Title: A Modular Phase IIa Multicentre Open-Label Study to Investigate DNA-damage Response Agents (or Combinations) in Patients With Advanced Cancer Whose Tumours Contain Molecular Alterations (PLANETTE)

Sponsor Study Code: D5339C00001

NCT Number: NCT04564027

Date: 15 February 2024

Abbreviated Clinical Study Report Synopsis	
Drug Substance	Ceralasertib
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A Modular Phase IIa Multicentre Open-Label Study to Investigate DNA-damage Response Agents (or Combinations) in Patients with Advanced Cancer Whose Tumours Contain Molecular Alterations (PLANETTE)

Study dates:

First subject enrolled: 01 December 2020

Last subject last visit: 28 March 2023

Date of early study termination: 31 March 2023

Enrolment into Cohort B was terminated early following an ad-hoc analysis of Cohort B and the primary analysis of Cohort A, based on the assessment of efficacy results and overall operational feasibility.

The analyses presented in this report are based on data cut-off date of 21 December 2022 for Cohort A and 28 April 2023 for Cohort B.

Phase of development:

Therapeutic exploratory (IIa)

International Co-ordinating Investigator:

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This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

Study Centres

This study was conducted at 18 centres (ie, centres that screened patients) in 3 countries.

Publications

Poster presentation:
Abida W, Sanay E, Lukashchuk N, Pierce A, de Graaf W, Lau A, et al. PLANETTE: A modular phase IIa multicenter open-label study evaluating the ATR inhibitor ceralasertib (AZD6738) in ATM mutant advanced solid tumors. J Clin Oncol 39, TPS189-TPS189(2021).

Objectives and Criteria for Evaluation

Table S1 Objectives and Endpoints - Cohort A (aST) [a]

Objectives	Endpoints
Primary	
• To obtain a preliminary assessment of the efficacy of ceralasertib in participants with ATM-altered aST refractory to standard treatments options, as assessed by ORR	• Investigator-assessed ORR, as defined by RECIST version 1.1
Secondary	
• To further assess the efficacy of ceralasertib	Investigator assessment, as defined by RECIST version 1.1: • DoR • Percentage change in tumour size • PFS
• To assess the safety and tolerability profile of ceralasertib	• AEs/SAEs • Vital signs, haematology, and clinical chemistry parameters

[a] Only the primary and secondary objectives are listed in this table. The exploratory objective and endpoints are described in the CSR. Results from certain exploratory endpoint analyses are reported in the CSR.

Abbreviations: AE, Adverse event; aST, Advanced solid tumour; ATM, Ataxia telangiectasia mutated; CSR, Clinical study report; DoR, Duration of response; ORR, Objective response rate; PFS, Progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; SAE: Serious adverse event.

Table S2 Objectives and Endpoints – Cohort B (mCRPC) [a]

Objectives	Endpoints
Primary	
• To obtain a preliminary assessment of the efficacy of ceralasertib in participants with ATM-altered mCRPC, as assessed by composite response rate	• Composite response rate (Investigator-assessed radiological response as defined by RECIST 1.1 for soft tissue and visceral lesions and by PCWG3 for bone lesions, PSA decline, and/or CTC conversion)
Secondary	
• To further assess the efficacy of ceralasertib	• ORR by RECIST 1.1 for soft tissue and visceral lesions and by PCWG3 criteria for bone lesions [b] • Proportion of participants with confirmed CTC count conversion from unfavourable to favourable [b] • Proportion of participants with confirmed PSA decline > 50% [b] • Best percentage change in tumour size • Duration of radiological response • Radiological PFS using RECIST 1.1 for soft tissues and visceral lesions and PCWG3 for bone lesions
• To assess the safety and tolerability profile of ceralasertib	• AEs/SAEs • Vital signs, haematology, and clinical chemistry parameters

[a] Only the primary and secondary objectives are listed in this table. The exploratory objectives and endpoints are described in the CSR. Results from certain exploratory endpoint analyses are reported in the CSR.

[b] Due to early termination of enrolment into Cohort B and subsequent small sample size, this secondary endpoint was not analysed.

Abbreviations: AE, Adverse event; ATM, Ataxia telangiectasia mutated; CSR, Clinical study report; CTC, Circulating tumour cell; DoR, Duration of response; mCRPC, Metastatic castration-resistant prostate cancer; ORR, Objective response rate; PCWG3, Prostate Cancer Working Group 3; PFS, Progression-free survival; PSA; Prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumours; SAE: Serious adverse event.

Study Design

The study was planned in a modular structure; however, there was only one module in this study, Module 1. Module 1 was a Phase IIa, open-label, multicentre study of ceralasertib monotherapy, administered orally, in 2 patient populations (Cohort A and Cohort B) whose tumours contained deleterious or suspected deleterious genetic alterations in the ataxia telangiectasia mutated (ATM) gene. Cohort A included patients with ATM-altered advanced solid tumour (aST), except patients with non-small-cell lung carcinoma (NSCLC) and prostate cancer. Cohort B included patients with ATM-altered metastatic castration-resistant prostate cancer (mCRPC).

Early Termination of Enrolment

On 28 March 2023, following a review of the primary analysis of Cohort A and ad-hoc data outputs from Cohort B of Module 1 of Study D5339C00001, the decision to terminate enrolment into Cohort B was made by AstraZeneca, based on the assessment of efficacy results and overall operational feasibility.

Target Population and Sample Size

The study included male and female patients aged ≥ 18 years with histologically-confirmed diagnosis of aST (excluding NSCLC) or mCRPC tumour, and a deleterious or suspected deleterious ATM mutation in tumour or blood (germline or circulating tumour deoxyribonucleic acid [ctDNA]). Patients had to submit a formalin fixed and paraffin embedded sample for central confirmation of ATM immunohistochemistry (IHC) and next-generation sequencing (NGS) status. Patients were eligible if they had no standard treatment options available or for whom the standard treatment options were contraindicated. Furthermore, patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 2 and a life expectancy ≥ 16 weeks.

Cohort A: It was planned to enrol a total of approximately 25 molecularly-eligible and centrally-confirmed patients dosed with ceralasertib 160 mg twice daily (BID) in Cohort A. In total, 30 patients were assigned to a starting dose of 160 mg ceralasertib BID. Of these, 28 patients were molecularly-eligible, centrally-confirmed, and evaluable for response.

Cohort B: It was planned to enrol a total of approximately 27 molecularly-eligible and centrally-confirmed patients dosed with ceralasertib 160 mg BID in Cohort B. In total, 15 patients were assigned to a starting dose of 160 mg ceralasertib BID. Of these, 13 patients were molecularly-eligible, centrally-confirmed, and evaluable for response.

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

The study intervention was ceralasertib (AZD6738), administered in both cohorts as oral tablet at a dose of 160 mg BID on Days 1 to 14 in 28-day cycles. The study intervention was manufactured by AstraZeneca R&D and the following batch numbers were used: L014883, L014884, L015885, L015920, L019910.

Duration of Treatment

Patients could receive study intervention until objective disease progression, or as long as they continued to show clinical benefit, as judged by the Investigator, or treatment discontinuation criteria were met.

Statistical Methods

General Principles:

- Demographic and baseline characteristics of patients were summarised by cohort and by assigned starting dose of ceralasertib. All safety data and pharmacokinetics (PK) data were summarised by cohort, by assigned starting dose of ceralasertib and time point. All efficacy data were summarised only for patients who were assigned to ceralasertib 160 mg BID as starting dose, by cohort.
- Continuous data were summarised using descriptive statistics (the number of patients [n], mean, standard deviation, median, 25th and 75th percentiles [where appropriate], minimum and maximum, unless otherwise stated).
- Log-transformed data were presented using geometric mean and geometric coefficient of variation.
- Categorical data were summarised in terms of the number of patients providing data at the relevant time point (n), frequency counts, and percentages.
- Confidence intervals (CIs) (80%) and p-values, when presented, were constructed at the 2-sided alpha level.
- Each cohort was analysed separately for the primary, secondary, and exploratory endpoints.
- No formal statistical hypothesis testing was conducted and no adjustments for centre or for covariates were performed.

Analysis Sets:

Population/Analysis Set	Description
Enrolled Analysis Set	All study participants who signed the ICF (including screening failures).
Evaluable for Response Set	Cohort A: All study participants with measurable baseline disease who received at least 1 dose of study intervention. Cohort B: All study participants with measurable disease and/or unfavourable CTC count at baseline who received at least 1 dose of study intervention.
Molecularly Eligible Centrally Confirmed Set [a]	All molecularly-eligible and centrally-confirmed participants who received at least 1 dose of study intervention.
Molecularly Eligible Centrally Confirmed and Evaluable for Response Set [a]	Cohort A: All molecularly-eligible and centrally-confirmed study participants with measurable baseline disease who received at least 1 dose of study intervention. Cohort B: All molecularly-eligible and centrally-confirmed study participants with measurable disease and/or unfavourable CTC count at baseline who receive at least 1 dose of study intervention.
CCI [redacted]	CCI [redacted]
CCI [redacted]	CCI [redacted]
Safety Analysis Set	All participants who received at least 1 dose of study intervention.

Population/Analysis Set	Description
Interim Analysis Set	All participants in the molecular eligible centrally-confirmed evaluable for response set with a chance to have at least 2 follow-up RECIST assessments (ie, all participants who received the first dose of ceralasertib at least 16 weeks prior to the DCO date).

[a] Participants with any or both of the following conditions were considered molecularly-eligible centrally-confirmed: 1) Centrally-confirmed deleterious or suspected deleterious ATM mutation by NGS; 2) Centrally-confirmed ATM IHC ≤ 5%.

Abbreviations: AE, Adverse event; ATM, Ataxia telangiectasia mutated; CTC, Circulating tumour cell; DCO, Data cut-off; ICF, Informed consent form; IHC, Immunohistochemistry; NGS, Next-generation sequencing; PDc, Pharmacodynamics; PK, Pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumours.

Determination of Sample Size:

- At the time of clinical study protocol (CSP) Amendment 2, 8 patients had been dosed with 240 mg BID in Cohort A, and 1 patient had been dosed with 240 mg BID in Cohort B. Following the reduction of the starting dose from 240 mg BID to 160 mg BID in CSP Amendment 2, the intention was to enrol an additional total of approximately 25 and approximately 27 patients in Cohort A and B, respectively, at the 160 mg BID dose.
- The primary objective of this study was to determine Investigator-assessed objective response rate (ORR) (Cohort A) and composite response rate (Cohort B) of study intervention. The planned number of molecularly-eligible centrally-confirmed patients was based on the desire to obtain adequate response, tolerability, safety, PK, and pharmacodynamics data while exposing as few patients as possible to study intervention and procedures.
- In Cohort A, the sample size of approximately 25 patients was expected to give adequate precision in the estimate of the ORR. CCI [redacted]
- In Cohort B, the sample size of approximately 27 patients was expected to give adequate precision in the estimate of composite response. CCI [redacted]
- Each Cohort A and Cohort B could have been further expanded CCI [redacted] CCI [redacted] each, in case of an efficacy signal, subject to an approved CSP amendment.

Statistical Analyses:

Primary Efficacy Variables:

The primary and secondary efficacy summaries and figures were provided only for patients who received 160 mg BID ceralasertib as starting dose on Cycle 1 Day 1. Listings were provided for all patients irrespective of their starting dose of ceralasertib.

- ORR - Cohort A: The primary analysis for Cohort A was planned to occur approximately 6 months after 25 molecularly-eligible centrally-confirmed evaluable for response patients were enrolled at a 160 mg BID starting dose. The final analysis comprised 28 patients. ORR was defined as the rate of patients who had a confirmed visit response (complete response or partial response prior to evidence of progression, as defined by Response Evaluation Criteria in Solid Tumours [RECIST]). Summaries were based on the Molecularly Eligible Centrally Confirmed Evaluable for Response Set as well as the Evaluable for Response Set and included the number and percentage of patients with a tumour response (complete response/partial response), together with a 2-sided 80% CI using the Clopper-Pearson method.
- Composite Response Rate - Cohort B: The primary analysis for Cohort B was planned to occur approximately 6 months after 27 molecularly-eligible centrally-confirmed evaluable for response patients were enrolled at a 160 mg BID starting dose. However, enrolment into Cohort B was incomplete because enrolment in the study was terminated after review of the primary analysis for Cohort A and ad-hoc outputs for Cohort B. Composite response was defined as the percentage of patients who had a composite response. Summaries were based on the Molecularly Eligible Centrally Confirmed Evaluable for Response Set as well as the Evaluable for Response Set Summaries and included the number and percentage of patients with a composite response, together with a 2-sided 80% CI using the Clopper-Pearson method.

Safety Evaluation:

- All safety summaries and analyses were based on the Safety Analysis Set.
- Exposure data were summarised and listed.
- All reported adverse events (AEs) were listed. Frequencies and percentages of patients reporting each preferred term (PT) were presented. AEs were summarised by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and MedDRA PT, by cohort.
- Details of any death were listed.
- Summaries of the laboratory safety variables were provided. All laboratory results collected were listed. All values were classified as low (below range), normal (within range), or high (above range), based on local laboratory reference ranges.
- Absolute values and change from baseline for vital signs were summarised by cohort and visit. Any values (observed and change) falling outside the reference range were flagged. All baseline physical examination findings were summarised by cohort.
- A shift table of baseline to maximum on treatment for ECOG PS was presented by cohort and by performance status Grade (0-4).

CCI [redacted]

Based on the primary outcome on the Molecular Eligible and Centrally Confirmed Evaluable for Response Set, CCI [redacted]
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- For Cohort A, with the CCI and CCI
  - CCI
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  - CCI
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- For Cohort B, with the CCI and CCI
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Interim Analyses:

- Cohort A: An administrative interim analysis was conducted approximately 4 months after approximately 18 molecularly-eligible centrally-confirmed evaluable for response patients dosed with ceralasertib 160 mg BID had been enrolled. The assessment of key efficacy and safety endpoints was performed. The purpose of the administrative interim analysis was to inform internal decision making only, with no planned adaptions to the study.
- Cohort B: A futility interim analysis was planned to be conducted approximately 6 months after at least 12 molecularly-eligible centrally-confirmed evaluable for response patients had been enrolled and dosed with ceralasertib 160 mg. No interim analysis was conducted for Cohort B; instead, an ad-hoc analysis was conducted after 12 patients were dosed (before central confirmation of their molecular eligibility and 6-month follow-up), which led to the recommendation to stop enrolment.

Study Population

Cohort A

- In Cohort A, a total of 54 patients were enrolled based on deleterious or suspected deleterious ATM mutation as per local NGS testing. Of these, 38 (70.4%) patients were assigned to study intervention. Of these 38 patients, 8 patients were assigned to a starting

dose of 240 mg ceralasertib BID (Days 1 to 14 in 28-day cycles) and 30 patients were assigned to a starting dose of 160 mg ceralasertib BID (Days 1 to 14 in 28-day cycles).

- At the time of the data cut-off (DCO) (21 December 2022), of the 38 treated patients, 3 (7.9%) patients were on study intervention and 35 (92.1%) patients had discontinued study intervention. The main reasons for discontinuation of study intervention were objective disease progression (19 [50.0%] patients) and subjective disease progression (9 [23.7%] patients).
- The most frequent primary tumour locations at diagnosis were as follows:
  - 240 mg dose group: pancreas (3 [37.5%] patients).
  - 160 mg dose group: gallbladder, pancreas (4 [13.3%] patients each), and colon (3 [10.0%] patients).
- The ATM status of the 38 patients who were assigned to study intervention (8 patients in the 240 mg dose group and 30 patients in the 160 mg dose group) was as follows:
  - 240 mg dose group:
    - CCI
    - CCI
    - CCI
  - 160 mg dose group:
    - Of the 30 patients who were assigned to study intervention, 28 patients were centrally confirmed to have an ATM alteration (molecularly-eligible centrally-confirmed), based on ATM mutation confirmed by tumour and/or ctDNA NGS testing and/or ATM protein deficiency confirmed by IHC testing of an archival tumour tissue sample (cut-off ≤ 5%).
    - All 28 patients had ATM mutation confirmed by tumour and/or ctDNA NGS testing CCI

  - Per individual tests, of the 28 patients who had centrally-confirmed ATM mutation, 22 patients had an evaluable tumour NGS test result, of which 18 patients were confirmed positive and 4 patients negative for ATM mutation; 27 patients had an evaluable ctDNA NGS test result, of which 26 patients were confirmed positive and 1 patient was negative for ATM mutation.
  - Furthermore, of the 28 patients with centrally-confirmed ATM alteration, 23 patients had an evaluable ATM IHC test result, of which 11 patients were ATM protein deficient and 12 patients were ATM protein proficient.

- The numbers of prior lines of anticancer therapies were as follows:
  - 240 mg dose group: 1 line for 2 (25.0%) patients, 2 lines for 3 (37.5%) patients, and 3 lines for 2 (25.0%) patients; no patient had more than 3 lines. The median number of prior lines of anticancer therapies was 2.0 (minimum 1, maximum 3).
  - 160 mg dose group: 1 line for 5 (16.7%) patients, 2 lines for 10 (33.3%) patients, 3 lines for 6 (20.0%) patients, and more than 3 lines for 9 (30.0%) patients. The median number of prior lines of anticancer therapies was 2.5 (minimum 1, maximum 7).

Cohort B

- In Cohort B, a total of 54 patients were enrolled based on deleterious or suspected deleterious ATM mutation as per local NGS testing. Of these, 16 (29.6%) patients were assigned to study intervention. Of these 16 patients, 1 patient was assigned to a starting dose of 240 mg ceralasertib BID (Days 1 to 14 in 28-day cycles) and 15 patients were assigned to a starting dose of 160 mg ceralasertib BID (Days 1 to 14 in 28-day cycles).
- At the time of the DCO (28 April 2023), all 16 treated patients had discontinued study intervention. The main reasons for discontinuation of study intervention were subjective disease progression (6 [37.5%] patients) and objective disease progression (5 [31.3%] patients).
- The ATM status of the 16 patients who were assigned to study intervention (1 patient in the 240 mg dose group and 15 patients in the 160 mg dose group) was as follows:
  - 240 mg dose group: CCI [redacted]
  - 160 mg dose group:
    - Of the 15 patients who were assigned to study intervention, 13 patients were centrally confirmed to have an ATM alteration (molecularly-eligible centrally-confirmed), based on ATM mutation confirmed by tumour and/or ctDNA NGS testing and/or ATM protein deficiency confirmed by IHC testing of an archival tumour tissue sample (cut-off ≤ 5%).

  - Of these 13 patients, 11 patients had ATM mutation confirmed by tumour and/or ctDNA NGS testing [redacted]
  - Per individual tests, of the 11 patients who had centrally-confirmed ATM mutation, 8 patients had an evaluable tumour NGS test result, of which 5 patients were confirmed positive and 3 patients were negative for ATM mutation; 11 patients had an evaluable ctDNA NGS test result and all 11 patients were confirmed positive for ATM mutation.
  - Furthermore, of the 13 patients with centrally-confirmed ATM alteration, 12 patients had an evaluable ATM IHC test result, of which 7 patients were ATM protein deficient and 5 patients were ATM protein proficient.

- The numbers of prior lines of anticancer therapies were as follows:
  - 240 mg dose group: 1 line for the single patient in this dose group.
  - 160 mg dose group: 1 line for 1 (6.7%) patient, 2 lines for 3 (20.0%) patients, 3 lines for 3 (20.0%) patients, and more than 3 lines for 8 (53.3%) patients. The median number of prior lines of anticancer therapies was 3.5 (minimum 1, maximum 7).

Summary of Efficacy Results

Cohort A

- In Cohort A (patients with ATM-altered aST), of the 30 patients who were assigned to receive a starting dose of 160 mg ceralasertib (BID, Days 1 to 14 in 28-day cycles), 28 patients were molecularly-eligible centrally-confirmed evaluable for response.
- Of these 28 patients, 2 (7.1%) patients had an objective response as defined by RECIST (1 patient had complete response and 1 patient had partial response). Both responders had ATM mutation as confirmed by tumour and ctDNA NGS and had ATM protein deficiency as confirmed by an IHC result of ≤ 5%.
- The overall ORR for Cohort A was 7.14% (80% CI 1.9, 17.9). The ORR for 11 patients with ATM protein deficiency was 18.18% (80% CI 4.9, 41.5). The ORR for 28 patients with centrally-confirmed ATM mutation was 7.14% (80% CI 1.9, 17.9).
- The response with 160 mg ceralasertib BID on Days 1 to 14 in 28-day cycles in Cohort A did not meet the predefined success criteria of the study, since the Cohort A primary analysis showed an observed response rate in line with the pre-specified No-go criterion.

Cohort B

- In Cohort B (patients with mCRPC), of the 15 patients who were assigned to receive a starting dose of 160 mg ceralasertib (BID, Days 1 to 14 in 28-day cycles), 13 patients were molecularly-eligible centrally-confirmed and evaluable for response.
- Of these 13 patients, 1 (7.7%) patient had a composite response (CTC count conversion). This patient had ATM mutation as confirmed by ctDNA NGS; ATM mutation status by tumour NGS and ATM protein expression status by IHC were unknown.

- The overall composite response rate for Cohort B was 7.69% (80% CI 0.8, 26.8). The composite response rate for 7 patients with ATM protein deficiency was 0% (80% CI 0.00, 28.0). The composite response rate for 11 patients with centrally-confirmed ATM mutation was 9.09% (80% CI 1.0, 31.0).
- Conclusions are limited for interpretation of Cohort B results because the required sample size was not met.

Summary of Pharmacokinetic Results

Analysis of drug concentration was an exploratory endpoint in this study. Full results are included in clinical study report Section 14 and Appendix 16.2.

Summary of Safety Results

In this study, there was an increased frequency and early onset of Grade ≥ 3 haematological toxicity among the patients who received the 240 mg ceralasertib starting dose in Cohort A (3 [37.5%] of 8 patients had anaemia, 2 [25.0%] of 8 patients had thrombocytopenia, and 1 [12.5%] of 8 patients had febrile neutropenia). Anaemia, neutropenia (including febrile neutropenia), and thrombocytopenia are considered expected events for ceralasertib monotherapy. However, given the observed increase in frequency and early onset of severe haematological AEs in the study, AstraZeneca took the decision to reduce the starting dose of ceralasertib from 240 mg BID to 160 mg BID to be implemented as an urgent safety measure. All Grade ≥ 3 AEs of anaemia, thrombocytopenia, neutropenia, and febrile neutropenia that occurred in the 240 mg dose group in Cohort A and Cohort B were reported as resolved, except for 1 patient in Cohort B with Grade 3 neutropenia who had a fatal cardiac arrest on the same day. The dose of 160 mg ceralasertib BID was well tolerated in this study.

Cohort A

- Overall, all 8 (100%) patients in the 240 mg dose group and all 30 (100%) patients in the 160 mg dose group had at least 1 AE.
  - In the 240 mg dose group, AEs by PT reported by ≥ 50% of patients were anaemia (6 [75.0%] patients), nausea (4 [50.0%] patients), fatigue (4 [50.0%] patients), dyspnoea (4 [50.0%] patients), and white blood cell count decreased (4 [50.0%] patients).
  - In the 160 mg dose group, none of the AEs by PT were reported by ≥ 50% of patients.
- All 8 (100.0%) patients in the 240 mg dose group and 21 (70.0%) of 30 patients in the 160 mg dose group had at least 1 AE that was assessed by the Investigator as possibly related to the study intervention.
  - In the 240 mg dose group, AEs assessed by the Investigator as possibly related to study intervention, by PT, that were reported by ≥ 50% of patients were nausea (4 [50.0%] patients) and white blood cell count decreased (4 [50.0%] patients).

- Six (75.0%) of 8 patients in the 240 mg dose group and 15 (50.0%) of 30 patients in the 160 mg dose group had at least 1 AE of Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher.
  - In the 240 mg dose group, 6 patients had AEs of Grade 3 (anaemia and neutrophil count decreased [each event experienced by 3 patients]; white blood cell count decreased [2 patients]; febrile neutropenia, headache, hypoxia, lymphocyte count decreased, pain in extremity, pleural effusion, rash maculo-papular, small intestinal obstruction, and thrombocytopenia [each event experienced by 1 patient]) and 5 patients had AEs of Grade 4 (platelet count decreased [2 patients]; and confusional state, sepsis, and thrombocytopenia [each event experienced by 1 patient]). None of the patients had AEs of Grade 5.
  - In the 160 mg dose group, 14 patients had AEs of Grade 3 (anaemia and thrombocytopenia [each event experienced by 3 patients]; aspartate aminotransferase increased and blood alkaline phosphatase increased [each event experienced by 2 patients]; alanine aminotransferase increased, blood bilirubin increased, blood creatine phosphokinase increased, decreased appetite, diarrhoea, dyspnoea, fatigue, gamma-glutamyltransferase increased, hypokalaemia, lymphopenia, neutropenia, pancytopenia, prostatitis, and vomiting [each event experienced by 1 patient]) and 3 patients had AEs of Grade 4 (alanine aminotransferase increased, blood bilirubin increased, and pancytopenia [each event experienced by 1 patient]). None of the patients had AEs of Grade 5.
- There were no AEs with outcome of death in this cohort.
- SAEs were reported for 6 (75.0%) of 8 patients in the 240 mg dose group and 4 (13.3%) of 30 patients in the 160 mg dose group. There was thus a higher percentage of patients with SAEs in the 240 mg dose group.
- AEs leading to discontinuation of study intervention were reported for none of the 8 patients in the 240 mg dose group and for 1 (3.3%) of 30 patients in the 160 mg dose group. The patient had the AE of decreased appetite of Grade 3.
- AEs leading to dose modification were reported for 4 (50.0%) of 8 patients in the 240 mg dose group and for 10 (33.3%) of 30 patients in the 160 mg dose group.
- In the 160 mg dose group, maximum mean decreases were observed in haemoglobin and neutrophil values on Cycle 2 Day 14 and platelet and lymphocyte values on Cycle 1 Day 14. Furthermore, maximum mean increases were observed in alanine transaminase, aspartate transaminase, and bilirubin values on Cycle 2 Day 1 and a maximum mean decrease in thyrotropin values on Cycle 4 Day 1. There were no other trends in haematology and clinical chemistry parameters during the study.
- There were no trends in vital signs during the study.

Cohort B

- Overall, 1 (100%) patient in the 240 mg dose group and 15 (100%) patients in the 160 mg dose group had at least 1 AE.
  - In the 160 mg dose group, the only AE by PT reported by ≥ 50% of patients was nausea (8 [53.3%] patients).
- The patient in the 240 mg dose group and 13 (86.7%) patients in the 160 mg dose group had at least 1 AE that was assessed by the Investigator as possibly related to the study intervention.
  - In the 160 mg dose group, none of the AEs assessed by the Investigator as possibly related to study intervention by PT were reported by ≥ 50% of patients.
- The patient in the 240 mg dose group and 8 (53.3%) of 15 patients in the 160 mg dose group had at least 1 AE of CTCAE Grade 3 or higher.
  - The patient in the 240 mg dose group had AEs of Grade 3 (diarrhoea, leukopenia, and neutropenia) and Grade 5 (cardiac arrest).
  - In the 160 mg dose group, 8 patients had AEs of Grade 3 (anaemia [5 patients] and device related infection, dyspnoea exertional, fatigue, groin pain, hypoglycaemia, pneumonia, and rash [each event experienced by 1 patient]).
- The patient in the 240 mg dose group had the AE with fatal outcome of cardiac arrest. There were no AEs with fatal outcome reported in the 160 mg dose group.
- The patient in the 240 mg dose group and 4 (26.7%) of 15 patients in the 160 mg dose group had at least 1 SAE.
- None of the patients in Cohort B had AEs leading to discontinuation of study intervention.
- AEs leading to dose modification were only reported in the 160 mg dose group, for 3 (20.0%) of 15 patients.
- In the 160 mg dose group, maximum mean decreases were observed in haemoglobin values on Cycle 5 Day 1, neutrophil values on Cycle 1 Day 14, platelet values on Cycle 2 Day 14, lymphocyte values on Cycle 1 Day 14, and thyrotropin values on Cycle 2 Day 14. There were no other trends in haematology and clinical chemistry parameters during the study.
- There were no trends in vital signs during the study.

Conclusions

- The primary analysis of efficacy of ceralasertib in patients in Cohort A with ATM-altered aST refractory to standard treatment options, as assessed by ORR, did not meet the predefined success criteria.
- Conclusions for the primary analysis of efficacy of ceralasertib in patients in Cohort B with ATM-altered mCRPC, as assessed by composite response rate, are limited due to the required sample size not being met.

- An increased frequency and early onset of Grade ≥ 3 haematological toxicity was noted among patients who received the 240 mg BID ceralasertib starting dose. AstraZeneca implemented 2 urgent safety measures, comprising additional safety haematology and clinical chemistry monitoring visits and a reduction of the starting dose of ceralasertib from 240 mg BID to 160 mg BID. No other safety concerns were identified during the study, and overall, the safety and tolerability profile of the 160 mg BID dose level was consistent with what is known for ceralasertib.