Clinical Study Report

Drug Substance	Olaparib (AZD2281, KU 0059436)
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A Randomised, Double-Blind, Placebo-Controlled, Multicentre Phase II Study to Compare the Efficacy, Safety and Tolerability of Olaparib Versus Placebo When Given in Addition to Abiraterone Treatment in Patients With Metastatic Castrate-Resistant Prostate Cancer Who Have Received Prior Chemotherapy Containing Docetaxel

Study dates: First patient enrolled: 01 April 2014
Last patient enrolled: 14 July 2015
Data cut-off date: 22 September 2017

Phase of development: Therapeutic exploratory (II)

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

Study centre(s)

This study was performed at 41 sites in 11 countries across 2 continents: Spain (7 sites), United Kingdom (6 sites), Italy (5 sites), Belgium (3 sites), Canada (3 sites), Czech Republic (3 sites), France (3 sites), Netherlands (3 sites), Russian Federation (4 sites), Poland (2 sites) and United States (2 sites).

Publications

Clarke N, Wiechno P, Alekseev B, Sala N, Jones R, Kocak I, et al. Olaparib combined with abiraterone in patients with metastatic castration-resistant prostate cancer: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol 2018 Jul;19(7):975-86.

Clarke N, Wiechno P, Alekseev B, Sala N, Jones R, Kocak I, et al. Olaparib combined with abiraterone in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC): A randomized phase II trial [abstract]. J Clin Oncol 2018;36(suppl):abstr 5003.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Variable
Priority	**Type**	**Description**	**Description**
Part A Primary	Safety	To assess the safety and tolerability of olaparib when given in addition to abiraterone and to recommend, by assessment of dose-limiting toxicities and other safety and tolerability data, a dose of olaparib for further study when given in addition to abiraterone.	Assessment of AEs graded by CTCAE v4.0, vital signs (including BP, pulse), and evaluation of laboratory parameters (clinical chemistry and haematology). Incidence of DLTs during the initial evaluation period.
Part B Primary	Efficacy	To compare the efficacy of olaparib when given in addition to abiraterone, with placebo given in addition to abiraterone, by assessment of rPFS (Investigator determined) using RECIST 1.1 and PCWG-2 criteria.	rPFS, defined as the time from randomisation to Investigator determined disease progression according to RECIST 1.1 (for soft tissue disease) and/or PCWG-2 criteria (for bone disease), or death.
Part A Secondary	PK	To evaluate the presence of any drug interaction between olaparib and abiraterone by determination of steady state exposure to olaparib in the presence and absence of abiraterone, and determination of steady state exposure to abiraterone in the presence and absence of olaparib.	Olaparib and abiraterone PK steady state parameters (where the data allow): $C_{ss,max}$, $t_{ss,max}$, $C_{ss,min}$, AUC_{ss}, AUC_{0-t}, $t_{ss,last}$, CL_{ss}/F and arithmetic ratios of $C_{ss,max}$, $C_{ss,min}$ and AUC_{ss} for each analyte in combination compared to alone.
Part B Secondary	Safety	To compare the safety and tolerability of olaparib when given in addition to abiraterone, with placebo given in addition to abiraterone.	Assessment of AEs graded by CTCAE v4.0, vital signs (including BP, pulse), and evaluation of laboratory parameters (clinical chemistry and haematology).

Objective			Variable
Priority	**Type**	**Description**	**Description**
Part B Secondary	Efficacy	To assess the antitumour activity of olaparib when given in addition to abiraterone, compared with placebo given in addition to abiraterone, by measurement of changes in circulating PSA and CTCs, calculation of overall radiological ORR (by RECIST 1.1 and PCWG-2 bone scan criteria) and malignant soft tissue ORR (by RECIST 1.1), DoR, TFST for prostate cancer, and TSST for prostate cancer.	Absolute and percentage change from baseline in PSA levels and PSA response. Change and best change from baseline in CTC numbers and CTC conversion rates. Tumour response in terms of ORR (malignant soft tissue response and overall radiological response [malignant soft tissue response by RECIST 1.1 and overall radiological response by RECIST 1.1 and PCWG-2]) and DoR. TFST, defined as the time from randomisation until the first subsequent therapy for prostate cancer (or death) and TSST, defined as the time from randomisation until the second subsequent therapy for prostate cancer (or death).
Part B Secondary	Efficacy	To assess the efficacy of olaparib when given in addition to abiraterone, compared with placebo given in addition to abiraterone, by assessment of OS.	OS, defined as time from randomisation to the date of death from any cause.
Part B Secondary	Efficacy	To assess the efficacy of olaparib when given in addition to abiraterone, compared with placebo given in addition to abiraterone, by assessment of time from randomisation to to second progression or death.	PFS2. Progression defined by local standard clinical practice. May involve any of: objective radiological progression, symptomatic progression, rises in PSA or death.
Part B Secondary	Efficacy	To investigate *BRCA* and *ATM* mutations as candidate predictors of response to olaparib. In addition to *BRCA* and *ATM* mutations, mutations in 12 other homologous recombination repair (HRR) genes could be explored. Note: This objective was dependent upon the number of evaluable samples obtained from the study.	*BRCA*, *ATM* and HRR mutation status; if the number of events in these groups is sufficient then the primary analysis of rPFS will be repeated in all *BRCA* and/or *ATM* and HRR mutation patients.
Part B Exploratory	Patient-reported outcome	To explore the effects of olaparib on pain and other prostate cancer-related symptoms compared to placebo.	Change from baseline in worst pain, general pain and pain interference in daily activities scales of the BPI-SF and the worst bone pain item. Change from baseline in the FAPSI-8, as derived from 8 items within the FACT-P, FAPSI-6 and the PCS, as derived from the 12 items in the prostate specific module of the FACT-P.

Objective			Variable
Priority	**Type**	**Description**	**Description**
Part B Exploratory	Patient-reported outcome	To explore the effects of olaparib on HRQoL compared to placebo.	Change from baseline, as measured by the FACT-P scales: FWB, PWB, EWB, SWB, the FACT-P total score, and the TOI score (the sum of the PWB, FWB and PCS scores).
Part B Exploratory	Patient-reported outcome	To assess the time to deterioration in pain.	Time to deterioration in the BPI-SF worst pain item and time to deterioration in the worst bone pain item.
Part B Exploratory	Patient-reported outcome	To assess time to deterioration in HRQoL.	Time to deterioration in HRQoL, as measured by FACT-P TOI score.
Part B Exploratory	Pharmaco-economic	To explore the impact of treatment and disease state on health state utility.	EQ-5D-5L health state utility index.
Part B Exploratory	Pharmaco-economic	To investigate the impact of treatment and disease progression on mCRPC management resource use.	Resource use was captured, focussing on in-patient and ICU admissions, length of stay, palliative interventions and reason for admission into hospital and interventions.
Part B Exploratory[a]	Laboratory	Future exploratory research into factors that may influence development of cancer and/or response to treatment (where response is defined broadly to include efficacy, tolerability or safety) may be performed on the collected and stored archival tumour samples (where available), blood samples (mandatory), urine samples (mandatory), and CTC samples (mandatory).	Analysis and outcome variables yet to be defined.
Part B Exploratory[a]	Laboratory	To explore whether resistance mechanisms to olaparib can be identified through analysis of tumour and blood samples – archival tumour sample (where available), blood sample at baseline and on disease recurrence (mandatory), and CTC samples (mandatory).	Analysis and outcome variables yet to be defined.
Part B Exploratory[a]	Laboratory	To collect and store DNA according to each country's local and ethical procedures for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to study treatments and/or susceptibility to disease (optional).	Analysis and outcome variables yet to be defined.

[a] These exploratory endpoints will be reported separately.

AE adverse event; *ATM* ataxia telangiectasia mutated gene; AUC_{0-t} area under the plasma concentration-time curve, from time zero to time of the last quantifiable concentration; AUC_{ss} area under the plasma concentration-

time curve at steady state; BP blood pressure; BPI-SF Brief Pain Inventory – Short Form; *BRCA* breast cancer gene; CL_{ss}/F apparent total body clearance of drug after extravascular administration across the dosing interval at steady state; $C_{ss,max}$ maximum plasma concentration at steady state; $C_{ss,min}$ minimum plasma concentration at steady state; CTCAE Common Terminology Criteria for Adverse Events; CTCs circulating tumour cells; DLT dose-limiting toxicity; DoR duration of response; EQ-5D-5L EuroQuol-5 Dimension, 5-Level; EWB emotional well-being; FACT-P Functional Assessment of Cancer Therapy – Prostate Cancer; FAPSI-6 Functional Assessment of Prostate Cancer Symptoms Index 6; FAPSI-8 Functional Assessment of Prostate Cancer Symptoms Index 8; FWB functional well-being; HRQoL health-related quality of life; ICU intensive care unit; mCRPC metastatic castrate-resistant prostate cancer; ORR objective response rate; OS overall survival; PCS Prostate Cancer Symptoms; PCWG-2 Prostate Cancer Working Group 2; PFS2 time from randomisation to second progression or death; PK pharmacokinetic; PSA prostate specific antigen; PWB physical well-being; RECIST 1.1 Response Evaluation Criteria in Solid Tumours version 1.1; rPFS radiological progression-free survival; SWB social well-being; TFST time to first subsequent therapy or death; TOI trial outcome index; $t_{ss,last}$ time to last quantifiable plasma concentration at steady state; $t_{ss,max}$ time to reach maximum plasma concentration at steady state; TSST time to second subsequent therapy or death.

Study design

This was a 2-part Phase II study in patients with metastatic castrate-resistant prostate cancer (mCRPC). Part A was an open-label safety run-in study to assess the safety, tolerability and pharmacokinetics (PK) of olaparib when given in addition to abiraterone 1000 mg once daily. Part B was a randomised, double-blind, placebo-controlled comparison of the efficacy, safety and tolerability of the dose of olaparib selected from Part A when given in addition to abiraterone, versus placebo in addition to abiraterone.

Target subject population and sample size

For Part A of the study, it was planned to enrol 15 to 18 evaluable patients (Cohorts 1 and 2) from approximately 4 sites in 1 or 2 countries. A further 12 patients could be recruited into a third cohort but this was not necessary as there were <4 dose-limiting toxicities (DLTs) in Cohort 2.

For Part B of the study, approximately 140 patients who had received prior chemotherapy containing docetaxel were planned to be randomised (1:1). Patients who were dosed in Part A of the study could not participate in Part B.

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

For Part A of the study, patients in Cohort 1 received olaparib 200 mg (administered as 2 x 100 mg tablets) twice daily (bid), Cohort 2 Group 1 received olaparib 300 mg (administered as 2 x 150 mg tablets) bid, and Cohort 2 Group 2 received olaparib 300 mg (administered as 2 x 150 mg tablets) bid starting after completion of the abiraterone PK profiling. Patients in all cohorts received 1000 mg abiraterone once daily in the morning and prednisone or prednisolone 5 mg bid. Cohort 3 was not required (ie, <4 DLTs were observed in Cohort 2).

For Part B of the study, each patient received olaparib 300 mg (administered as 2 x 150 mg tablets) bid or matching placebo. Patients also received 1000 mg abiraterone once daily in the morning and prednisone or prednisolone 5 mg bid.

Investigational product	Dosage form and strength	Manufacturer	Batch number
Olaparib	100 mg tablet	AbbVie Deutschland GmbH and Co. KGa	1000110206 (Part A) 25171B900 (Part A) 25171B900 (Part A) 34193B900 (Part A) 37202B900 (Part A and B) 1000073095 (Part B) 13-002366AZ (Part B) 37201B900 (Part B)
Olaparib	150 mg tablet	AbbVie Deutschland GmbH and Co. KGa	27176B900 (Part A) 27178B900 (Part A) 27175B900 (Part A) 39211B900 (Part A) 1000088515 (Part B) 13-002365AZ (Part B) 14-000634AZ (Part B) 14-001884AZ (Part B) 41225B900 (Part B) 46242B900 (Part B)
Placebo to olaparib 100 mg	Placebo to match olaparib 100 mg tablet	Penn Pharmaceutical Services Ltd	009142 009510 13-001473AZ
Placebo to olaparib 150 mg	Placebo to match olaparib 150 mg tablet	Penn Pharmaceutical Services Ltd	009511 009671 009974 13-001109AZ 14-002405AZ

Duration of treatment

Patients continued to receive study treatment until disease progression, or until a time when the Investigator considered that they were no longer deriving clinical benefit, or they stopped taking treatment for any other reason including having met any of the criteria for treatment discontinuation.

Statistical methods

The primary endpoint of Part B was radiological progression-free survival (rPFS; defined by Response Evaluation Criteria in Solid Tumours version 1.1 [RECIST 1.1] and/or Prostate Cancer Working Group 2 [PCWG-2] as assessed by the Investigator, and expressed in

months). The primary analysis was planned to be performed once approximately 100 progression events had occurred, with a further final analysis of time from randomisation to second progression or death (PFS2) and overall survival (OS) once approximately 60% of patients had died. Prior to database lock for the primary analysis, the decision was taken to combine these analyses with all endpoints evaluated using data available when approximately 100 progression events had occurred, since it was anticipated that 60% of patients would have died at this point. The primary endpoint of rPFS was analysed using the log rank test. The hazard ratio (HR), 80% confidence interval (CI) and 95% CI were estimated. In addition, the 1-sided and 2-sided p-values were calculated to test the hypothesis of HR <1 (olaparib improves survival) versus the null hypothesis of HR=1 (no treatment effect). Patients who were not known to have progressed or died at the time of the analysis were censored at the time of the latest date of assessment from either their last evaluable RECIST 1.1 assessment or their last evaluable PCWG-2 assessment. If the patient progressed or died after 2 or more missed visits (ie, 2 or more visits where neither a RECIST 1.1 visit scan nor a PCWG-2 visit scan were done), they were censored at the time of the latest evaluable RECIST 1.1 or PCWG-2 assessment. If the patient had no evaluable visits or did not have baseline data, they were censored at Day 1 unless they died within 2 visits of baseline (in which case their date of death was used).

Separate log rank tests comparing rPFS between treatments in subsets of the full analysis set based on key baseline demographics and disease characteristics (eg, age, race, Eastern Cooperative Oncology Group [ECOG] performance status) as well as ataxia telangiectasia mutated gene (*ATM*), breast cancer susceptibility gene (*BRCA*), composite *BRCA*/*ATM* and composite homologous recombination repair gene (HRR) mutation categories were planned, when sufficient events occurred in each treatment group (at least 5 events).

Subject population

A data cut-off date of 22 September 2017 was used for the analysis reported in this CSR.

Part A: A total of 16 patients were enrolled in Cohorts 1 (3 patients) and 2 (Group 1: 7 patients; Group 2: 6 patients) from 2 sites in the United Kingdom and 1 site in Belgium. All 16 (100%) patients received treatment with olaparib and abiraterone according to the dosing schedule. Of these, 3 (18.8%) patients, 2 in Cohort 1 and 1 in Cohort 2 (Group 1), completed the study and 13 (81.3%) patients terminated the study, most commonly due to worsening of the condition under investigation (10 of 13 [76.9%] patients).

Important protocol deviations were reported only for Cohort 2 (2 patients in Group 1 and 2 patients in Group 2) and were related to laboratory assessment criteria (Group 1) and investigational product compliance (Group 2).

Part B: A total of 171 patients were enrolled and 142 patients were randomised at 36 sites in 11 countries; all randomised patients received treatment with olaparib or placebo, each co-administered with abiraterone. In the olaparib+abiraterone arm, 64 (90.1%) patients discontinued treatment with olaparib and in the placebo+abiraterone arm, 63 (88.7%) patients discontinued treatment with placebo. The proportion of patients who discontinued

olaparib/placebo due to an AE was lower in the placebo+abiraterone arm compared with the olaparib+abiraterone arm (7 [11.1%] patients versus 19 [29.7%] patients).

Important protocol deviations were reported for a total of 4 patients in the olaparib+abiraterone arm and 2 patients in the placebo+abiraterone arm. Eligibility criteria were violated in 3 patients in the olaparib+abiraterone arm and 1 patient in the placebo+abiraterone arm; the remaining deviations were related to investigational product compliance.

For demographic and baseline characteristics, the 2 treatment groups in Part B differed in respect of some characteristics that could have affected disease prognosis, being worse in the olaparib+abiraterone arm compared with the placebo+abiraterone arm:

- Patients in the olaparib+abiraterone arm were generally older than those in the placebo+abiraterone arm (median age: 70 years versus 67 years).
- The mean time from initial diagnosis of prostate cancer to first dose was longer in the olaparib+abiraterone arm compared with the placebo+abiraterone arm (68.1 months versus 59.5 months).
- A higher percentage of patients in the olaparib+abiraterone arm had American Joint Committee on Cancer (AJCC) Stage IV disease at diagnosis compared with the placebo+abiraterone arm (50.7% versus 38.0%).
- Median (range) baseline prostate specific antigen (PSA) was higher in the olaparib+abiraterone arm compared with the placebo+abiraterone arm (86.20 μg/mL [0.2 to 3475.4 μg/mL] versus 46.82 μg/mL [1.4 to 3140.0 μg/mL], respectively).

Overall, the demographic and baseline disease characteristics were representative of the intended patient population in Parts A and B of this study.

Summary of efficacy results

Efficacy data were collected in Part B of the study only.

The primary objective of the study was met; from the results of the log rank test for rPFS based on local radiological assessment, a clinically meaningful and statistically significant improvement in rPFS for olaparib+abiraterone-treated patients compared with placebo+abiraterone-treated patients was observed (HR 0.651; 1-sided p=0.017; 2-sided p=0.034). The median rPFS was 13.8 months in the olaparib+abiraterone arm versus 8.2 months in the placebo+abiraterone arm; a prolongation of 5.6 months with olaparib. All prespecified sensitivity analyses (evaluation time bias, attrition bias, excluding patients with deviations and only bone scan PCWG-2 progression events) were consistent with the primary analysis, confirming the robustness of the rPFS results.

Benefit of olaparib+abiraterone over placebo+abiraterone was seen across all predefined subgroups; median rPFS in these subgroups was generally consistent with the primary rPFS analysis. In the analyses of rPFS by HRR status (panel of 15 genes), the treatment effect was similar irrespective of HRRm status; rPFS improvement with olaparib+abiraterone versus placebo+abiraterone in the 3 HRR subgroups (HRRm positive, negative and partly characterised) was consistent with the overall effect in the full analysis set.

For PFS2, analysed using the log rank test, there was a nonstatistically significant 21% reduction in the risk of second progression or death in the olaparib+abiraterone arm (HR 0.788, 1-sided p=0.140; 2-sided p=0.280) and median PFS2 was 4.8 months longer in the olaparib+abiraterone arm (23.3 months) than in the placebo+abiraterone arm (18.5 months), indicating that the antitumour effect of olaparib co-administered with abiraterone was carried over to subsequent therapy, when compared with placebo co-administered with abiraterone.

The efficacy of olaparib was also assessed by analysis of OS using the log rank test; the HR numerically favoured olaparib+abiraterone compared with placebo+abiraterone (HR 0.911; 95% CI: 0.600, 1.384; 1-sided p=0.331; 2-sided p=0.662), which suggested no OS detriment for olaparib+abiraterone-treated patients. Median OS was 22.7 months in the olaparib+abiraterone arm and 20.9 months in the placebo+abiraterone arm.

The remaining secondary endpoints analysed using the log rank test were time to first subsequent therapy or death (TFST) and time to second subsequent therapy or death (TSST); both showed a numerical improvement in favour of olaparib+abiraterone-treated patients compared with placebo+abiraterone-treated patients with HRs of 0.781 (95% CI: 0.540, 1.130) and 0.809 (95% CI: 0.545, 1.201), respectively. Median TFST was 13.5 months in the olaparib+abiraterone arm and 9.7 months in the placebo+abiraterone arm. Median TSST was similar between the treatment arms (19.6 months in the olaparib+abiraterone arm and 18.0 months in the placebo+abiraterone arm).

The antitumour activity of olaparib was also assessed by evaluation of other secondary variables: overall radiological objective response rate (ORR) and soft tissue ORR were identical and were similar between the olaparib+abiraterone arm (27.3%) and the placebo+abiraterone arm (31.6%); odds ratio 0.813 (95% CI: 0.285, 2.261). For overall radiological ORR, the proportion of patients with stable disease for ≥12 weeks was higher in the olaparib+abiraterone arm (48.5%) than in the placebo+abiraterone arm (21.1%) and there was a similar trend for soft tissue ORR (48.5% versus 31.6%, respectively).

For all patients with an objective response, including those without measurable disease at baseline, median DoR from onset of response was 5.7 months longer in the olaparib+abiraterone arm (17.8 months versus 12.1 months in the placebo+abiraterone arm). In a sensitivity analysis for patients with an objective response and measurable disease at baseline, median DoR from onset of response was similar in the olaparib+abiraterone arm (13.7 months) and in the placebo+abiraterone arm (12.1 months). Median time to onset of response was 2.8 months in both arms, irrespective of measurable disease at baseline.

Analysis of the secondary efficacy variables, circulating tumour cell (CTC) count and PSA, showed a similar CTC conversion rate in the olaparib+abiraterone and placebo+abiraterone arms (50.0% and 46.4%, respectively); the median best percentage change in PSA was similar in both the olaparib+abiraterone and placebo+abiraterone arms (-54.16% and -49.85%, respectively), as was the confirmed PSA response rate (PSA_{50}; 47.9% and 42.3%, respectively).

The results from the analyses of patient reported outcome measures (FACT-P total score improvement rate, BPI-SF worst pain deterioration and worst bone pain deterioration) showed no detriment for the olaparib+abiraterone arm compared with the placebo+abiraterone arm. Similarly, the results from the analyses of pharmacoeconomic measures did not show any notable differences between the treatment arms.

Summary of pharmacokinetic results

Pharmacokinetics were evaluated using data from patients in Part A of the study using the PK analysis set.

The data show that when olaparib was co-administered with abiraterone, the Gmean PK parameter ratios of non-log transformed data for peak plasma concentration ($C_{ss,max}$) and trough plasma concentration ($C_{ss,min}$) were slightly lower (approximately 15% and 22% lower, respectively) and the overall exposure based on steady state area under the plasma curve (AUC_{ss}) was similar (AUC_{ss} 1.4% lower) compared with olaparib administered as monotherapy. The individual ratio data show that all $C_{ss,min}$ ratios were below 1 and that the AUC_{ss} and $C_{ss,max}$ ratios were distributed both above and below 1 (ranging between 31% lower and 22% higher for $C_{ss,max}$ and between 26% lower and 20% higher for AUC_{ss}) indicating no clear trend for exposure in combination to be higher or lower than that in monotherapy.

The data show that when abiraterone was co-administered with olaparib, the Gmean PK parameter ratios of non-log transformed data for AUC_{ss}, $C_{ss,max}$ and $C_{ss,min}$ were slightly lower (approximately 13%, 19% and 5%, respectively) compared with abiraterone administered as monotherapy. The individual patient ratio data show that the AUC_{ss}, $C_{ss,max}$ and $C_{ss,min}$ ratios were distributed both above and below 1 (ranging between 54% lower and 52% higher for AUC_{ss}, 63% lower and 75% higher for $C_{ss,max}$ and 34% lower and 50% higher for AUC_{ss}) indicating no clear trend for exposure in combination to be higher or lower than that in monotherapy.

Based on the available data, there appeared to be no evidence of changes in the exposure to olaparib when co-administered with abiraterone or vice versa. However, the numbers of patients for evaluation of a drug-drug interaction between olaparib and abiraterone were small (n=4 for the within patient DDI assessment and n=12 for the between patient DDI assessment with 6 patients each in Groups 1 and 2) and interpatient variability was moderate to high, so there were insufficient data to formally rule out a drug-drug interaction and no statistical analyses were performed.

Summary of safety results

Part A: As per the study design, the mean (SD) total duration of olaparib and abiraterone combination treatment exposure for patients in Cohort 1 (1013.0 [391.81]) was longer compared with Cohort 2 (382.7 [355.69] for Group 1 and 308.0 [239.38] for Group 2). In each cohort, the median total and actual treatment durations observed for the applicable olaparib and abiraterone monotherapy and combination treatments were similar, showing that patients were able to receive the assigned treatment and interruptions had little impact on treatment duration.

At the time of assessment by the Safety Committee, no DLT was reported and, therefore, they agreed to proceed with the dose of 300 mg bid in Part B of the study.

All 16 patients had an adverse event (AE) in Part A. All 3 patients in Cohort 1 and 9 of 13 patients in Cohort 2 had an AE that the Investigator considered as causally related to 1 or both of the study treatments, olaparib and abiraterone. Whilst the majority of reported AEs were Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or 2 in intensity, 5 of 16 patients had an event of CTCAE Grade ≥3 including back pain, pneumonia, pulmonary embolism and fall in Cohort 1, and cellulitis, sepsis, blood potassium decreased, eye haemorrhage, haemoglobin decreased and wound secretion in Cohort 2; of these, 1 patient in Cohort 2 had a Grade 3 AE (blood potassium decreased) that was considered by the Investigator as causally related to both olaparib and abiraterone.

Of the AEs defined as AESI, 1 case of pneumonitis (CTCAE Grade 1) was reported for a patient in Cohort 1.

Two patients in Cohort 1 and 3 patients in Cohort 2 had serious adverse events (SAEs: humerus fracture, pyrexia, pneumonia, urinary tract infection, eye haemorrhage, intestinal obstruction and cellulitis) during the study, none of which were considered as related to study treatment by the Investigator. No AEs with a fatal outcome were reported; PPD from Cohort 2 died due to disease under investigation.

Part B: The median total duration of exposure (for olaparib/placebo, abiraterone and combination treatment) was longer in the olaparib+abiraterone arm (309 days [10.2 months], 338 days [11.1 months] and 339 days [11.2 months] for olaparib, abiraterone and combination treatment, respectively) compared with the placebo+abiraterone arm (253 days [8.3 months] each for placebo, abiraterone and combination treatment), which was consistent with the delayed time to disease progression. Median total and actual treatment durations were similar for each treatment, showing no significant impact of dose interruptions on treatment duration.

The number of patients who had at least 1 AE was higher in the olaparib+abiraterone arm when compared with the placebo+abiraterone arm (93.0% versus 80.3%). The majority of AEs were CTCAE Grade 1 or 2 in intensity. The most commonly reported AEs (>20% of patients) observed in the olaparib+abiraterone arm were: nausea (38.0%), anaemia (31.0%), constipation (25.4%), back pain (25.4%), asthenia (22.5%), fatigue (21.1%) and vomiting (21.1%). In the placebo+abiraterone arm, the most commonly reported AE (>20% of patients)

was nausea (21.1%). A higher percentage of patients in the olaparib+abiraterone arm, compared with the placebo+abiraterone arm, had AEs that were considered by the Investigator as related to both olaparib and abiraterone (45.1% versus 12.7%) and had AEs of CTCAE Grade ≥3 (53.5% versus 28.2%). The most commonly reported events of Grade ≥3 were anaemia (21.1% versus 0%) and pneumonia (5.6% versus 4.2%).

A difference in incidence of ≥10% (by preferred term) between patients in the olaparib+abiraterone arm compared with the placebo+abiraterone arm was seen for the following AEs: nausea (38.0% versus 21.1%), anaemia (31.0% versus 2.8%), constipation (25.4% versus 11.3%), cough (15.5% versus 2.8%), pyrexia (14.1% versus 1.4%) and neutropenia (11.3% versus 0%). Of these, nausea, anaemia, cough and neutropenia are events expected in patients treated with olaparib.

Of the AEs defined as adverse events of special interest (AESI), 3 patients had AEs from the category of pneumonitis and diffuse alveolar damage events: 2 patients in the olaparib+abiraterone arm had AEs of pneumonitis, 1 of which was fatal, and 1 patient in the placebo+abiraterone arm had an SAE of interstitial lung disease. Another 2 patients, both in the placebo+abiraterone arm, had new primary malignancies (malignant melanoma and squamous cell carcinoma of the tongue). There were no reports of myelodysplastic syndrome or acute myeloid leukaemia in the study.

The total number of deaths during Part B (including the survival follow-up period) was similar for both treatment groups: 60.6% of patients in the olaparib+abiraterone arm and 63.4% of patients in the placebo+abiraterone arm. The majority of reported deaths occurred ≥30 days after last treatment dose and were attributed to the disease under investigation (42.3% of patients in each arm). In total, there were 5 deaths attributed to an AE in the study; 4 in the olaparib+abiraterone arm (pneumonitis [considered by the Investigator as causally related], cardiac failure, ischaemic stroke and mediastinitis) and 1 in the placebo+abiraterone arm (pyelonephritis chronic).

More patients in the olaparib+abiraterone arm had SAEs compared with the placebo+abiraterone arm (35.2% versus 19.7%); 9.9% of patients in the olaparib+abiraterone arm had SAEs that were considered as related to study treatment versus 1.4% of patients in the placebo+abiraterone arm. The most commonly reported SAEs in the olaparib+abiraterone arm were anaemia, pneumonia and urinary tract infection.

Adverse events leading to discontinuation of olaparib/placebo were more commonly reported for patients in the olaparib+abiraterone arm compared with the placebo+abiraterone arm (29.6% versus 9.9%). Anaemia (5.6%) and nausea (4.2%) were the most commonly reported single events leading to discontinuation of study treatment for patients in the olaparib+abiraterone arm.

A higher percentage of patients in the olaparib+abiraterone arm compared with the placebo+abiraterone arm had AEs leading to dose reduction (16.9% versus 0%) or dose interruption (25.4% versus 11.3%). In the olaparib+abiraterone arm, anaemia (8.5%) was the

most common AE leading to dose reduction and the most common AEs leading to dose interruption were anaemia and urinary tract infection (4.2% each).

Cardiovascular events were more frequently reported in patients with mCRPC receiving olaparib in combination with abiraterone (olaparib+abiraterone arm) versus abiraterone alone (placebo+abiraterone arm). Overall, 7 patients in the olaparib+abiraterone arm had a total of 8 cardiovascular events of interest: myocardial infarction (4 events, including 1 patient who also reported a cerebrovascular disorder AE), cardiac failure (2 events), PPD and, of these, 2 events had a fatal outcome. The events with fatal outcome were ischaemic stroke and cardiac failure. There were 2 patients in the placebo+abiraterone arm who were reported with a cardiovascular event of interestPPD , neither of which had a fatal outcome.

Laboratory values for the haematology parameters of haemoglobin, neutrophils, leukocytes, platelets and lymphocytes showed decreases on olaparib+abiraterone treatment, consistent with the known safety profile of olaparib. With the exception of haemoglobin levels, the changes in haematological parameters observed on olaparib+abiraterone therapy were generally mild or moderate in severity with low numbers of patients with events of maximum CTCAE Grade 3 or 4.

Conclusion(s)

- In Part A of the study, at the time of assessment by the Safety Committee, no DLT had been reported and therefore they agreed to proceed with the dose of 300 mg bid in Part B of the study. Based on PK analysis, there appeared to be no evidence of changes in the exposure to olaparib when co-administered with abiraterone or vice versa; however, there were insufficient data to formally rule out a DDI and no statistical analyses were performed.

- In Part B, some of the baseline characteristics in the olaparib+abiraterone arm that could affect disease prognosis (eg, age, PSA, time from diagnosis to randomisation, AJCC staging at diagnosis) were worse than in the placebo+abiraterone arm. This may have skewed efficacy results in disfavour of the combination arm.

- The primary objective of Part B of the study regarding rPFS was met: a clinically meaningful and statistically significant improvement for olaparib+abiraterone-treated patients compared with placebo+abiraterone-treated patients was observed where HR was 0.651 (1-sided p=0.017; 2-sided p=0.034) and the median rPFS was 5.6 months longer in the olaparib+abiraterone arm than in the placebo+abiraterone arm (13.8 versus 8.2 months). The rPFS results were also consistent across predefined subgroups, including composite HRR mutation categories (positive, negative and partly characterised).

- Outcomes for the secondary efficacy endpoints of PFS2, TFST and TSST were numerically in favour of olaparib+abiraterone-treated patients. These data together indicated that the rPFS benefit of olaparib+abiraterone treatment was maintained

beyond the immediate treatment period and that olaparib+abiraterone provided a meaningful delay to when patients required further anticancer therapy. No detrimental effect on OS was seen. Objective response rate, PSA response and CTC conversion rate were similar between the olaparib+abiraterone arm and the placebo+abiraterone arm.

- The nature and severity of the observed AEs were consistent with the known safety profiles of olaparib or abiraterone. An imbalance was observed for cardiovascular events, which were more frequently reported in the olaparib+abiraterone arm than in the placebo+abiraterone arm.

- The clinical significance of the cardiovascular observations in the olaparib+abiraterone arm is unclear. The analysis of cardiovascular events from both arms was impacted by the size of the safety analysis set, some imbalances in relevant baseline characteristics, lack of confirmation of cardiac failure diagnoses and lack of biological plausibility that olaparib would contribute to, and increase, the cardiovascular risk over that known for abiraterone monotherapy.

- Based on the available data from this study, the benefit-risk profile of olaparib in combination with abiraterone is favourable in the target population, with a statistically significant and clinically meaningful increase in rPFS over abiraterone alone and a safety profile that is deemed acceptable and manageable.