Hall MJ, et al. Maintenance Olaparib for Germline *BRCA*-mutated Metastatic Pancreatic Cancer. N Engl J Med. 2019;381(4):317-27.

Hammel P, Kindler HL, Reni M, Van Cutsem E, Macarulla T, Hall MJ, et al. Health-related quality of life in patients with a germline *BRCA* mutation and metastatic pancreatic cancer receiving maintenance olaparib. Ann Oncol. 2019;30(12):1959-68.

Golan T, Kindler HL, Park JO, Reni M, Macarulla T, Hammel P, et al. Geographic and Ethnic Heterogeneity of Germline *BRCA1* or *BRCA2* Mutation Prevalence Among Patients With Metastatic Pancreatic Cancer Screened for Entry Into the POLO Trial. J Clin Oncol. 2020;38(13):1442-54.

Objectives and Criteria for Evaluation

Table S1 Objectives and Outcome Variables

Objective			Outcome variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To determine the efficacy of olaparib maintenance monotherapy compared to placebo by PFS.	PFS by BICR using modified RECIST v1.1.[a]
Secondary	Efficacy	To determine the efficacy of olaparib maintenance monotherapy compared to placebo.	OS (observed and predicted using observed PFS and OS data) [a, b, c] Time from randomisation to second progression (PFS2) [a, b] Time from randomisation to first subsequent therapy or death (TFST) [a, b, c] Time from randomisation to second subsequent therapy or death (TSST) [a, b, c] Time from randomisation to study treatment discontinuation or death (TDT) [a, b, c] ORR by BICR using modified RECIST v1.1 criteria for evaluable patients [a] DCR at 16 weeks by BICR using modified RECIST v1.1 criteria [a]
Secondary	Efficacy	To assess the effect of olaparib on HRQoL as measured by the EORTC QLQ-C30 global QoL scale.	Adjusted mean change from baseline in global QoL score from the EORTC-QLQ-C30 questionnaire. [a, b]

Table S1 Objectives and Outcome Variables

Objective			Outcome variable
Priority	**Type**	**Description**	**Description**
Secondary	Safety	To assess the safety and tolerability of olaparib maintenance monotherapy.	AEs [a, b, c] Physical examination, vital signs including blood pressure, pulse, ECG and laboratory findings including clinical chemistry and haematology. [a, b]
CCI			

Table S1 Objectives and Outcome Variables

Objective			Outcome variable
Priority	**Type**	**Description**	**Description**
CCI [redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[a] Outcome measure reported in the CSR for PFS analysis (DCO 15 January 2019).
[b] Outcome measure reported in the CSR for final OS analysis (DCO 21 July 2020).
[c] Outcome measure reported in the CSR for CCI [redacted] (DCO 21 July 2021).
AE = Adverse event; BICR = Blinded independent central review; *BRCA* = Breast cancer susceptibility gene; CSR = Clinical Study Report; DCO = Data cut-off; DCR = Disease control rate; ECG = Electrocardiogram; CCI [redacted]
HRQoL = Health-related quality of life; ORR = Objective response rate; OS = Overall survival; CCI [redacted]; PFS = Progression-free survival; PFS2 = Time from randomisation too second progressions or death; QLQ-C30 = Quality of life questionnaire for cancer patients; CCI [redacted]; QoL = Quality of life; RECIST = Response Evaluation Criteria in Solid Tumours; TDT = Time to discontinuation of treatment or death; TFST = Time to first subsequent therapy or death; TSST = Time to second subsequent therapy or death.

Study Design

This was a randomised double blinded Phase III study in patients with *gBRCAm* metastatic pancreatic carcinoma who had disease control (defined as absence of objective progression) after receiving a minimum of 16 weeks of first-line platinum-based therapy (there was no limitation on the duration of chemotherapy as long as the patient remained progression

free). All patients must have had a known deleterious or suspected deleterious *gBRCA* mutation to be randomised; this could have been determined prior to enrolment into the study or could have been assessed as part of the enrolment procedure for the study (via the centrally provided Myriad BRAC*Analysis*® or BRACAnalysis CDx® tests). Patients were randomised in a 3:2 ratio to receive either monotherapy olaparib 300 mg tablet bd (N=92) or matching placebo bd (N=62) until disease progression or development of unacceptable toxicity. There was no intention to cap duration of assigned blinded therapy for these patients. The primary analysis was based on assessment of disease progression by Response Evaluation Criteria in Solid Tumours (RECIST) using BICR; however, a sensitivity analysis was also performed using the investigator assessment.

Target Subject Population and Sample Size

It was intended to randomise a total of approximately 145 patients with histologically or cytologically confirmed metastatic *gBRCAm* pancreatic adenocarcinoma who were to have received a minimum of 16 weeks of continuous first-line platinum-based chemotherapy and were without evidence of disease progression.

The global recruitment to the study closed when 154 patients were randomised and the DCO for the primary analysis of PFS (15 January 2019) took place when 104 PFS events had occurred (67.5% maturity), approximately 48 months after the first patient was randomised. The study was sized assuming a true treatment effect was a PFS hazard ratio (HR) of 0.54, assuming 80% power and 2.5% alpha (1-sided), with 3:2 randomisation (olaparib:placebo). This translated to a 3.4 month improvement in median PFS over an assumed 4 month median PFS for placebo, if PFS was exponentially distributed.

Investigational Product and Comparator: Dosage, Mode of Administration, and Batch Numbers

Olaparib tablets were manufactured by CCI on behalf of AstraZeneca, as 150 mg and 100 mg green, film-coated tablets. Placebo tablets were manufactured by CCI on behalf of AstraZeneca, with the appearance to match each strength of olaparib. Olaparib tablets were dosed at 300 mg bd orally. The following batch numbers of olaparib and olaparib matching placebo were used up to the time of the PFS analysis DCO (15 January 2019):

- Olaparib: CCI
- Placebo: CCI

The following are additional batch numbers of olaparib and olaparib matching placebo that were used between the PFS analysis DCO (15 January 2019) and final formal analysis of OS (DCO 21 July 2020):

- Olaparib: CCI [redacted]
- Placebo: CCI [redacted]

The following are additional batch numbers of olaparib and olaparib matching placebo that were used between the final formal analysis of OS (DCO 21 July 2020) and the CCI [redacted] (DCO 21 July 2021):

- Olaparib: CCI [redacted]
- Placebo: CCI [redacted]

Duration of Treatment

Patients were to continue to receive study treatment until objective radiological disease progression as per modified RECIST version 1.1 as assessed by the investigator and as long as in the investigator's opinion they were benefiting from treatment and did not meet any other discontinuation criteria.

Statistical Methods

The primary outcome variable for the study of PFS by BICR was assessed at the primary DCO (15 January 2019). Final formal analysis of OS, pre-specified to occur when approximately 106 deaths had occurred, was assessed at the final OS DCO (21 July 2020) using a log rank test using the Breslow approach for handling ties for generation of the p-value. CCI [redacted]

The investigator's assessment of PFS was analysed using the same methods as the BICR assessed PFS; the p-value was generated using a log rank test using the Breslow approach for handling ties for and the HR and its CI were estimated from the U and V statistics obtained directly from the LIFETEST model.

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Subject Population

Of the 154 patients randomised into the study (92 patients to olaparib and 62 patients to placebo), 90 olaparib patients and 61 placebo patients received study treatment.

At the time of the CCI [redacted] DCO (21 July 2021), 11 patients (12.0%) in the olaparib arm and 2 patients (3.2%) in the placebo arm remained on study treatment. This represents approximately 4 times the proportion of patients in the olaparib versus placebo arm.

A total of 79 patients (85.9%) in the olaparib arm and 59 patients (95.2%) in the placebo arm discontinued treatment. The most common reasons for discontinuation of study treatment in both arms were objective and subjective disease progression (55.4% and 18.5% patients, respectively in the olaparib arm compared with 74.2% and 14.5% patients, respectively in the placebo arm). A small proportion of patients in both treatment arms discontinued treatment due to AEs (7.6% of patients in the olaparib arm and 3.2% of patients in the placebo arm).

In total, 83.1% of patients terminated the study, with the most common reason (72.1%) being due to death.

As reported in the CSR for the PFS analysis (DCO 15 January 2019), the olaparib and placebo treatment arms were generally well balanced in terms of age, race, and ethnicity. The patient demographics including medical and surgical history were in line with expectations.

Baseline characteristics were generally well balanced between the 2 treatment groups and the patients randomised were representative of the intended target population.

Summary of Efficacy Results

Sensitivity Analysis of PFS

As a sensitivity analysis for ascertainment bias, the primary analysis of PFS by BICR was repeated using investigator assessed RECIST data.

At the CCI [redacted] DCO (21 July 2021), there were 119 PFS events/154 patients (77.3% mature), as assessed by the investigator. There was a clinically relevant improvement in PFS by investigator assessment for patients in the olaparib arm compared with the placebo arm as evidenced by a 50% reduction in risk of progression or death. Median PFS was 6.7 months in the olaparib arm and 3.7 months in the placebo arm, a prolongation of 3 months with olaparib.

Based on Kaplan-Meier (KM) estimates, the PFS HR translated into a clinically meaningful increase in the percentage of patients who remained alive and progression free in the olaparib arm at 12 months (40.2%), 18 months (30.4%), 24 months (29.0%), 36 months (21.1%), 48 months (18.5%), and 60 months (15.4%), compared with 10.8%, 9.0%, 5.4%, 5.4%, 5.4%, and not calculable (no patients at risk), respectively, in the placebo arm.

Progression-free survival (based on BICR) was the primary endpoint for the study and was analysed at the PFS DCO (15 January 2019) and reported in the CSR for the PFS analysis (HR 0.53; 95% CI 0.35, 0.82; p=0.0038). At the PFS DCO (15 January 2019), the sensitivity analysis of PFS by investigator assessment confirmed the robustness of the analysis by BICR assessment with an HR of 0.51 (95% CI 0.34, 0.78). Hence, with the longer follow-up and higher number of events, the sensitivity analysis of PFS by investigator assessment at the final OS DCO (21 July 2020) and CCI DCO (21 July 2021) is consistent with the sensitivity analysis of PFS by investigator and further supports the analysis of PFS by BICR at the PFS DCO (15 January 2019).

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Summary of Safety Results

At the time of the extended OS DCO (21 July 2021) the total treatment duration was 42789 days (1406 months) for the olaparib arm and 12320 days (405 months) for the

placebo arm; this represents an additional 4722 total treatment days (155 total treatment months) in the olaparib arm and an additional 836 total treatment days (approximately 27 total treatment months) in the placebo arm.

In the olaparib arm, the most common AEs (reported by ≥20% patients) were nausea, fatigue, diarrhoea, abdominal pain, anaemia, constipation, decreased appetite, back pain, vomiting, and arthralgia. Except for constipation, back pain, and arthralgia, all of these AEs are known adverse drug reactions (ADRs) for olaparib as monotherapy. In the placebo arm, the most common AEs (reported by ≥20% of patients) were abdominal pain, fatigue, nausea, and back pain.

The majority of the events that were reported at a ≥5% greater frequency in the olaparib arm compared with the placebo arm are known ADRs for olaparib. The non-ADR AEs which occurred more frequently in the olaparib arm (a ≥5% greater frequency in the olaparib arm) were: alanine aminotransferase increased, anxiety, arthralgia, aspartate aminotransferase increased, constipation, depression, dry mouth, gamma-glutamyl transferase increased, hyperglycaemia, influenza, influenza like illness, insomnia, nasopharyngitis, and pyrexia.

Adverse events of Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥3 were reported in 48.9% of patients in the olaparib arm and 24.6% in the placebo arm. Anaemia and fatigue were the only AEs of CTCAE Grade ≥3 reported in ≥5% of patients in the olaparib arm.

Serious adverse events (SAEs) were reported by a higher proportion of patients in the olaparib arm than the placebo arm (31.1% versus 16.4% respectively). Anaemia was the most common SAE (reported in ≥5% of patients) and was reported in 7 patients (7.8%) in the olaparib arm compared with no patients in the placebo arm.

The majority of deaths occurring on study treatment were due to disease under investigation and there was a higher proportion of patients that had died due to disease progression in the placebo arm compared with the olaparib arm. There was one AE with an outcome of death in the olaparib arm [redacted]

Adverse events leading to olaparib or placebo dose reductions occurred in a higher proportion of olaparib-treated patients (17.8%) compared with placebo-treated patients (4.9%). The most common AEs leading to dose reduction (reported in ≥2% of patients) in the olaparib arm were anaemia, asthenia, fatigue, and vomiting. Adverse events leading to olaparib or placebo treatment interruptions occurred in a higher proportion of olaparib-treated patients (42.2%) compared with placebo-treated patients (6.6%). The most common (≥5% of patients) AE leading to treatment interruption of olaparib was anaemia (12.2%).

Only a small number of patients discontinued study treatment due to AEs (8.9% in the olaparib arm versus 1.6% in the placebo arm). One-third of the AEs leading to discontinuation of study treatment resolved after treatment was stopped.

The adverse events of special interest in this study were myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML), new primary malignancies (NPM) and pneumonitis. From the start of POLO (first subject randomised 29 January 2015) up to the CCI DCO of 21 July 2021, there were no events of MDS/AML in either treatment arm. There were no new NPM events since the final OS DCO (21 July 2020); therefore, there remained 2 patients in the placebo arm that had an NPM. There were no new events of pneumonitis since the final OS DCO (21 July 2020); therefore, there remained 2 olaparib-treated patients who reported pneumonitis.

Conclusions

POLO demonstrated a positive benefit/risk profile for olaparib maintenance monotherapy in metastatic pancreatic adenocarcinoma patients with a deleterious or suspected deleterious germline mutation in *BRCA1* and/or *BRCA2*. This is evidenced by the following:

- At the PFS DCO (15 January 2019), the study met its primary objective, demonstrating a statistically significant and clinically meaningful improvement in PFS as assessed by BICR with olaparib 300 mg bd maintenance therapy compared with placebo (HR 0.53; 95% CI 0.35, 0.82; p=0.0038; median PFS 7.4 months versus 3.8 months, respectively). The sensitivity analysis of the primary endpoint using the investigator assessment of PFS was conducted again at the time of the CCI (DCO 21 July 2021) and was consistent with both the results from BICR and the sensitivity analysis by the investigator and the DCO for the PFS analysis.
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- CCI

- The olaparib safety and tolerability profile observed in this study was generally consistent with that observed in previous studies of olaparib monotherapy and is supportive of long-term use of olaparib 300 mg bd tablet in the maintenance setting.