2. SYNOPSIS

Study centers

A total of 25 study centers in the United States (US) participated in this study.

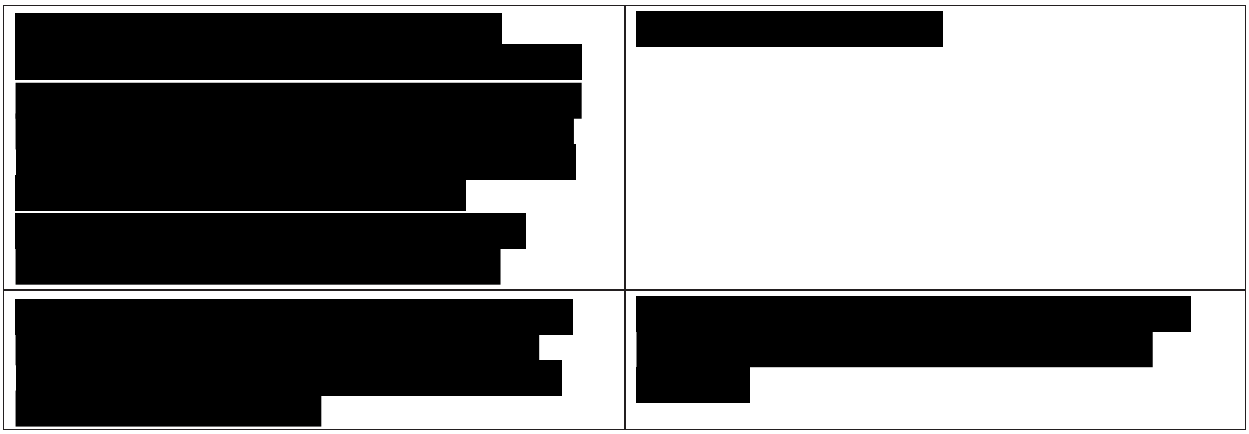
Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and endpoints

Primary Objective:	**Outcome Measure:**
To determine the efficacy of the combination of cediranib and olaparib in patients with recurrent platinum resistant epithelial ovarian, fallopian tube and/or primary peritoneal cancer who do not carry deleterious or suspected deleterious germline *BRCA* mutations, as assessed by objective response rate (ORR).	ORR by Independent central review (ICR) using RECIST version 1.1
Secondary Objectives:	**Outcome Measures:**
To assess the efficacy of the combination of cediranib and olaparib in this patient population by ORR, duration of response (DoR), disease control rate (DCR), progression-free survival (PFS), time to treatment discontinuation or death (TDT) and overall survival (OS).	ORR by Investigator assessment using RECIST 1.1; DoR, PFS and DCR by ICR and Investigator assessment using RECIST 1.1, TDT and OS.
To assess the efficacy of the combination of cediranib and olaparib in patients carrying a somatic deleterious or suspected deleterious variant in either of the *BRCA* genes (*BRCA1* or *BRCA2)* or in HRR-associated genes identified with current and potential future tumor based *BRCA* or HRR gene mutation assays as assessed by ORR, DoR, DCR, PFS and OS	ORR, DoR, PFS and DCR by ICR and Investigator assessment using RECIST 1.1, and OS
To evaluate disease related symptoms and health-related quality of life when compared with baseline data	European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ) C30 and OV-28
Safety Objective:	**Outcome Measure:**
To evaluate the safety and tolerability of the combination of cediranib and olaparib	Adverse events (AEs), and treatment emergent changes in vital signs and laboratory parameters
Exploratory Objectives:	**Outcome Measure:**



AE adverse event; *BRCA* Breast cancer susceptibility gene; DCR disease control rate; DoR duration of response; EORTC QLQ-C30 European Organization for Research and Treatment of Cancer quality of life questionnaire for cancer patients; [redacted] HRR homologous recombination repair; ICR independent central review; ORR objective response rate; OS overall survival; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1; PFS progression-free survival; [redacted] TDT time to treatment discontinuation or death; [redacted]

Study design

This was an open-label, Phase IIb, single-arm, multicenter study to assess the efficacy and safety of the combination of cediranib and olaparib in platinum-resistant relapsed high grade serous, high grade endometroid or clear cell ovarian, fallopian tube, or primary peritoneal carcinoma who had received at least 3 prior lines of therapy for advanced ovarian cancer and who had no evidence of deleterious or suspected deleterious *gBRCA* mutation(s) as defined by a test conducted in an appropriately accredited laboratory (eg, Clinical Laboratory Improvement Amendments [CLIA]-certified) that included comprehensive deoxyribonucleic acid (DNA) sequencing and large rearrangement analysis of *BRCA1* and *BRCA2*. Enrollment of the patients who had prior antiangiogenic treatment such as bevacizumab, either in a first-line or a recurrent setting, was optional.

Target patient population and sample size

To be eligible to enter the study, all patients were required to be ≥18 years of age with measurable disease (as assessed by the Investigator), defined as at least 1 lesion that could be accurately measured at baseline by computed tomography (CT)/magnetic resonance imaging (MRI) and be suitable for repeated assessment per RECIST 1.1. The planned recruitment was for approximately 60 treated patients, with the analysis of overall survival (OS) to occur along with objective response rate (ORR) at 8 months after the last patient received her first dose of investigational product (IP).

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

Patients received a starting dose of 30 mg cediranib once daily (qd) and 200 mg olaparib twice daily (bid) via orally administered tablets. Dose modification was allowed per protocol-defined guidelines.

Duration of treatment

Patients continued to receive open-label IPs until objective radiological disease progression, unacceptable toxicity, or withdrawal of consent.

Statistical methods

The study originally planned to recruit 100 treated patients over approximately 12 months. The primary analysis was scheduled to occur at 8 months after the last patient received her first dose of IP (approximately 20 months after study start), allowing all patients to have at least 4 RECIST follow-up assessments.

The study plan was subsequently amended so as to recruit approximately 60 treated patients, and the revised planned analysis of OS, originally planned at 12 months after the last patient received her first dose of IP, was now to occur at 8 months after the last patient received her first dose of IP. Based on the revised duration of recruitment and assuming a median PFS of 6 months as originally planned and a median of 12 months for OS, 80% PFS events and 57% OS events were expected to occur at the time of the analysis.

The primary analysis for the CSR was to be based on the confirmed ORR (with a target of 20%) by Independent Central Review (ICR) using RECIST 1.1 criteria and supported by the Investigator assessment of ORR and by other efficacy endpoints (duration of response [DoR], disease control rate [DCR], progression-free survival [PFS], overall survival [OS], and time to treatment discontinuation or death [TDT]), patient-reported outcomes (PROs), and safety and tolerability data.

Subject population

A total of 95 patients were screened, from which 62 patients were enrolled in the study and 60 patients received study treatment (cediranib and olaparib). Patient demographics were as expected for this patient population of heavily pre-treated ovarian cancer patients. Of the 60 treated patients, 58 patients had received at least the per-protocol minimum of 3 lines of prior treatment and the median was 4 prior lines of treatment; 2 patients were protocol deviations due to having received only 2 prior lines of treatment.

Disease progression was the primary reason for discontinuing IP for 53.3% of patients. A total of 23.3% of patients discontinued either or both IPs due to adverse events (AEs) (5.0% cediranib only, 1.7% olaparib only, and 18.3% both cediranib and olaparib), 11.7%

discontinued IP due to withdrawal of consent, and 8.3% discontinued IP due to other reasons (not specified).

The most common concomitant medications (antiemetics, antipropulsives, and natural opium alkaloids) taken by patients during the study were related to nausea, hypertension, and pain.

Summary of efficacy results

- The mean ORR by ICR was 15.6% by posterior distribution.
- Sixteen patients (26.7%) had response according to Investigator assessment (either confirmed or unconfirmed), all of which were partial response (PR). Of these, 10 patients (16.7%) had confirmed response.
- Of the 9 patients in the evaluable for response analysis set who were positive for somatic *BRCA1*, *BRCA2*, or HRR mutations, 2 patients (22.2%) were responders, both of whom had PR, and both of whom were *tBRCA2*; in the 42 *BRCA1*-, *BRCA2*-, or HRR-negative patients, 6 patients (14.3%) were responders.
- The median DoR from onset of response was 8.3 months (36.0 weeks) by ICR and 10.3 months (45.0 weeks) by Investigator assessment.
  - The median DoR from onset of response was 7.5 months (32.6 weeks) in patients who were positive for somatic *BRCA1*, *BRCA2*, or HRR mutations versus 10.3 months (45.0 weeks) for mutation-negative patients.
  - A total of 14 patients (23.7%) had disease control at 6 months by ICR and 16 patients (26.7%) had disease control at 6 months by Investigator assessment. The DCR at 6 months was similar in patients who were positive for somatic *BRCA1*, *BRCA2*, or HRR mutations versus those who were mutation-negative.
- Median PFS was 5.1 months by ICR and 3.8 months by Investigator assessment.
- The median time to discontinuation of treatment or death was 3.5 months.
- Median OS was 13.2 months.
- Most European Organization for Research and Treatment of Cancer quality of life questionnaire for cancer patients (EORTC QLQ-C30) and OV28 scales showed some worsening over 24 weeks, but scores generally remained stable for pain (C30), emotional functioning (C30), body image (OV28), and sexuality (OV28)
- For all EORTC QLQ-C30 and OV28 scales, the most commonly reported best observed change from baseline response was “stayed the same,” except for fatigue, where most had a best response of “deteriorated.” A best response of “improved” was observed in 25% of evaluable patients for pain and 21.9% for body image.
- Some patients reported meaningful disease symptom improvement at Week 8, particularly for pain and constipation.
- Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) responses demonstrated that nausea and

decreased appetite were more common than vomiting and dizziness. Those who experienced these symptoms generally reported them to be mild to moderate in severity and causing limited interference on daily activities.

- Due to the small number of patients (n=2) with CA-125 progression, the median time to CA-125 progression could not be calculated.

Summary of safety results

- The median actual treatment duration (excluding dose interruptions and planned "no dose" periods for intermittent dosing) was 3.5 months for cediranib and 3.4 months for olaparib.
- Deaths were reported in 36 patients (60.0%) in the Full Analysis Set (FAS). The majority of reported deaths (33 patients, 91.7% of deaths in the FAS) were due to disease progression and were attributed to the disease under investigation only.
- Four patients (6.7%) had serious adverse events (SAEs) of nausea and 2 patients (3.3%) had SAEs of vomiting; all other SAEs were isolated events occurring in single patients (1.7%). No causally treatment-related AEs with outcome of death were recorded. There were no events of myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) reported during the course of the study.
- Overall, the most common AEs leading to IP discontinuation were nausea (3 patients, 5.0%), fatigue (3 patients, 5.0%), thrombocytopenia (2 patients, 3.3%), and vomiting (2 patients, 3.3%). Of these, all resulted in discontinuation of both cediranib and olaparib except for 1 patient who was discontinued from olaparib only due to an AE of nausea. All other AEs leading to IP discontinuation occurred in single patients overall.
- The reported AEs were generally mild or moderate in severity. The most common (reported in ≥10% of patients) Grade ≥3 AEs were hypertension (18 patients, 30.0%), fatigue (13 patients, 21.7%), diarrhea (8 patients, 13.3%), and nausea (7 patients, 11.7%).
- The most common AEs were fatigue (68.3%; related: 61.7%), nausea (68.3%; related: 56.7%), diarrhea (66.7%; related: 63.3%), hypertension (66.7%; related: 60.0%), vomiting (41.7%; related: 33.3%), decreased appetite (36.7%; related: 31.7%), abdominal pain (35.0%; related: 13.3%), headache (35.0%; related: 23.3%), constipation (30.0%; related: 15.0%), hypomagnesemia (25.0%; related: 8.3%), dyspnea (23.2%; related: 8.3%), anemia (20.0%; related: 15.0%), and hyponatremia (20.0%; related: 5.0%). This is consistent with the known safety profiles of olaparib and cediranib treatments.
- The incidence of CTCAE Grade 3 hematology parameter values was low, and there were no Grade 4 hematology parameter values.
- The most common changes in clinical chemistry parameters were reported as Grade 1 or 2; there were 3 patients (5.0%) with Grade 3 abnormal bilirubin and 1 patient (1.7%) each with Grade 3 abnormal ALT, Grade 3 abnormal ALP, and Grade 3 abnormal AST. One patient (1.7%) had Grade 4 abnormal ALT.
- Three patients met predefined criteria for potential Hy's Law, of which 1 event was determined to be a case of drug-induced liver injury (DILI).

- Overall, there were no clear trends in mean systolic blood pressure (SBP) or diastolic blood pressure (DBP) after baseline; although, hypertension was frequently observed in individual patients. Body weight was observed to decrease over time after baseline.

Conclusion(s)

- Cediranib/olaparib showed limited evidence of antitumor activity based on the posterior probability calculations, but did not meet the target of 20% ORR in this heavily pre-treated (4 lines and platinum resistant/refractory), non-*gBRCAm* ovarian cancer patient population, with 88.3% of the patients already exposed to a vascular endothelial growth factor inhibitor (VEGFi), bevacizumab.
- For most EORTC QLQ-C30 and OV28 scale scores, some worsening in mean scores was observed over 24 weeks; mean pain scores remained generally stable, and improvements in pain were observed at 8 weeks by nearly half of evaluable patients.
- The safety findings of this study are consistent with the known safety profiles of cediranib and olaparib, with some evidence of overlapping toxicity and increase in Grade ≥3 AEs.
- The toxicity was considered manageable with an effective toxicity management, including dose interruptions, dose reductions, and/or the use of supportive care approach.
- Overall, the safety and tolerability profiles were considered acceptable for the patient population for which standard of care therapy does not exist or has proven ineffective or intolerable.
- Low numbers of patients with somatic *BRCAm* or HRRm do not permit a firm conclusion of impact of the biomarkers on response to treatment.

Clinical Study Report Errata	
Drug Substance	cediranib (AZD2171) plus olaparib (AZD2281)
Study Code	D8488C00001
Edition Number	Version 1.0
Version 1.0	26 April 2021

Clinical Study Report Errata

A single arm, open-label, Phase IIb study to assess the efficacy and safety of the combination of cediranib and olaparib tablets in women with recurrent platinum-resistant epithelial ovarian cancer, including fallopian tube and/or primary peritoneal cancer who do not carry a deleterious or suspected deleterious germline BRCA mutation

Study dates: First patient screened: 17 January 2017
Last patient enrolled: 28 November 2018
The analyses presented in this report are based on a database lock date of 25 September 2019

Phase of development: Therapeutic exploratory (II)

International Co-ordinating Investigator:

Sponsor's Responsible Medical Officer:

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

This submission/document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

1 CLARIFICATION ON HY'S LAW CASE STATEMENT

Purpose: To clarify that no cases of potential Hy's Law met the criteria for Hy's Law.

Section	Page	Original text	Revised text
2 Synopsis	6 in full CSR; 5 in standalone synopsis document	Three patients met predefined criteria for potential Hy's Law, of which 1 was determined to be a case of potential DILI.	Three patients met predefined criteria for potential Hy's Law, of which 1 was determined to be a case of potential DILI. None of the reports of abnormalities in liver function parameters were consistent with the criteria of Hy's Law.
12.4.2.4 Elevations in alanine aminotransferase or aspartate aminotransferase accompanied by elevations in total bilirubin	96	Three patients met predefined criteria for potential Hy's Law, of which 1 was determined to be a case of potential DILI.	Three patients met predefined criteria for potential Hy's Law, of which 1 was determined to be a case of potential DILI. None of the reports of abnormalities in liver function parameters were consistent with the criteria of Hy's Law.
12.6 Safety evaluation conclusions	99	Three patients met predefined criteria for potential Hy's Law, of which 1 was determined to be a case of potential DILI.	Three patients met predefined criteria for potential Hy's Law, of which 1 was determined to be a case of potential DILI. None of the reports of abnormalities in liver function parameters were consistent with the criteria of Hy's Law.
13.1 Discussion	100	Three patients met predefined criteria for potential Hy's Law, of which 1 was determined to be a case of potential DILI.	Three patients met predefined criteria for potential Hy's Law, of which 1 was determined to be a case of potential DILI. None of the reports of abnormalities in liver function parameters were consistent with the criteria of Hy's Law.