Clinical Study Report Synopsis	
Drug Substance	Olaparib, Adavosertib (AZD1775), Ceralasertib (AZD6738)
Study Code	D5336C00001
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A Phase II, Open Label, Randomised, Multi-centre Study to Assess the Safety and Efficacy of Agents Targeting DNA Damage Repair in Combination with Olaparib versus Olaparib Monotherapy in the Treatment of Metastatic Triple Negative Breast Cancer Patients Stratified by Alterations in Homologous Recombinant Repair (HRR)-related Genes (including BRCA1/2) (VIOLETTE)

Study dates:
First subject enrolled: 21 February 2018
Last subject enrolled: 09 November 2020
Date of early study termination: 09 November 2020 (for meeting pre specified efficacy criteria to stop the study according to the interim analysis of Stratum A)
The analyses presented in this report are based on a data cut-off date of 13 November 2020 for Strata A and B and 08 November 2019 for Stratum C

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 Centres

A total of 95 study centres randomised at least one patient. This study was conducted in 15 countries in Asia, Europe, and North America (Belgium, Canada, Czech Republic, France, Germany, Ireland, Italy, Netherlands, Poland, Portugal, Republic of Korea, Spain, Taiwan, United Kingdom, and United States).

Publications

None at the time of writing this report.

Objectives and Criteria for Evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the efficacy of the combination of ceralasertib + olaparib and the combination of adavosertib + olaparib compared with olaparib monotherapy by assessment of PFS Patient populations: *BRCAm,* non *BRCAm HRRm*, non *HRRm*	• PFS using BICR according to RECIST 1.1 • Sensitivity analysis of PFS using Investigator assessments according to RECIST 1.1
Secondary	
• To assess the efficacy of the combination of ceralasertib + olaparib and the combination of adavosertib + olaparib compared with olaparib monotherapy by assessment of PFS Patient populations: *HRRm*, All	• PFS using BICR according to RECIST 1.1 • Sensitivity analysis of PFS using Investigator assessments according to RECIST 1.1
• To assess the efficacy of the combination of ceralasertib + olaparib and the combination of adavosertib + olaparib compared with olaparib monotherapy in terms of ORR Patient populations [a]: *BRCAm*, *HRRm*, non *BRCAm HRRm*, All, non *HRRm*	• Objective response using BICR according to RECIST 1.1 • Sensitivity analysis of objective response using Investigator assessments according to RECIST 1.1
• To assess the efficacy of the combination of ceralasertib + olaparib and the combination of adavosertib + olaparib compared with olaparib monotherapy in terms of DoR and tumour change Patient populations: *BRCAm*, non *BRCAm HRRm*, non *HRRm*	• DoR and tumour change using BICR according to RECIST 1.1 • Sensitivity analysis of DoR, and tumour change using Investigator assessments according to RECIST 1.1
• To assess the efficacy of the combination of ceralasertib + olaparib and the combination of adavosertib + olaparib compared with olaparib monotherapy in terms of OS Patient populations [a]: *BRCAm*, *HRRm*, non *BRCAm HRRm*, All, non *HRRm*	• Time to death for any cause
• To compare the efficacy of the combination of ceralasertib + olaparib with the combination of adavosertib + olaparib in terms of PFS and ORR	• PFS and objective response using BICR according to RECIST 1.1

Objectives	Endpoints
Patient populations [a]: *BRCAm*, *HRRm*, non *BRCAm HRRm*, All, non *HRRm*	• Sensitivity analysis of PFS and objective response using Investigator assessments according to RECIST 1.1
• To compare the efficacy of the combination of ceralasertib + olaparib with the combination of adavosertib + olaparib in terms of DoR and tumour change Patient populations: *BRCAm*, non *BRCAm HRRm*, non *HRRm*	• DoR and tumour change using BICR according to RECIST 1.1 • Sensitivity analysis of DoR and tumour change using Investigator assessments according to RECIST 1.1
• To compare the efficacy of the combination of ceralasertib + olaparib with the combination of adavosertib + olaparib in terms of OS Patient populations [a]: *BRCAm*, *HRRm*, non *BRCAm HRRm*, All, non *HRRm*	• Time to death for any cause
• To explore the frequency of and describe the nature of tumour HRR (including *BRCA*) mutation(s) in tumour samples and to compare this with germline *HRR* (including *BRCA*) mutation status [b] Patient population: All	• Mutation status of CCI genes
• To assess exposure to olaparib, ceralasertib, and adavosertib in all patients Patient population [a]: All	• Cmin,ss
Safety	
• To assess the safety and tolerability of the combination of ceralasertib + olaparib and the combination of adavosertib + olaparib compared with olaparib monotherapy Patient population [a]: All	• AEs (severity graded by CTCAE Version 4.03) • Laboratory tests (clinical chemistry, haematology, and urinalysis) • Vital signs (pulse and BP) • ECG data • ECOG PS
Exploratory	
• CCI	• C
• CCI	• CCI
• CCI	• CCI

Objectives	Endpoints
• CCI [redacted]	• CCI [redacted]

[a] The patient populations analysed differ from the planned analyses.
[b] The germline *HRR* mutation status of patients was not collected.
[c] Results of these exploratory analyses are reported outside of the CSR of this study.

Note: Study objectives are defined for the following patient populations: *BRCAm* = Patients from Stratum A (Patient Population A); *HRRm* = Patients from Stratum A and Stratum B (Patient Population D); Non *BRCAm HRRm* = Patients from Stratum B (Patient Population B); All = Patients from any stratum (Patient Population E); Non *HRRm* = Patients from Stratum C (Patient Population C).

Abbreviations: AE: Adverse event; BICR: Blinded independent central review; BP: Blood pressure; *BRCA*: Breast cancer susceptible gene; *BRCAm*: Breast cancer susceptible gene mutation; Cmin,ss: Minimum concentration at steady state; CSR: Clinical study report; CTCAE: Common Terminology Criteria for Adverse Event; CCI [redacted]; DoR: Duration of response; ECG: Electrocardiogram; ECOG PS: Eastern Cooperative Oncology Group performance status; CCI [redacted] HRR: Homologous recombination repair; *HRRm*: Homologous recombination repair gene mutation; CCI [redacted]; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; PRO: Patient-reported outcome; RECIST 1.1: Response Evaluation Criteria In Solid Tumours Version 1.1.

Study Design

This was a prospective, open-label, randomised, multi-centre Phase II study that assessed the efficacy and safety of olaparib monotherapy versus olaparib in combination with an inhibitor of ataxia telangiectasia and Rad3-related protein (ATR) (ceralasertib) and olaparib monotherapy versus olaparib in combination with an inhibitor of mitosis inhibitor protein kinase (WEE1) (adavosertib) in a second- or third-line setting in patients with triple-negative breast cancer (TNBC) prospectively stratified by presence/absence of qualifying tumour mutation in genes involved in the homologous recombination repair (HRR) pathway.

The study patient population was stratified as follows:

- Stratum A: Patients with mutations in *BRCA1* or *BRCA2* (*BRCAm*)
- Stratum B: Patients with mutations in any of CCI genes involved in the HRR pathway (CCI [redacted]) and no mutation in *BRCA1* and no mutation in *BRCA2* (non *BRCAm HRRm*)
- Stratum C: Patients without detected tumour mutations in any of the CCI genes in the HRR pathway mentioned above (non *HRRm*)

Within each Stratum A, B, and C there was further stratification by whether the patient received prior platinum-based therapy (yes/no).

The 3 treatment arms were:

- Treatment Arm 1: 300 mg twice daily (BD) olaparib continuous (28-day cycle)
- Treatment Arm 2: 160 mg once daily (OD) ceralasertib Days 1 to 7 and 300 mg BD olaparib continuous (28-day cycle)
- Treatment Arm 3: 150 mg BD adavosertib Days 1 to 3 and Days 8 to 10 and 200 mg BD olaparib continuous (21-day cycle). The adavosertib dose was reduced from 175 mg to 150 mg BD through implementation of clinical study protocol (CSP) Amendment 4, due to safety concerns.

Patients were randomised, using the randomisation ratio 1:1:1, to olaparib monotherapy, olaparib + ceralasertib combination therapy, or olaparib + adavosertib combination therapy.

Target Population and Sample Size

The key inclusion criteria were as follows: Male or female patients ≥ 18 years of age; progressive cancer at the time of study entry; histologically or cytologically confirmed TNBC at initial diagnosis with evidence of metastatic or incurable advanced locoregional disease; at least one and no more than 2 prior lines of treatment for metastatic or incurable advanced locoregional disease with an anthracycline and/or a taxane, unless contraindicated, in either the neo-adjuvant, adjuvant, or metastatic setting; confirmed presence of qualifying *HRR* mutation or absence of any *HRR* mutation in tumour tissue by the Lynparza *HRR* assay; at least one measurable lesion that could be accurately assessed at baseline by computed tomography.

Approximately 450 patients were planned to be randomised to one of the 3 treatment arms. Following the closure of the adavosertib + olaparib arm, the planned number of patients to be randomised was adjusted to approximately 350.

Investigational Products: Dosage, Mode of Administration and Batch Numbers

The investigational products (IPs) in this study were olaparib, ceralasertib, and adavosertib.

Table S2 Study Treatments

	Investigational Products		
IP Name:	Olaparib	Ceralasertib (AZD6738)	Adavosertib (AZD1775) *
Dose Formulation:	Film-coated tablet	Film-coated tablet	Dry-filled capsules
Dose Strength:	100 mg, 150 mg	20 mg, 80 mg, or 100 mg	25 mg, 50 mg, 75 mg, 100 mg, or 200 mg
Route of Administration:	Oral	Oral	Oral

	Investigational Products		
Dosing Instructions:	Administered continuously, tablets taken at the same time each day, approximately 12 hours apart, taken with approximately 250 mL water **Olaparib monotherapy treatment arm:** 300 mg (2 × 150 mg tablets) olaparib BD; without food restrictions; 28-day cycle **Ceralasertib + olaparib treatment arm:** 300 mg (2 × 150 mg tablets) olaparib BD, taken together with ceralasertib; fasting from at least 2 hours prior to ceralasertib dose to at least 1-hour post-dose; 28-day cycle **Adavosertib + olaparib treatment arm *:** 200 mg (2 × 100 mg tablets) olaparib BD; fasting from approximately 2 hours prior to AZD1775 dose to 2 hours post-dose; 21-day cycle Further details are provided in CSP Section 7.2 (Appendix 16.1.1)	Administered from Day 1 to Day 7 (inclusive) of every 28-day cycle, 160 mg OD, taken with approximately 250 mL water, fasting from at least 2 hours prior to dose to at least 1 hour post-dose Further details are provided in CSP Section 7.2 (Appendix 16.1.1)	Administered from Day 1 to Day 3 (inclusive) and Day 8 to Day 10 (inclusive) of every 21-day cycle, 150 mg BD, taken with approximately 250 mL water, fasting from approximately 2 hours prior to dose to 2 hours post-dose Further details are provided in CSP Section 7.2 (Appendix 16.1.1)
Batch/Lot Number(s):	Provided in Appendix 16.1.6 of the CSR		
Labelling:	Labels were prepared in accordance with GMP		
Provider/Sourcing:	AstraZeneca		

* The adavosertib + olaparib arm was closed in April 2019.

Abbreviations: BD: Twice daily; CSP: Clinical study protocol; CSR: Clinical study report; GMP: Good Manufacturing Practice; IP: Investigational product; OD: Once daily.

Duration of Treatment

The planned duration of treatment was until confirmed progressive disease (PD) or until any other discontinuation criteria were met.

Statistical Methods

General Principles:

Statistical analyses were done for 5 patient populations: *BRCAm* population (ie, patients from Stratum A; Patient Population A), non *BRCAm HRRm* population (ie, patients from Stratum B; Patient Population B), non *HRRm* population, (ie, patients from Stratum C; Patient

Population C), *HRRm* population (ie, patients from Stratum A and Stratum B; Patient Population D), All population (ie, patients from any stratum; Patient Population E).

All statistical tests were pairwise, ie, comparing 2 treatment arms and there were no "overall" tests of global null hypotheses (same distribution in all 3 treatment arms). Results of statistical analyses were presented using 2-sided 90% confidence intervals (CIs) and 2-sided p-values for pairwise comparisons between ceralasertib + olaparib versus olaparib monotherapy, adavosertib + olaparib versus olaparib monotherapy, and ceralasertib + olaparib versus adavosertib + olaparib (as secondary analysis).

The primary statistical analysis was the comparison of progression-free survival (PFS) based on blinded independent central review (BICR) for each combination treatment arm to olaparib for the 3 patient populations *BRCAm*, non *BRCAm HRRm*, and non *HRRm*. A secondary statistical analysis was the comparison of PFS based on BICR for each combination treatment arm to olaparib for the 2 patient populations *HRRm* and All.

Secondary outcome measures were analysed for the 3 patient populations *BRCAm*, non *BRCAm HRRm*, and non *HRRm*, except: objective response rate (ORR) (BICR only) was analysed for all 5 patient populations; tumour mutation status was analysed only for the All patient population; and PK outcome measures were analysed also for the All patient population. Response Evaluation Criteria In Solid Tumours Version 1.1 (RECIST)-based primary and secondary outcome measures based on Investigator assessments were also analysed for sensitivity purposes.

Safety outcome measures were analysed for the patient populations *BRCAm*, non *BRCAm HRRm*, non *HRRm*, and All. The exploratory outcome measure CCI [redacted] was analysed for the non *HRRm* patient population only due to early study termination.

Continuous variables (except those with censoring) were summarised by the number of observations (n), mean, standard deviation (SD), minimum, first quartile, median, third quartile, and maximum if the quartiles were included and the number of observations (n), mean, SD, median, minimum, maximum if the quartiles were excluded. Categorical variables were summarised by frequency counts and percentages for each category. Percentages were calculated using the number of observations with non-missing values as the denominator. Survival functions for right-censored time-to-event variables (ie, PFS and overall survival [OS]) were estimated by Kaplan-Meier product limit estimators and plotted over time (Kaplan-Meier curves).

Multiplicity adjustment were considered within each of the 3 patient populations *BRCAm*, non *BRCAm HRRm*, and non *HRRm* for PFS. No further adjustments for multiplicity were planned.

For the non *HRRm* population an interim analysis was triggered when 75 patients had been recruited and assessed for at least 8 weeks, in order to assess the proportion of patients with non-progressive disease.

For each of the 3 primary patient populations (*BRCAm*, non *BRCAm HRRm*, non *HRRm*) an interim analysis for PFS was planned to be triggered when 44 PFS events for the ceralasertib + olaparib versus olaparib monotherapy pairwise comparison in that particular patient population had occurred. In fact, interim analyses were performed for *BRCAm* and non *HRRm*; no interim analysis was performed for non *BRCAm HRRm*, given that this stratum had not reached the required number of events/patients at the time of early study termination.

For each of the 3 primary patient populations (*BRCAm*, non *BRCAm HRRm*, non *HRRm*) the final analysis for PFS was planned to be triggered when 68 PFS events for the ceralasertib + olaparib versus olaparib monotherapy pairwise comparison in that particular patient population had occurred. Only non *HRRm* had met the trigger for final analysis at the time of early study termination.

An initial OS analysis was performed at the same time as the primary analysis of PFS. A further analysis of OS was not performed as planned due to the early closure of the study.

Analysis Sets:

- Full Analysis Set (FAS): The FAS included all randomised patients with treatment arms assigned in accordance with the randomisation, regardless of the IP actually received.
- Safety Analysis Set: The Safety Analysis Set included all patients who received at least one dose of IP (regardless of whether that was the randomised IP intended or indeed whether, in rare cases, a patient received IP without being randomised), according to the IP they actually received.
- Pharmacokinetic (PK) Analysis Set: All patients who received at least one dose of IP per the protocol and for whom there was at least one reportable PK concentration included in the PK Analysis Set. The PK Analysis Set was a subset of the Safety Analysis Set and analyses using the PK Analysis Set were based on IP patients actually received.

Statistical Analyses:

- The primary analysis of PFS was based on BICR for patient populations *BRCAm*, non *BRCAm HRRm*, and non *HRRm*. The PFS was analysed using pairwise log-rank tests stratified for prior platinum-based therapy (yes/no) for generation of the p-value. Pairwise hazard ratios (HRs) and 2-sided 90% CIs were estimated from a proportional hazards model stratified for prior platinum-based therapy (yes/no). The 2-sided 80% and 60% CIs were also estimated. Kaplan-Meier curves for PFS were presented by treatment arm, overall, and separately by prior platinum-based therapy (yes/no). The primary analysis of PFS was repeated using Investigator-assessed RECIST data (sensitivity analysis).
- Analysis of objective response based on BICR included logistic regression model and was done for all 5 patient populations. The covariate study treatment of prior platinum-based

therapy was included only for patient populations *BRCAm*, *HRRm*, and All. Analysis of duration of response (DoR) based on BICR included DoR in responding patients estimated by Kaplan-Meier curves by treatment arm (for patient population *non HRRm*) and also displayed in swimmer plots (for patient populations *BRCAm*, non *BRCAm HRRm*, and non *HRRm*). Analysis of tumour size change at Week 16 based on BICR (for patient population non *HRRm*) included analysis of covariance (ANCOVA) or non-parametric ANCOVA model. The ANCOVA for tumour size change at Week 16 included factors for study treatment arms and prior platinum-based therapy and covariates of baseline target lesion tumour size and time from baseline scan to randomisation. Analysis of OS for the 3 main patient populations (*BRCAm*, non *BRCAm HRRm*, and non *HRRm*) was performed in analogy to the primary analysis of PFS.

- Total and actual exposure of all 3 IPs were summarised by treatment arm.
- Plasma concentrations for each measured drug substance were listed by nominal sample time and by treatment arm. Plasma concentrations at different time points were summarised using summary statistics.
- Adverse events and deaths were summarised by treatment arm.
- Safety laboratory test results were classified as low (below range), normal (within range), and high (above range); shift tables based on Common Terminology Criteria for Adverse Event (CTCAE) grade were provided; time courses of continuous safety laboratory test results were summarised graphically and in tables. Time courses of continuous vital signs variables were summarised graphically and in tables. A summary of QT interval corrected for heart rate using Fridericia's formula (QTcF) data over time by treatment arm was provided and boxplots were presented; shifts in QTcF results were summarised graphically and in tables; categorical electrocardiogram (ECG) variables were presented in frequency shift tables.
- A shift table for Eastern Cooperative Oncology Group performance status (ECOG PS) data was provided.

Decision to Close Adavosertib + Olaparib Arm and Decision to Stop the Study

In the meeting on 17 April 2019, the Independent Safety Review Committee (ISRC) recommended to close the adavosertib + olaparib arm across all biomarker strata as a result of increased toxicity and no suggestion of benefit (the adavosertib + olaparib arm met the pre-specified futility criteria). This recommendation was ratified by the AstraZeneca Unblinded Review Committee (URC) after review of efficacy data of Stratum C (futility interim analysis) and implemented in CSP Amendment 5. The ISRC and AstraZeneca URC agreed that the study should continue unchanged for the other 2 treatment arms. Investigators were notified of the ISRC's recommendation and the AstraZeneca URC's ratification and instructed to contact patients in the adavosertib + olaparib arm, who were advised to stop taking adavosertib immediately. Furthermore, it was recommended that all patients were reconsented and patients who received treatment with adavosertib + olaparib were to be offered the opportunity to continue olaparib monotherapy at the approved dose (300 mg BD) at the patient's next treatment cycle. Patients continued on olaparib monotherapy on a 21-day

cycle and increased to the approved dose at the start of their next treatment cycle ensuring a minimum 10-day wash-out period from adavosertib to olaparib 300 mg BD dosing to avoid drug-drug interaction.

On 05 November 2020, the AstraZeneca URC met to review the data outputs from the interim analysis of the *BRCAm* population (Stratum A) and recommended to stop the study, as the pre-specified criteria to stop the study based on the observed HR had been met. Investigators were notified on 09 November 2020. Any patients screened up until 09 November 2020 were permitted to be randomised within the 28-day window of screening. Furthermore, patients receiving treatment in the combination arm in Strata A and B (at that point in time there were no patients on the combination therapy in Stratum C) were to stop the combination treatment and switch to olaparib monotherapy. The end of the study was defined in the CSP as the point where the final OS analysis was completed for all 3 strata. After the decision to stop the study, this definition was no longer applicable.

Study Population

Study population data were analysed for Patient Populations A, B, C, and E. As per statistical analysis plan (SAP), study population data were not analysed for Patient Population D.

Patient Population A (Stratum A, *BRCAm*)

- A total of 117 patients were enrolled; of these, 96 (100.0%) patients were randomised to one of the 3 treatments arms (olaparib monotherapy, ceralasertib + olaparib combination therapy, and adavosertib + olaparib combination therapy) and included in the FAS.
- No notable differences between treatment arms regarding demographic and patient characteristics at baseline were reported. With regard to patient disease history, the majority of patients had an ECOG PS score of 0 in the olaparib monotherapy (27 [62.8%] patients) and in the ceralasertib + olaparib arm (25 [62.5%] patients), while the majority of patients in the adavosertib + olaparib arm (8 [61.5%] patients) had an ECOG PS score of 1.
- The majority of patients in the FAS received study treatment (93 [96.9%] patients); of the treated patients, the majority discontinued study treatment (27 [64.3%] patients in the olaparib arm, 25 [64.1%] patients in the ceralasertib + olaparib arm, and 11 [91.7%] patients in the adavosertib + olaparib arm). The main reason for discontinuation of olaparib treatment was disease progression (27 [64.3%] patients in the olaparib arm, 21 [53.8%] patients in the ceralasertib + olaparib arm, and 9 [75.0%] patients in the adavosertib + olaparib arm); the main reason for discontinuation of non-olaparib treatment was disease progression (22 [56.4%] patients in the ceralasertib + olaparib arm, and 2 [16.7%] patients in the adavosertib + olaparib arm). Among the treated patients, 3 (7.7%) patients in the ceralasertib + olaparib arm and 1 (8.3%) patient in the adavosertib + olaparib arm each discontinued olaparib treatment and non-olaparib treatment due to an adverse event (AE).

- After the adavosertib + olaparib arm was closed in April 2019 due to recommendation by the ISRC and ratification by the AstraZeneca URC, 8 (66.7%) patients in that treatment arm continued with olaparib monotherapy.
- At the time of data cut-off (13 November 2020), 59 (61.5%) patients were ongoing in the study (ie, were on treatment or in Survival Follow-up). Among those patients who terminated the study (37 [38.5%] patients), the main reason for termination was death (31 [32.3%] of treated patients).
- All 96 patients randomised in Stratum A were included in the FAS; of these, 3 patients were excluded from the Safety Analysis Set because they did not receive treatment and a further 2 patients were excluded from the PK Analysis Set because they had no reportable PK concentration data.

Patient Population B (Stratum B, non *BRCAm HRRm*)

- A total of 75 patients were enrolled; of these, 47 (100.0%) patients were randomised to one of the 3 treatments arms (olaparib monotherapy, ceralasertib + olaparib combination therapy, and adavosertib + olaparib combination therapy) and included in the FAS.
- No notable differences between treatment arms regarding demographic and patient characteristics at baseline were reported. With regard to patient disease history, there were some numerical differences regarding the tumour grade between the adavosertib + olaparib arm and the 2 other treatment arms.
- The majority of patients in the FAS received study treatment (46 [97.9%] patients); of the treated patients, the majority discontinued study treatment (16 [84.2%] patients in the olaparib arm, 15 [75.0%] patients in the ceralasertib + olaparib arm, and 7 [100.0%] patients in the adavosertib + olaparib arm). The main reason for discontinuation of olaparib treatment was disease progression (16 [84.2%] patients in the olaparib arm, 13 [65.0%] patients in the ceralasertib + olaparib arm, and 5 [71.4%] patients in the adavosertib + olaparib arm); the main reason for discontinuation of non-olaparib treatment was disease progression (13 [65.0%] patients in the ceralasertib + olaparib arm, and 3 [42.9%] patients in the adavosertib + olaparib arm). Among the treated patients, 2 (10.0%) patients in the ceralasertib + olaparib arm discontinued olaparib treatment and non-olaparib treatment due to an AE.
- After the adavosertib + olaparib arm was closed in April 2019 due to recommendation by the ISRC and ratification by the AstraZeneca URC, 3 (42.9%) patients in that treatment arm continued with olaparib monotherapy.
- At the time of data cut-off (13 November 2020), 20 (42.6%) patients were ongoing in the study (ie, were on treatment or in Survival Follow-up). Among those patients who terminated the study (27 [57.4%] patients), the main reason for termination was death (25 [53.2%] of treated patients).
- All 47 patients randomised in Stratum B were included in the FAS; of these, 1 patient was excluded from the Safety Analysis Set because the patient did not receive treatment and a further 3 patients were excluded from the PK Analysis Set because they had no reportable PK concentration data.

Patient Population C (Stratum C, non *HRRm*)

- A total of 293 patients were enrolled in Patient Population C; of these, 130 (100.0%) patients were randomised to one of the 3 treatment arms (olaparib monotherapy, ceralasertib + olaparib combination therapy, and adavosertib + olaparib combination therapy) and included in the FAS.
- No notable differences between treatment arms regarding demographic and patient characteristics at baseline were reported. With regard to patient disease history, the majority of patients in the adavosertib + olaparib arm (19 [70.4%] patients) had an ECOG PS score of 0, while in the olaparib monotherapy arm and in the ceralasertib + olaparib arm the percentages of patients with ECOG PS scores of 0 or 1 were similar (0: 28 [54.9%] patients in the olaparib monotherapy arm and 26 [50.0%] patients in the ceralasertib + olaparib arm; 1: 23 [45.1%] patients in the olaparib monotherapy arm and 26 [50.0%] patients in the ceralasertib + olaparib arm).
- The majority of patients in the FAS received study treatment (126 [96.9%] patients); of the treated patients, the majority discontinued study treatment (41 [83.7%] patients in the olaparib arm, 41 [82.0%] patients in the ceralasertib + olaparib arm, and 25 [92.6%] patients in the adavosertib + olaparib arm). The main reason for discontinuation of olaparib treatment was disease progression (38 [77.6%] patients in the olaparib arm, 35 [70.0%] patients in the ceralasertib + olaparib arm, and 14 [51.9%] patients in the adavosertib + olaparib arm); the main reason for discontinuation of non-olaparib treatment was disease progression (37 [74.0%] patients in the ceralasertib + olaparib arm, and 12 [44.4%] patients in the adavosertib + olaparib arm). Among the treated patients, 4 (8.0%) patients in the ceralasertib + olaparib arm and 7 (25.9%) patients in the adavosertib + olaparib arm each discontinued olaparib treatment and no patients discontinued non-olaparib treatment due to an AE.
- After the adavosertib + olaparib arm was closed in April 2019 due to recommendation by the ISRC and ratification by the AstraZeneca URC, 4 (14.8%) patients in that treatment arm continued with olaparib monotherapy.
- At the time of data cut-off (08 November 2019), 63 (48.5%) patients were ongoing in the study (ie, were on treatment or in Survival Follow-up). Among those patients who terminated the study (67 [51.5%] patients), the main reason for termination was death (52 [40.0%] of treated patients), followed by patient withdrawal (10 [7.7%] of treated patients).
- All 130 patients randomised in Stratum C were included in the FAS; of these 4 patients were excluded from the Safety Analysis Set because they did not receive treatment and a further 6 patients were excluded from the PK Analysis Set because they had no reportable PK concentration data.

Patient Population E (Strata A, B, and C)

- Overall, across Strata A, B, and C a total of 273 (100.0%) patients completed Screening Part 2 and were randomised to one of the 3 treatment arms and included in the FAS (olaparib monotherapy arm 114 patients, ceralasertib + olaparib arm 112 patients, and adavosertib + olaparib arm 47 patients).

- No notable differences between treatment arms regarding demographic and patient characteristics at baseline were reported.
- The majority of patients in the FAS received study treatment (265 [97.1%] patients); of the treated patients, the majority discontinued study treatment (84 [76.4%] patients in the olaparib arm, 81 [74.3%] patients in the ceralasertib + olaparib arm, and 43 [93.5%] patients in the adavosertib + olaparib arm). The main reason for discontinuation of olaparib treatment was disease progression (81 [73.6%] patients in the olaparib arm, 69 [63.3%] patients in the ceralasertib + olaparib arm, and 28 [60.9%] patients in the adavosertib + olaparib arm); the main reason for discontinuation of non-olaparib treatment was disease progression (72 [66.1%] patients in the ceralasertib + olaparib arm, and 17 [37.0%] patients in the adavosertib + olaparib arm). Among the treated patients, 9 (8.3%) patients in the ceralasertib + olaparib arm and 8 (17.4%) patients in the adavosertib + olaparib arm each discontinued olaparib treatment and non-olaparib treatment due to an AE.
- After the adavosertib + olaparib arm was closed in April 2019 due to recommendation by the ISRC and ratification by the AstraZeneca URC, 15 (32.6%) patients in that treatment arm continued with olaparib monotherapy.
- At the time of data cut-off (13 November 2020 for Strata A and B and 08 November 2019 for Stratum C), 142 (52.0%) patients were ongoing in the study (ie, were on treatment or in Survival Follow-up). Among those patients who terminated the study (131 [48.0%] patients); the main reason for termination was death (108 [39.6%] of treated patients), followed by patient withdrawal (12 [4.4%] of treated patients).
- Overall, 196 (71.8%) patients had at least one important protocol deviation. The percentage of patients in each treatment arm with at least one important protocol was similar across all 3 treatment arms (olaparib monotherapy arm 68.4%, ceralasertib + olaparib arm 72.3%, and adavosertib + olaparib arm 78.7%). The main categories of important protocol deviations concerned informed consent (79 [28.9%] patients), visit schedule (72 [26.4%] patients), administration of study treatment (65 [23.8%] patients), inclusion/exclusion criteria (54 [19.8%] patients), and procedures/tests (34 [12.5%] patients). Overall, 4 (1.5%) patients had at least one COVID-19-related important protocol deviation.

<u>Overall Conclusions for the Patient Populations</u>

- Overall, a high number of important protocol deviations was recorded. In accordance with the SAP, a per-protocol analysis was not performed, and individual data points were not excluded from the analyses due to important protocol deviations. The percentage of patients who had at least one important protocol deviation was approximately 70% in each of Patient Populations A, B, and C. While the high number of important protocol deviations needs to be acknowledged, individual important protocol deviations were very heterogeneous in nature. The high number of protocol deviations by itself does not change the interpretation of the final study results. Following a patient-level safety review of patients with important protocol deviations related to inclusion/exclusion criteria and who also experienced a serious adverse event (SAE), there was no evidence that these patients exhibited any additional significant safety concerns that were attributable to the study treatment as a result of the important protocol deviation.

- There were largely no imbalances between the 3 treatment arms with regard to demographic and baseline characteristics, medical history, and prior and concomitant medications.
- The patient population recruited to the study was representative of the target population for the IPs. The disease history and medical history was generally typical of a population of patients with advanced TNBC. The concomitant medications used were generally typical of the co-morbidities seen in a population of patients with TNBC and reasonable in the clinical context.
- Because of the early closure of the adavosertib + olaparib arm, and thus lower number of patients randomised to this arm, interpretation of any differences between this arm and the other treatment arms is limited.

Summary of Efficacy Results

The ISRC recommended to close the adavosertib + olaparib arm across all biomarker strata as a result of increased toxicity and no suggestion of benefit (review of unblinded safety outputs of Strata A, B, and C, with focus on Stratum C; 17 April 2019). This recommendation was ratified by the AstraZeneca URC after review of efficacy data of Stratum C (futility interim analysis; 17 April 2019). The interpretation of efficacy results of the adavosertib + olaparib arm and comparison with the olaparib monotherapy arm and ceralasertib + olaparib arm is limited due to a lower number of patients with available data in the adavosertib + olaparib arm, the nature of the analysis (intent-to-treat), and the fact that some of the patients switched from adavosertib + olaparib treatment to olaparib monotherapy. Furthermore, the study was stopped following recommendation by the AstraZeneca URC after the interim analysis of Stratum A data (05 November 2020).

Patient Population A (Stratum A, *BRCAm*)

- According to the primary efficacy analysis of PFS in patients with tumour mutation status *BRCAm*, there was no statistically significant difference in PFS per BICR between olaparib monotherapy and ceralasertib + olaparib combination therapy (HR [90% CI; p-value] was 1.02 [0.63, 1.66; 0.9403] for the ceralasertib + olaparib versus olaparib comparison). This finding was confirmed in several sensitivity analyses, including Investigator assessment of PFS.
- Secondary efficacy analyses:
  - The odds ratio (90% CI; likelihood ratio p-value) for the comparison of ORR of ceralasertib + olaparib versus olaparib was 1.25 (0.61, 2.61; 0.6090). There was no statistically significant difference between olaparib monotherapy and ceralasertib + olaparib combination therapy with regard to ORR per BICR.
  - The number (percentage) of patients with an objective response (complete response [CR] or partial response [PR]) was 19 (44.2%) patients in the olaparib monotherapy arm and 20 (50.0%) patients in the ceralasertib + olaparib arm. The median DoR of

responders per BICR from onset of response was 20.0 weeks in the olaparib monotherapy arm and 32.0 weeks in the ceralasertib + olaparib arm.

- The change in target lesions per BICR at Week 16 was similar in the olaparib monotherapy arm and ceralasertib + olaparib combination therapy arm (mean change [SD] was -27.7% [34.33] in the olaparib monotherapy arm versus -33.8% [37.77] in the ceralasertib + olaparib combination therapy arm).
- The OS data were immature; it is not possible to draw a conclusion on OS benefit at this data cut.

Patient Population B (Stratum B, non *BRCAm HRRm*)

- According to the primary efficacy analysis of PFS in patients with tumour mutation status non *BRCAm HRRm*, there was no statistically significant difference in PFS per BICR between olaparib monotherapy and ceralasertib + olaparib combination therapy; however, there was a numerical difference in favour of the combination therapy (HR [90% CI; p-value] was 0.54 [0.28, 1.03; 0.1274] for the ceralasertib + olaparib versus olaparib comparison). The lack of a statistically significant difference between both treatment arms was confirmed in several sensitivity analyses, including Investigator assessment of PFS.
- Secondary efficacy analyses:
  - The odds ratio (90% CI; likelihood ratio p-value) for the comparison of ORR of ceralasertib + olaparib versus olaparib was 1.42 (0.36, 6.02; 0.6769). There was no statistically significant difference between olaparib monotherapy and ceralasertib + olaparib combination therapy with regard to ORR per BICR.
  - The number (percentage) of patients with an objective response (CR or PR) was 3 (15.0%) patients in the olaparib monotherapy arm and 4 (20.0%) patients in the ceralasertib + olaparib arm. The median DoR of responders per BICR from onset of response was 16.8 weeks in the olaparib monotherapy arm and 17.1 weeks in the ceralasertib + olaparib arm.
  - The change in target lesions per BICR at Week 16 was similar in the olaparib monotherapy arm and ceralasertib + olaparib combination therapy arm (mean change [SD] was 4.9% [35.78] in the olaparib monotherapy arm versus 4.9% [35.72] in the ceralasertib + olaparib combination therapy arm).
  - The OS data were immature; it is not possible to draw a conclusion on OS benefit at this data cut.

Patient Population C (Stratum C, non *HRRm*)

- According to the primary efficacy analysis of PFS in patients with tumour mutation status non *HRRm*, there was no statistically significant difference in PFS per BICR between olaparib monotherapy and ceralasertib + olaparib combination therapy (HR [90% CI; p-value] was 0.76 [0.50, 1.14; 0.2959] for the ceralasertib + olaparib versus olaparib

comparison). This finding was confirmed in several sensitivity analyses, including Investigator assessment of PFS.

- Analysis of PFS by subgroups (prior platinum treatment, age group, line of therapy in metastatic setting, site of metastases, previous treatment with immuno-oncology drugs) indicated a statistically significant difference between ceralasertib + olaparib combination therapy versus olaparib monotherapy in the group of patients previously treated with immune-oncology drugs (HR [90% CI] was 0.35 [0.13, 0.92]). All other subgroups indicated no statistically significant differences. This interpretation is limited by the relatively small number of patients in the subgroups.
- Secondary efficacy endpoint analyses:
  - There was a statistically significant difference between olaparib monotherapy and ceralasertib + olaparib combination therapy with regard to ORR per BICR, favouring the ceralasertib + olaparib combination therapy (odds ratio [90% CI; p-value] was 4.45 [1.30, 21.20; 0.0425] for the ceralasertib + olaparib versus olaparib comparison). This finding was supported by the sensitivity analysis based on Investigator assessment of ORR (odds ratio [90% CI; p-value] was 13.41 [3.11, 134.65; 0.0011] for the ceralasertib + olaparib versus olaparib comparison). Given the result of the primary analysis, ie, no statistically significant differences in PFS, the interpretation of the clinical meaningfulness of the difference in ORR is limited.
  - The number (percentage) of patients with an objective response (CR or PR) was 2 (3.9%) patients in the olaparib monotherapy arm and 8 (15.4%) patients in the ceralasertib + olaparib arm. The median DoR of responders per BICR from onset of response was 11.4 weeks in the olaparib monotherapy arm versus 24.1 weeks in the ceralasertib + olaparib combination therapy arm.
  - The change in target lesion size at Week 16 indicated an increase in the ceralasertib + olaparib arm and in the olaparib monotherapy arm (mean [SD] change was 5.7% [40.46] for ceralasertib + olaparib versus 40.3% [76.18] for olaparib). There was a statistically significantly smaller increase in the ceralasertib + olaparib arm compared to the olaparib monotherapy arm (Least-squares mean difference [90% CI; p-value] was -34.56 [-54.61, -14.51; 0.0051] for the ceralasertib + olaparib versus olaparib comparison). The sensitivity analysis of target lesions at Week 16 based on Investigator assessment also showed a statistically significantly smaller change in tumour lesion size in the ceralasertib + olaparib arm compared to olaparib monotherapy. Given the result of the primary analysis, ie, no statistically significant difference in PFS, the interpretation of the clinical meaningfulness of the difference in tumour target size is limited.
  - The OS data were immature; it is not possible to draw a conclusion on OS benefit at this data cut.
  - There were no striking findings and no clinically meaningful difference between treatment arms for any of the CCI [redacted]

CCI

Patient Population D (Strata A and B, *HRRm*)

- According to the secondary efficacy analysis of patients with tumour mutation status *HRRm*, there was no statistically significant difference between olaparib monotherapy and ceralasertib + olaparib combination therapy with regard to PFS per BICR.
- There was no statistically significant difference between olaparib monotherapy and ceralasertib + olaparib combination therapy with regard to ORR per BICR.

Patient Population E (Strata A, B, and C)

- According to the secondary efficacy analysis of all patients, there was no statistically significant difference between olaparib monotherapy and ceralasertib + olaparib combination therapy with regard to PFS per BICR.
- There was no statistically significant difference between olaparib monotherapy and ceralasertib + olaparib combination therapy with regard to ORR per BICR.

Summary of Pharmacokinetic Results

The exposure to olaparib measured as Cmin,ss at steady state after doses of 300 mg, as monotherapy or in combination with ceralasertib, in this study was as expected and consistent with data for the equivalent dose from other studies.

Summary of Safety Results

Patient Population A (Stratum A, *BRCAm*)

- The median total treatment duration (min [last dose date where dose > 0 mg, date of death, date of data cut-off] - first dose date + 1) and the median actual treatment duration (total exposure, excluding dose interruptions) of olaparib were 173.5 and 166.0 days, respectively, in the olaparib monotherapy arm; both 183.0 days in the ceralasertib + olaparib arm; and 147.5 and 142.5 days, respectively, in the adavosertib + olaparib arm. The median total treatment duration and median actual treatment duration of ceralasertib in the ceralasertib + olaparib arm were both 175.0 days. The median total treatment duration and median actual treatment duration of adavosertib in the adavosertib + olaparib arm were 86.5 and 83.5 days, respectively.
- The mean relative dose intensity of olaparib was 93.90% in the olaparib monotherapy arm, 84.91% in the ceralasertib + olaparib arm, and 95.82% in the adavosertib + olaparib arm. The mean relative dose intensity of ceralasertib in the ceralasertib + olaparib arm was 91.72%. The mean relative dose intensity of adavosertib in the adavosertib + olaparib arm was 83.32%.
- AEs of any category were reported for 39 (92.9%) patients in the olaparib monotherapy arm, 38 (97.4%) patients in the ceralasertib + olaparib arm, and 12 (100.0%) patients in the adavosertib + olaparib arm. The most frequently reported AEs (reported by at least 25% of patients in a given treatment arm) by preferred term (PT) were as follows:

  - Olaparib monotherapy arm: Nausea (22 [52.4%] patients), anaemia (16 [38.1%] patients), vomiting (13 [31.0%] patients), fatigue (12 [28.6%] patients), and asthenia (11 [26.2%] patients)
  - Ceralasertib + olaparib arm: Anaemia and nausea (22 [56.4%] patients each), asthenia (15 [38.5%] patients), and fatigue (12 [30.8%] patients)
  - Adavosertib + olaparib arm: Anaemia and neutropenia (8 [66.7%] patients each), diarrhoea, fatigue, and nausea (7 [58.3%] patients each), vomiting (5 [41.7%] patients), leukopenia (4 [33.3%] patients), constipation, alanine aminotransferase increased, platelet count decreased, and decreased appetite (3 [25.0%] patients each)
- AEs of CTCAE Grade 3 or higher were reported for 11 (26.2%) patients in the olaparib monotherapy arm, 17 (43.6%) patients in the ceralasertib + olaparib arm, and 10 (83.3%) patients in the adavosertib + olaparib arm. The most frequently reported events of CTCAE Grade 3 or higher by system organ class (SOC) (reported by at least 20% of patients in any treatment arm) were as follows:
  - Ceralasertib + olaparib arm: Blood and lymphatic system disorders (12 [30.8%] patients)
  - Adavosertib + olaparib arm: Blood and lymphatic system disorders (7 [58.3%] patients), gastrointestinal disorders, and general disorders and administration site conditions (3 [25.0%] patients each)
- AEs causally related to olaparib were reported for 32 (76.2%) patients in the olaparib monotherapy arm, 34 (87.2%) patients in the ceralasertib + olaparib arm, and 12 (100.0%) patients in the adavosertib + olaparib arm. Adverse events causally related to ceralasertib were reported for 34 (87.2%) patients and AEs causally related to ceralasertib and olaparib were reported for 34 (87.2%) patients. Adverse events causally related to adavosertib were reported for 12 (100.0%) patients and AEs causally related to adavosertib and olaparib were reported for 12 (100.0%) patients.
- In the ceralasertib + olaparib arm, 1 adverse event of special interest (AESI) in the category of pneumonitis was reported; 1 (2.6%) patient experienced an AE of pneumonitis. This event occurred 101 days after the start of study treatment and resolved after 30 days. The AE was considered causally related to olaparib and ceralasertib and led to the permanent discontinuation of ceralasertib and olaparib.
- In the ceralasertib + olaparib arm, 1 AESI in the category of new primary malignancy (other than myelodysplastic syndrome [MDS]/ acute myeloid leukemia [AML]) was reported for 1 patient, the event occurred after the 30-day follow-up period. The patient experienced an SAE of cholangiocarcinoma 303 days after first dose of study treatment. The patient died 436 days after first dose of study treatment (296 days after the last dose of study medication) and the primary cause of death was assessed by the Investigator to be cholangiocarcinoma. The SAE was not considered causally related to olaparib or ceralasertib.
- A total of 12 (27.9%) patients in the olaparib monotherapy arm, 14 (35.0%) patients in the ceralasertib + olaparib arm and 5 (38.5%) patients in the adavosertib + olaparib arm

died during the study. The majority of deaths were related to the disease under study. None of the deaths were considered to be causally related to the study treatment.

- SAEs were reported for 8 (19.0%) patients in the olaparib monotherapy arm, 6 (15.4%) patients in the ceralasertib + olaparib arm, and 6 (50.0%) patients in the adavosertib + olaparib arm. Serious AEs reported for at least 2 patients by PT were as follows:
  - Olaparib monotherapy arm: Anaemia (2 [4.8%] patients)
  - Ceralasertib + olaparib arm: Anaemia (2 [5.1%] patients)
  - Adavosertib + olaparib arm: Febrile neutropenia and neutropenia (2 [16.7%] patients each)
- AEs leading to discontinuation of study treatment were reported for none of the patients in the olaparib monotherapy arm, 4 (10.3%) patients in the ceralasertib + olaparib arm, and 1 (8.3%) patient in the adavosertib + olaparib arm. There were no AEs leading to discontinuation of treatment reported for at least 2 patients by PT in any of the treatment arms.
- AEs leading to reduction of study treatment were reported for 8 (19.0%) patients in the olaparib monotherapy arm, 14 (35.9%) patients in the ceralasertib + olaparib arm, and 8 (66.7%) patients in the adavosertib + olaparib arm.
- AEs leading to the interruption of olaparib were reported for 17 (40.5%) patients in the olaparib monotherapy arm, 9 (23.1%) patients in the ceralasertib + olaparib arm, and 4 (33.3%) patients in the adavosertib + olaparib arm. Adverse events leading to interruption of ceralasertib were reported for 11 (28.2%) patients and AEs leading to interruption of adavosertib were reported for 7 (58.3%) patients.
- There were no clinically important trends or changes over time from baseline in clinical chemistry, and urinalysis parameters. Across the haematology and clinical chemistry parameters, excursions of values outside the reference ranges over time were reported; these are in line with the patient population and their disease status.
- There were clinically important trends or changes over time from baseline in haematology, in particular in leucocytes, neutrophils and platelets.
- Some haematology abnormalities were reported as AEs and SAEs. The following haematology abnormalities were reported as SAEs:
  - Olaparib monotherapy arm: Anaemia (2 [4.8%] patients)
  - Ceralasertib + olaparib arm: Anaemia (2 [5.1%] patients) and normocytic anaemia (1 [2.6%] patient; led to discontinuation of study treatment)
  - Adavosertib + olaparib arm: Febrile neutropenia and neutropenia (2 [16.7%] patients each), leukopenia and thrombocytopenia (1 [8.3%] patient each)
- Some clinical chemistry laboratory abnormalities were reported as AEs, none were reported as SAEs.
- In the ceralasertib + olaparib arm, 1 (2.6%) patient had values of alanine aminotransferase (ALT) $\geq 3 \times$ upper limit of normal (ULN) or aspartate aminotransferase (AST) $\geq 3 \times$ ULN and total bilirubin $\geq 2 \times$ ULN. The case was discussed as a potential Hy's

Law case and it was concluded that the case was not a Hy's Law case, but was related to disease progression (liver metastases).

- There were no clinically important trends or changes over time from baseline in vital signs and ECGs, or QTcFs in particular. One ECG abnormality was reported as an AE:
  - Olaparib monotherapy arm: Atrioventricular block first degree (1 [2.4%] patient)
- There were no clinically significant changes in physical examination reported as AEs in this study.
- Overall, the safety and tolerability profile in Stratum A was consistent with the known safety profiles for olaparib monotherapy and ceralasertib + olaparib combination therapy, and no unexpected safety findings were detected in these arms. The adavosertib + olaparib combination was closed due to a higher-than-expected incidence of haematological toxicity (febrile neutropenia), which resulted in the submission of 2 Urgent Safety Measures. The adavosertib + olaparib combination was subsequently discontinued due to increased toxicity and no suggestion of benefit.

<u>Patient Population B (Stratum B, non *BRCAm HRRm*)</u>

- The median total treatment duration and median actual treatment duration of olaparib were both 96.0 days in the olaparib monotherapy arm; 83.5 and 59.5 days, respectively, in the ceralasertib + olaparib arm; and 52.0 and 45.0 days, respectively, in the adavosertib + olaparib arm. The median total treatment duration and median actual treatment duration of ceralasertib in the ceralasertib + olaparib arm were 67.0 and 57.5 days, respectively. The median total treatment duration and median actual treatment duration of adavosertib in the adavosertib + olaparib arm were 40.0 and 30.0 days, respectively.
- The mean relative dose intensity of olaparib was 94.77% in the olaparib monotherapy arm, 87.96% in the ceralasertib + olaparib combination therapy arm, and 107.80% in the adavosertib + olaparib combination therapy arm. The mean relative dose intensity of ceralasertib in the ceralasertib + olaparib arm was 96.51%. The mean relative dose intensity of adavosertib in the adavosertib + olaparib arm was 99.37%.
- AEs of any category were reported for 18 (94.7%) patients in the olaparib monotherapy arm, 19 (95.0%) patients in the ceralasertib + olaparib arm, and 7 (100.0%) patients in the adavosertib + olaparib arm. The most frequently reported AEs (reported by at least 25% of patients in a given treatment arm) by PT were as follows:
  - Olaparib monotherapy arm: Nausea (8 [42.1%] patients), anaemia, fatigue, and vomiting (5 [26.3%] patients each)
  - Ceralasertib + olaparib arm: Nausea (11 [55.0%] patients), anaemia (10 [50.0%] patients), neutropenia, and vomiting (6 [30.0%] patients each), asthenia, and diarrhoea (5 [25.0%] patients each)
  - Adavosertib + olaparib arm: Nausea and white blood cell count decreased (4 [57.1%] patients each), abdominal pain, diarrhoea, and vomiting (3 [42.9%] patients each), alanine aminotransferase increased, arthralgia, aspartate aminotransferase increased, asthenia, constipation, decreased appetite, fatigue, neutropenia, neutrophil count

decreased, platelet count decreased, and upper respiratory tract infection (2 [28.6%] patients each)

- AEs of CTCAE Grade 3 or higher were reported for 6 (31.6%) patients in the olaparib monotherapy arm, 9 (45.0%) patients in the ceralasertib + olaparib arm, and 6 (85.7%) patients in the adavosertib + olaparib arm. The most frequently reported events of CTCAE Grade 3 or higher by SOC (reported by at least 20% of patients in any treatment arm) were as follows:
  - Ceralasertib + olaparib arm: Blood and lymphatic system disorders (7 [35.0%] patients)
  - Adavosertib + olaparib arm: Investigations (4 [57.1%] patients), blood and lymphatic system disorders, and infections and infestations (2 [28.6%] patients each)
- AEs causally related to olaparib were reported for 17 (89.5%) patients in the olaparib monotherapy arm, 17 (85.0%) patients in the ceralasertib + olaparib arm, and 7 (100.0%) patients in the adavosertib + olaparib arm. Adverse events causally related to ceralasertib were reported for 16 (80.0%) patients and AEs causally related to ceralasertib and olaparib were reported for 16 (80.0%) patients. Adverse events causally related to adavosertib were reported for 7 (100.0%) patients and AEs causally related to adavosertib and olaparib were reported for 7 (100.0%) patients.
- In the adavosertib + olaparib arm, 1 AESI in the category of MDS was reported; 1 (14.3%) patient experienced an SAE of pancytopenia. The event occurred 22 days after the start of study treatment and resolved after 5 days, MDS/AML was not diagnosed. The SAE was considered causally related to olaparib and adavosertib and led to the interruption of olaparib and adavosertib.
- A total of 12 (60.0%) patients in the olaparib monotherapy arm, 8 (40.0%) patients in the ceralasertib + olaparib arm, and 5 (71.4%) patients in the adavosertib + olaparib arm died during the study. The majority of deaths were related to the disease under study. None of the deaths were considered to be causally related to the study treatment.
- SAEs were reported for 2 (10.5%) patients in the olaparib monotherapy arm, 5 (25.0%) patients in the ceralasertib + olaparib arm, and 4 (57.1%) patients in the adavosertib + olaparib arm. There were no SAEs reported for at least 2 patients by PT in any of the treatment arms.
- AEs leading to discontinuation of study treatment were reported for none of the patients in the olaparib monotherapy arm, 3 (15.0%) patients in the ceralasertib + olaparib arm, and 1 (14.3%) patient in the adavosertib + olaparib arm. Adverse events leading to the discontinuation of treatment reported for at least 2 patients by PT were as follows:
  - Ceralasertib + olaparib arm: Neutrophil count decreased (2 [10.0%] of patients)
- AEs leading to reduction of study treatment were reported for none of the patients in the olaparib monotherapy arm, 5 (25.0%) patients in the ceralasertib + olaparib arm, and 1 (14.3%) patient in the adavosertib + olaparib arm.
- AEs leading to the interruption of olaparib were 2 (10.5%) patients in the olaparib monotherapy arm, 8 (40.0%) patients in the ceralasertib + olaparib arm, and 3 (42.9%) patients in the adavosertib + olaparib arm. Adverse events leading to interruption of

ceralasertib were reported for 5 (25.0%) patients and AEs leading to interruption of adavosertib were reported for 3 (42.9%) patients.

- There were no clinically important trends or changes over time from baseline in clinical chemistry, and urinalysis parameters. Across the haematology and clinical chemistry parameters, excursions of values outside the reference ranges over time were reported; these are in line with the patient population and their disease status.
- There were clinically important trends or changes over time from baseline in haematology, in particular in leucocytes, neutrophils and platelets.
- Some haematology abnormalities were reported as AEs and SAEs. The following haematology abnormalities were reported as SAEs:
  - Ceralasertib + olaparib arm: Anaemia, febrile neutropenia, and platelet count decreased (1 [5.0%] patient each)
  - Adavosertib + olaparib arm: Neutropenia, pancytopenia, and white blood cell count decreased (1 [14.3%] patient each)
- Some clinical chemistry laboratory abnormalities were reported as AEs and SAEs. The following clinical chemistry laboratory abnormality was reported as an SAE:
  - Adavosertib + olaparib arm: Hyperglycaemia (1 [14.3%] patient)
- None of the patients met the criteria for a potential Hy's Law case.
- There were no clinically important trends or changes over time from baseline in vital signs and ECGs, or QTcFs in particular. One patient in the olaparib monotherapy arm had QTcF of > 500 msec 1 day after their last dose of study treatment. The following ECG abnormalities were reported as AEs:
  - Olaparib monotherapy arm: Sinus tachycardia (1 [5.3%] patient)
  - Adavosertib + olaparib arm: Tachycardia (1 [14.3%] patient; reported as an unrelated SAE).
- There were no clinically significant changes in physical examination reported as AEs in this study.
- Overall, the safety and tolerability profile in Stratum B was consistent with the known safety profiles for olaparib monotherapy, ceralasertib + olaparib combination therapy, and adavosertib + olaparib combination therapy. A higher-than-expected incidence of haematological toxicity (febrile neutropenia) was observed in the adavosertib + olaparib combination arm, which resulted in the submission of 2 Urgent Safety Measures. The adavosertib + olaparib combination was subsequently discontinued due to increased toxicity and no suggestion of benefit.

<u>Patient Population C (Stratum C, non *HRRm*)</u>

- The median total treatment duration and median actual treatment duration of olaparib were both 65.0 days in the olaparib monotherapy arm; 83.5 and 76.0 days, respectively, in the ceralasertib + olaparib arm; and 69.0 and 57.0 days, respectively, in the adavosertib + olaparib arm. The median total treatment duration and median actual treatment duration of ceralasertib in the ceralasertib + olaparib arm were 75.5 and 67.5 days, respectively.

The median total treatment duration and median actual treatment duration of adavosertib in the adavosertib + olaparib arm were 60.0 and 57.0 days, respectively.

- The mean relative dose intensity of olaparib was 94.39% in the olaparib monotherapy arm, 89.42% in the ceralasertib + olaparib arm, and 85.80% in the adavosertib + olaparib arm. The mean relative dose intensity of ceralasertib in the ceralasertib + olaparib arm was 98.73%. The mean relative dose intensity of adavosertib in the adavosertib + olaparib arm was 85.63%.
- AEs of any category were reported for 48 (98.0%) patients in the olaparib monotherapy arm, 50 (100.0%) patients in the ceralasertib + olaparib arm, and 27 (100.0%) patients in the adavosertib + olaparib arm. The most frequently reported AEs (reported by at least 25% of patients in a given treatment arm) by PT were as follows:
  - Olaparib monotherapy arm: Nausea (26 [53.1%] patients), anaemia and vomiting (17 [34.7%] patients each), and fatigue (13 [26.5%] patients)
  - Ceralasertib + olaparib arm: Nausea (31 [62.0%] patients), anaemia (26 [52.0%] patients), vomiting and fatigue (16 [32.0%] patients each), and asthenia (13 [26.0 %] patients)
  - Adavosertib + olaparib arm: Nausea and diarrhoea (15 [55.6%] patients each), anaemia (14 [51.9%] patients), neutropenia (11 [40.7%] patients), thrombocytopenia (8 [29.6%] patients), vomiting and fatigue (7 [25.9%] patients each)
- AEs of CTCAE Grade 3 or higher were reported for 22 (44.9%) patients in the olaparib monotherapy arm, 25 (50.0%) patients in the ceralasertib + olaparib arm, and 20 (74.1%) patients in the adavosertib + olaparib arm. The most frequently reported AEs of CTCAE Grade 3 or higher, by SOC (reported by at least 20% of patients in any treatment arm) were as follows:
  - Ceralasertib + olaparib arm: Blood and lymphatic system disorders (12 [24.0%] patients)
  - Adavosertib + olaparib arm: Blood and lymphatic system disorders (14 [51.9%] patients)
- AEs causally related to olaparib were reported for 42 (85.7%) patients in the olaparib monotherapy arm, 44 (88.0%) patients in the ceralasertib + olaparib arm, and 24 (88.9%) patients in the adavosertib + olaparib arm. Adverse events causally related to ceralasertib were reported for 42 (84.0%) patients and AEs causally related to ceralasertib and olaparib were reported for 41 (82.0%) patients. Adverse events causally related to adavosertib were reported for 26 (96.3%) patients and AEs causally related to adavosertib and olaparib were reported for 23 (85.2%) patients.
- In the olaparib monotherapy arm, 1 AESI in the category of pneumonitis was reported; 1 (2.0%) patient experienced an AE of lung infiltration. This event occurred 7 days after the start of study treatment and resolved after 24 days. The AE was not considered causally related to olaparib.
- In the ceralasertib + olaparib arm, 1 AESI in the category of pneumonitis was reported; 1 (2.0%) patient) experienced an AE of pneumonitis. This event occurred 217 days after

the start of study treatment and was not resolved at the data cut-off date. The AE was not considered causally related to ceralasertib or olaparib.

- A total of 18 (35.3%) patients in the olaparib monotherapy arm, 18 (34.6%) patients in the ceralasertib + olaparib arm, and 16 (59.3%) patients in the adavosertib + olaparib arm died during the study. The majority of deaths were related to the disease under study. None of the deaths were considered to be causally related to the study treatment.
- SAEs were reported for 11 (22.4%) patients in the olaparib monotherapy arm, 13 (26.0%) patients in the ceralasertib + olaparib arm, and 7 (25.9%) patients in the adavosertib + olaparib arm. SAEs reported for at least 2 patients by PT were as follows:
  - Ceralasertib + olaparib arm: Pneumonia (2 [4.0%] patients)
  - Adavosertib + olaparib arm: Febrile neutropenia (3 [11.1%] patients) and thrombocytopenia (2 [7.4%] patients)
- AEs leading to discontinuation of study treatment were reported for 2 (4.1%) patients in the olaparib monotherapy arm, 5 (10.0%) patients in the ceralasertib + olaparib arm, and 7 (25.9%) patients in the adavosertib + olaparib arm. Adverse events leading to the discontinuation of treatment reported for at least 2 patients by PT were as follows:
  - Adavosertib + olaparib arm: Neutropenia (4 [14.8%] patients), thrombocytopenia and neutrophil count decreased (2 [7.4%] patients each)
- AEs leading to reduction of study treatment were reported for 7 (14.3%) patients in the olaparib monotherapy arm, 13 (26.0%) patients in the ceralasertib + olaparib arm, and 10 (37.0%) patients in the adavosertib + olaparib arm.
- AEs leading to the interruption of olaparib were reported for 14 (28.6%) patients in the olaparib monotherapy arm, 11 (22.0%) patients in the ceralasertib + olaparib arm, and 7 (25.9%) patients in the adavosertib + olaparib arm. Adverse events leading to interruption of ceralasertib were reported for 10 (20.0%) patients and AEs leading to interruption of adavosertib were reported for 15 (55.6%) patients.
- There were no clinically important trends or changes over time from baseline in clinical chemistry and urinalysis parameters. Across the haematology and clinical chemistry parameters, excursions of values outside the reference ranges over time were reported; these are in line with the patient population and their disease status.
- There were clinically important trends or changes over time from baseline in haematology, in particular in leucocytes, neutrophils and platelets.
- Some haematology abnormalities were reported as AEs and SAEs. The following haematology abnormalities were reported as SAEs:
  - Olaparib monotherapy arm: Anaemia, febrile neutropenia and platelet count decreased (1 [2.0%] patient each)
  - Adavosertib + olaparib arm: Febrile neutropenia (3 [11.1%] patients), thrombocytopenia (2 [7.4%] patients), anaemia, leukopenia, neutropenia, and platelet count decreased (1 [3.7%] patient each). The SAEs of febrile neutropenia, leukopenia, and thrombocytopenia led to the discontinuation of 1 patient.

- Some clinical chemistry laboratory abnormalities were reported as AEs and SAEs. The following clinical chemistry abnormality was reported as an SAE:
  - Olaparib monotherapy arm: Hyponatraemia (1 [2.0%] patient).
- Three patients, one in each treatment arm, had values of ALT ≥ 3 × ULN or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN. All 3 cases were discussed as potential Hy's Law cases and it was concluded that these cases were not Hy's Law cases, but were related to disease progression (liver metastases).
- There were no clinically important trends or changes over time from baseline in vital signs and ECGs, or QTcFs in particular. One patient in the olaparib monotherapy arm had an QTcF of > 500 msec at their Week 12 and Week 52 visits (last observation on treatment). The following ECG abnormalities were reported as AEs:
  - Olaparib monotherapy arm: Sinus tachycardia, tachycardia and electrocardiogram QT prolonged (1 [2.0%] patient each)
  - Ceralasertib + olaparib arm: Tachycardia and electrocardiogram QT prolonged (1 [2.0%] patient each)
  - Adavosertib + olaparib arm: Extrasystoles, supraventricular tachycardia and tachycardia (1 [3.7%] patient each)
- Overall, the safety and tolerability profile in Stratum C was consistent with the known safety profiles for olaparib monotherapy, ceralasertib + olaparib combination therapy, and adavosertib + olaparib combination therapy. A higher-than-expected incidence of haematological toxicity (febrile neutropenia) was observed in the adavosertib + olaparib combination arm, which resulted in the submission of 2 Urgent Safety Measures. The adavosertib + olaparib combination was subsequently discontinued due to increased toxicity and no suggestion of benefit.

<u>Patient Population E (Strata A, B, and C)</u>

- The median total treatment duration and median actual treatment duration of olaparib were 100.0 and 88.5 days, respectively, in the olaparib monotherapy arm; 111.0 and 98.0 days, respectively, in the ceralasertib + olaparib arm; and 98.5 and 75.0 days, respectively, in the adavosertib + olaparib arm. The median total treatment duration and median actual treatment duration of ceralasertib in the ceralasertib + olaparib arm were both 91.0 days. The median total treatment duration and median actual treatment duration of adavosertib in the adavosertib + olaparib arm were 58.5 and 55.5 days, respectively.
- The mean relative dose intensity of olaparib was 94.27% in the olaparib monotherapy arm, 87.54% in the ceralasertib + olaparib arm, and 91.76% in the adavosertib + olaparib arm. The mean relative dose intensity of ceralasertib in the ceralasertib + olaparib arm was 95.82%. The mean relative dose intensity of adavosertib in the adavosertib + olaparib arm was 87.02%.
- AEs of any category were reported for 105 (95.5%) patients in the olaparib monotherapy arm, 107 (98.2%) patients in the ceralasertib + olaparib arm, and 46 (100.0%) patients in the adavosertib + olaparib arm. The most frequently reported AEs (reported by at least 25% of patients in a given treatment arm) by PT were as follows:

  - Olaparib monotherapy arm: Nausea (56 [50.9%] patients), anaemia (38 [34.5%] patients), vomiting (35 [31.8%] patients), and fatigue (30 [27.3%] patients)
  - Ceralasertib + olaparib arm: Nausea (64 [58.7%] patients), anaemia (58 [53.2%] patients), asthenia (33 [30.3%] patients), fatigue (32 [29.4%] patients), and vomiting (31 [28.4%] patients)
  - Adavosertib + olaparib arm: Nausea (26 [56.5%] patients), diarrhoea (25 [54.3%] patients), anaemia (23 [50.0%] patients), neutropenia (21 [45.7%] patients), fatigue (16 [34.8%] patients), and vomiting (15 [32.6%] patients)
- AEs of CTCAE Grade 3 or higher were reported for 39 (35.5%) patients in the olaparib monotherapy arm, 51 (46.8%) patients in the ceralasertib + olaparib arm, and 36 (78.3%) patients in the adavosertib + olaparib arm. The most frequently reported events of CTCAE Grade 3 or higher by SOC (reported by at least 20% of patients in any treatment arm) were as follows:
  - Ceralasertib + olaparib arm: Blood and lymphatic system disorders (31 [28.4%] patients)
  - Adavosertib + olaparib arm: Blood and lymphatic system disorders (23 [50.0%] patients), investigations (10 [21.7%] patients)
- AEs causally related to olaparib were reported for 91 (82.7%) patients in the olaparib monotherapy arm, 95 (87.2%) patients in the ceralasertib + olaparib arm, and 43 (93.5%) patients in the adavosertib + olaparib arm. AEs causally related to ceralasertib or ceralasertib and olaparib were reported for 92 (84.4%) and 91 (83.5%) patients, respectively, in the ceralasertib + olaparib arm. Adverse events causally related to adavosertib or adavosertib and olaparib were reported for 45 (97.8%) and 42 (91.3%) patients, respectively, in the adavosertib + olaparib arm.
- The following AESIs were reported across treatment arms:
  - In the olaparib monotherapy arm, 1 AESI in the category of pneumonitis was reported for 1 (0.9%) patient in Stratum C, the patient experienced an AE of lung infiltration.
  - In the ceralasertib + olaparib arm, 2 AESIs in the category of pneumonitis was reported for 2 (1.8%) patients (1 patient in Stratum A and 1 patient in Stratum C), both patients experienced an AE of pneumonitis.
  - In the adavosertib + olaparib arm, 1 AESI in the category of MDS was reported for 1 (2.2%) patient in Stratum B, the patient experienced an SAE of pancytopenia, MDS/AML was not diagnosed.
  - In the ceralasertib + olaparib arm, 1 AESI in the category of new primary malignancy (other than MDS/AML) was reported in 1 patient in Stratum A. The patient experienced an SAE of cholangiocarcinoma. The event occurred after the 30-day follow-up period and is therefore not included in the AESI tables.
- A total of 42 (36.8%) patients in the olaparib monotherapy arm, 40 (35.7%) patients in the ceralasertib + olaparib arm, and 26 (55.3%) patients in the adavosertib + olaparib arm

died during the study. The majority of deaths were related to the disease under study. None of the deaths were considered to be causally related to the study treatment.

- SAEs were reported for 21 (19.1%) patients in the olaparib monotherapy arm, 24 (22.0%) patients in the ceralasertib + olaparib arm, and 17 (37.0%) patients in the adavosertib + olaparib arm. SAEs reported for at least 2 patients by PT were as follows:
  - Olaparib monotherapy arm: Anaemia (3 [2.7%] patients) and nausea (2 [1.8%] patients)
  - Ceralasertib + olaparib arm: Anaemia and pneumonia (3 [2.8%] patients each), and pleural effusion (2 [1.8%] patients)
  - Adavosertib + olaparib arm: Febrile neutropenia (5 [10.9%] patients), neutropenia (4 [8.2%] patients), thrombocytopenia (3 [6.5%] patients), leukopenia, nausea and vomiting (2 [4.3%] patients each)
- AEs leading to discontinuation of study treatment were reported for 2 (1.8%) patients in the olaparib monotherapy arm, 12 (11.0%) patients in the ceralasertib + olaparib arm, and 9 (19.6%) patients in the adavosertib + olaparib arm. Adverse events leading to discontinuation of study treatment reported for at least 2 patients by PT were as follows:
  - Ceralasertib + olaparib arm: Anaemia and neutrophil count decreased (2 [1.8%] patients each)
  - Adavosertib + olaparib arm: Neutropenia (4 [8.7%] patients), neutrophil count decreased and thrombocytopenia (2 [4.3%] patients each)
- AEs leading to reduction of study treatment were reported for 15 (13.6%) patients in the olaparib monotherapy arm, 32 (29.34%) patients in the ceralasertib + olaparib arm, and 14 (41.3%) patients in the adavosertib + olaparib arm.
- Overall, the safety and tolerability profile in Stratum E was consistent with the known safety profiles for olaparib monotherapy, ceralasertib + olaparib combination therapy, and adavosertib + olaparib combination therapy. A higher-than-expected incidence of haematological toxicity (febrile neutropenia) was observed in the adavosertib + olaparib combination arm, which resulted in the submission of 2 Urgent Safety Measures. The adavosertib + olaparib combination was subsequently discontinued due to increased toxicity and no suggestion of benefit.

Conclusions

- According to the analysis of the primary endpoint, ie, analysis of PFS per BICR, there was no statistically significant difference in PFS per BICR between olaparib monotherapy and ceralasertib + olaparib combination therapy in Patient Populations A, B, and C.
- According to the ORR and change in target lesion size at Week 16 of the secondary efficacy analysis, there were statistically significant differences in favour of ceralasertib + olaparib combination therapy compared to olaparib monotherapy in Patient Population C. However, given the result of the analysis of the primary endpoint (ie, no statistically significant difference in PFS), the interpretation of the clinical meaningfulness of the difference in ORR and in tumour target size is limited.

- The safety and tolerability profile of the adavosertib + olaparib combination arm did not show a favourable risk-benefit profile and this arm was terminated early. Overall, the safety and tolerability profile of olaparib monotherapy and the ceralasertib + olaparib combination therapy was consistent with the known safety profiles of olaparib and the combination treatment.