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A Multicentre Phase II Study of AZD1775 plus Chemotherapy in Patients with Platinum-Resistant Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Study dates:
First patient enrolled: 28 January 2015
Last patient last visit: 13 December 2018
The analyses presented in this report are based on a database lock date of 14 February 2019.

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

2. SYNOPSIS

Study centre(s)

The study was sponsored by AstraZeneca at 20 global investigational sites including 18 study centres in the United States, 1 in Canada, and 1 in the Netherlands.

Publications

Moore et al. 2015

Moore et al. 2017

Moore et al. 2019

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To evaluate the objective response rate (ORR) of AZD1775 in combination with carboplatin, paclitaxel, gemcitabine, or pegylated liposomal doxorubicin (PLD) in patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer.	The primary endpoint of this study was ORR for the arms included in the efficacy assessment, defined as the proportion of patients achieving a complete or partial tumour response according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 (Eisenhauer et al 2009).
Secondary	Efficacy	To evaluate the duration of response (DoR) of AZD1775 in combination with gemcitabine, PLD, carboplatin, or paclitaxel.	DoR, defined as the time from first documented tumour response until the date of documented progression or death from any cause.
Secondary	Safety	To evaluate the safety and tolerability of AZD1775 in combination with paclitaxel, gemcitabine, carboplatin or PLD in patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer.	Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and deaths; clinically significant changes in safety-related laboratory parameters according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.03) and abnormal vital signs.

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Secondary	Efficacy	To evaluate the disease control rate (DCR) of AZD1775 in combination with carboplatin, paclitaxel, gemcitabine, or PLD in patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer.	DCR, defined as the proportion of patients achieving a complete response (CR), partial response (PR), or stable disease (SD) according to RECIST v1.1 criteria.
Secondary	Efficacy	To evaluate the cancer antigen-125 (CA-125) response of AZD1775 in combination with carboplatin, paclitaxel, gemcitabine, or PLD in patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer.	Gynecologic Cancer Intergroup (GCIG) CA-125 response, defined as the proportion of patients achieving a 50% reduction in CA-125 levels from baseline, if baseline level is ≥2 x the upper limit of normal (ULN) within 2 weeks prior to starting treatment. Response must be confirmed and maintained for at least 28 days.
Secondary	Pharmacokinetics	To characterise the PK of AZD1775 plus carboplatin, AZD1775 plus paclitaxel, AZD1775 plus PLD, and AZD1775 plus gemcitabine.	Plasma PK parameters of AZD1775 plus carboplatin, AZD1775 plus paclitaxel, AZD1775 plus PLD, and AZD1775 plus gemcitabine.
Secondary	Pharmacokinetics	To assess the drug interaction between AZD1775 plus carboplatin, AZD1775 plus paclitaxel, AZD1775 plus gemcitabine, and AZD1775 plus PLD.	Plasma PK parameters of AZD1775 plus carboplatin, AZD1775 plus paclitaxel, AZD1775 plus gemcitabine, and AZD1775 plus PLD.
Exploratory	Pharmacogenetics	To identify genetic alterations in breast cancer genes 1 and 2 (*BRCA1* and *BRCA2*) and other relevant genes, including *TP53,* from analysis of archived or fresh tumour tissue collected at baseline, and to determine if the presence of a genetic alteration is predictive of clinical outcomes.	Molecular analysis of tumour tissue samples will be reviewed and correlated with clinical data.

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Exploratory	Pharmacogenetics	To analyse changes in plasma circulating free tumour DNA (cfDNA) over time, from baseline, to restaging, and at disease progression. (This exploratory analysis will be reported separately from the Clinical Study Report [CSR].)	Blood samples will be collected to analyse cfDNA concentrations and molecular alterations.
Exploratory	Efficacy	To obtain preliminary estimates of the overall survival (OS) and progression-free survival (PFS) of AZD1775 in combination with gemcitabine, PLD, carboplatin, or paclitaxel.	OS, defined as the time from first dose to death from any cause, and PFS, defined as the time from first dose to the first documentation of disease progression (according to RECIST v1.1 criteria) as determined by the Investigator or death from any cause, whichever comes first.
Exploratory	Pharmacogenetics	To collect and store DNA for future research into genes/genetic variations that may influence PK or response to AZD1775 (i.e., absorption, distribution, metabolism, excretion, safety, and efficacy) and/or susceptibility to the development of cancers.	Correlation of genetic polymorphisms with variation in PK, safety or response observed in patients treated with AZD1775. Data generated may be reported separately and may also form part of a pooled analysis with other AZD1775 studies.

Study design

This was a multicentre Phase II study designed to assess the efficacy of AZD1775 plus chemotherapy in patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Target patient population and sample size

The target population for this study was patients with platinum-resistant (defined as experiencing disease recurrence within 6 months of completing treatment) epithelial ovarian, fallopian tube, or primary peritoneal cancer. All patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, in addition to adequate haematologic, liver and renal function.

Following the first database lock on 27 December 2016, 12 patients continued to receive study treatment since they were still experiencing clinical benefit in the opinion of the investigator. Following the second database lock (14 December 2018), 8 patients were continuing to receive study treatment. A total of 20 patients continued to receive treatment following the 2 database locks because they were continuing to experience clinical benefit in the opinion of the Investigator. The most common reason for treatment discontinuation was disease progression (54 patients, 57.4%).

A total of 95 patients were enrolled into the study. Ninety-four patients (98.9%) received study treatment. One patient was a screen failure but was counted as enrolled and not assigned to a cohort due to data entry error.

Patients were treated on the following treatment arms.

Table S2 GYN 49 Treatment Arms

Treatment Arm	Drug Dosing	Number of Patients Treated
Arm A	AZD1775 175 mg by mouth (PO) daily days (D)1-2, 8-9, 15-16 + gemcitabine 800 mg/m^2 IV D1, 8, 15 q28D*	9
Arm B	AZD1775 225 mg PO twice daily (BID) x 5 doses D1-3, 8-10, 15-17 + paclitaxel 80 mg/m^2 IV D1, 8, 15 q28D	38
Arm C	AZD1775 225 mg PO BID x 5 doses D1-3 + carboplatin AUC 5 IV D1 q21D	23
Arm C2	AZD1775 225 mg PO BID x 5 doses D1-3, 8-10, 15-17 + carboplatin AUC 5 IV D1 q21D	12
Arm D-175 mg	AZD1775 175 mg PO BID x 5 doses D1-3 + PLD 40 mg/m^2 IV D1 q28D	6
Arm D-225 mg	AZD1775 225 mg PO BID x 5 doses D1-3 + PLD 40 mg/m^2 IV D1 q28D	6

*The original gemcitabine dose was 1000 mg/m^2 for the first 4 patients treated on Arm A. This was decreased to 800 mg/m^2 after Amendment 2. The remaining 5 patients were treated at this dose.

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

AstraZeneca manufactured and supplied AZD1775 dry-filled capsules for oral use. The capsules were supplied at 2 strengths, 25 and 100 mg in open-labelled bottles.

Additional information about the investigational product may be found in the IB.

Patients were advised to return any unused AZD1775 in the original bottles, in addition to returning any empty bottles.

All study drugs were kept in a secure place under appropriate storage conditions. The investigational product label on the bottle and the IB specified the appropriate storage.

Labels were prepared in accordance with Good Manufacturing Practice and local regulatory guidelines. The labels fulfilled Good Manufacturing Practice Annex 13 requirements for labelling.

The details of AZD1775 are presented in Section 7.1 of the CSP (Appendix 16.1.1) and batch numbers are presented in Appendix 16.1.6.

Duration of treatment

Ninety-four out of 95 enrolled patients initiated their assigned AZD1775 plus chemotherapy regimen on Cycle 1. AZD1775 was taken at home by the study patients and they were to report any missed doses in a dosing diary. In addition, drug accountability was monitored by the site at each study visit.

The first patient started treatment on 2 Feb 2015, and the last patient started dosing on 17 April 2018 (Appendix 16, Listing 16.2.5.1). The extent of exposure to AZD1775 as of the data cut-off (14 December 2018), including dose interruptions and reductions, is summarised in Table 14.3.1.1 to Table 14.3.1.3.

Following the first database lock on 27 December 2016, 12 patients (2 on Arm B, 3 on Arm C, and 7 on Arm D) continued to receive study treatment since they were still experiencing clinical benefit in the opinion of the investigator. Following the second database lock (14 December 2018), 8 patients (5 on Arm B and 3 on Arm C2) were continuing to receive study treatment. A total of 20 patients continued to receive treatment following the 2 database locks because they were continuing to experience clinical benefit in the opinion of the Investigator.

The median (range) number of initiated cycles for the overall population was 4 (1-23). The median (range) time on study treatment was 3.1 months (0-19 months) for all patients.

The median (range) of total exposure to AZD1775 was 3.1 months (0 to 19 months) for all patients on the study. The median (range) total exposure to chemotherapy was 3.0 months (0-19 months).

The AZD1775 median (range) relative dose intensity (RDI) was 90.8% (20-101%) for all patients in this study. The chemotherapy median (range) RDI was 87.4% (41-100%) for all patients. The mean (± standard deviation) RDI of AZD1775 and of chemotherapy were 86.7% (±15.31) and 83.2 (±17.66), respectively, for the overall patient population.

Statistical methods

The statistical analyses were performed using SAS by Sarah Cannon Development Innovations under the direction of the Biometrics Group, AstraZeneca.

Tumour Response
Patients underwent regular tumour assessments until documented objective disease progression as defined by RECIST v1.1. At each restaging visit the RECIST data for a patient was assigned a response of CR, PR, SD, or PD depending on the status of the disease compared with baseline and previous assessments.

Progression of Target Lesions (TL) was calculated in comparison with what the tumour burden was at nadir (i.e., smallest sum of diameters previously recorded on study). In the absence of progression, tumour response (CR, PR, or SD) was calculated in comparison to the baseline tumour measurements obtained before starting treatment.

CA-125 response
Serum samples were collected for the CA-125 tumour marker on all patients at baseline (within 14 days prior to Cycle 1 Day 1), Day 1 of each cycle, and at the end-of-study treatment visit.

For patients in the CA-125 analysis set, CA-125 response was defined as a 50% reduction in CA-125 levels from baseline. The response had to be confirmed and maintained for at least 28 days. Patients who had both a CA-125 response and whose CA-125 level fell to within the normal range could be classified as CA-125 complete responders.

Pharmacokinetics
Pharmacokinetic analysis based on AZD1775 plasma concentration data was performed by Covance on behalf of AstraZeneca. The PK parameters were calculated using non-compartmental methods with plasma concentrations of AZD1775 and chemotherapy agents. The following parameters were determined as data permitted:

- AZD1775: C_{max}, dose-normalized C_{max}, C_{8hr}, t_{max}, t_{last}, AUC_{0-t}, dose-normalized AUC_{0-t}
- Gemcitabine and metabolite dFdU: C_{max} , t_{max} , AUC_{0-t} , t_{last}, metabolite:parent ratio (MR AUC_{0-t})
- Paclitaxel: C_{max}, t_{max}, AUC_{0-t}, t_{last}, AUC, $t_{1/2\lambda z}$, clearance (CL), V_z, and V_{ss}
- Carboplatin: C_{max}, t_{max}, AUC_{0-t}, t_{last}, AUC, $t_{1/2\lambda z}$, CL, V_z, and V_{ss}
- PLD: C_{max}, t_{max}, AUC_{0-t}, t_{last}, AUC, $t_{1/2\lambda z}$, CL, V_z, and V_{ss}

Safety
All patients who received at least 1 dose of AZD1775, gemcitabine, paclitaxel, PLD, or carboplatin were included in the assessment of the safety.

Exposure
The total time on study treatment as well as total exposure to study treatment and the amount delivered relative to the intended amount were summarised. The number of patients with

pauses and reductions in the dose intensities of AZD1775, gemcitabine, paclitaxel, PLD and carboplatin were also summarised.

Adverse Events

Adverse Events were graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, whenever possible. The AE reporting period for safety surveillance began when the patient was included into the trial (date of first signature of informed consent) and continued through the trial's post treatment follow-up period, defined as 30 days after last study drug administration.

Patient population

- One hundred and twenty-six patients were consented, 95 were enrolled and 94 patients received study drug. At the time of data cut-off, 20 patients (21.3%) overall [7 patients (18.4%) in Arm B, 3 patients (13.0%) in Arm C, 3 patients (25%) in Arm C2, 2 patients (33.3%) in Arm D-175 mg AZD1775, and 5 patients (83.3%) in Arm D-225 mg AZD1775] remained on treatment, and 74 patients discontinued treatment. The most common reason for treatment discontinuation was progressive disease (54 patients, 57.4%).
- There was 1 important protocol deviation. One patient was enrolled onto Arm B despite meeting an exclusion criterion.
- All patients were female. The median age was 60 years with 37.2% of patients ≥65 years of age.
- Eighty-five patients (90.4%) had a serous epithelial tumour histology, an additional 4 patients (4.3%) had clear cell epithelial carcinoma histology, and 1 patient each (1.1%) had endometrioid carcinoma, mucinous epithelial carcinoma, or mixed epithelial carcinoma. Histology for 2 patients (2.1%) was missing.
- All patients had prior systemic therapy. Eighty-eight patients (93.6%) had prior disease-related surgery and 1 patient (1.1%) had prior radiotherapy treatment.
- Eighty-nine patients (94.7%) received concomitant dexamethasone.
- Ninety patients (95.7%) received a mandatory 5-HT3 antagonist, including 78 patients (83.0%) who received concomitant ondansetron. The 4 patients who did not receive a 5-HT3 antagonist were in violation of the protocol, but did not meet the criteria of an important protocol violation.

Although the numbers of patients in each treatment arm were small, the demographic and baseline disease characteristics were representative of the intended patient population for this study, and there were no notable baseline or demographic characteristics considered to have affected the outcome of the study. The usage of concomitant medication appeared to be reasonable in the clinical context. The study was well conducted, with only one important protocol deviation.

Summary of efficacy results

- The ORR (per Investigator's assessment) for the overall patient population was 31.9% (30 out of 94 patients) and the DCR was 73.4% (69 out of 94 patients).
- A total of 3.2% (3 of 94 patients) had a best overall response of CR, 28.7% (27 of 94 patients) demonstrated a confirmed PR.
- The ORR and DCR for the treatment arms are as follows:

Arm	ORR	DCR
Arm A	1/9 (11.1%)	3/9 (33.3%)
Arm B	11/38 (28.9%)	27/38 (71.1%)
Arm C	7/23 (30.4%)	19/23 (82.6%)
Arm C2	8/12 (66.7%)	12/12 (100.0%)
Arm D-175 mg	2/6 (33.3%)	3/6 (50.0%)
Arm D-225 mg	1/6 (16.7%)	5/6 (83.3%)
Overall	30/94 (31.9%)	69/94 (73.4%)

- The highest response rate was seen in Cohort C2 with an ORR of 66.7% and a DCR of 100%.
- The median PFS was 5.5 months (95% CI 3.9-7.2). At the time of data cut-off 14 December 2018, 37 patients (39.4%) were censored for progression-free survival.

Arm	Median PFS	95% CI
Arm A	1.7	(0.3-5.5)
Arm B	5.5	(3.7-7.4)
Arm C	4.2	(2.8-8.9)
Arm C2	12.0	(2.7-NC)
Arm D-175 mg	2.7	(0.5-NC)
Arm D-225 mg	NC	(NC-NC)
Overall	5.5	(3.9-7.2)

See Table S2 for Treatment Arm Information

- The longest median PFS (12.0 months) was seen in Cohort C2.
- The median OS was 19.2 months (95% CI 12.4 - 19.2). At time of data cut-off for analysis, 63 patients (67.0%) were censored for overall survival.

Arm	Median OS	90% CI
Arm A	16.0	(2.2-NC)
Arm B	NC	(11.6-NC)
Arm C	8.9	(6.5-NC)
Arm C2	19.2	(12.4-19.2)
Arm D-175 mg	6.2	(2.0-NC)

Arm	Median OS	90% CI
Arm D-225 mg	NC	(NC-NC)
Overall	19.2	(12.4-19.2)

See Table S2 for Treatment Arm Information

- The longest median OS (19.2 months) was seen in Cohort C2.
- The median DoR for the overall population was 10.8 months (95% CI 5.8-NC).
- In the CA-125 analysis set, the overall CA-125 response rate was 42.9% (30/70) (90% CI 32.8%-53.4%).

This Phase II study provides preliminary evidence of anti-tumour activity of AZD1775 in combination with one of the commonly used chemotherapy regimens (gemcitabine, paclitaxel, carboplatin, or PLD) in patients with primary platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal tumours. This anti-tumour activity was highest in the carboplatin combination with weekly AZD1775, achieving a 66.7% response rate.

Summary of pharmacokinetic results

- There were no apparent pharmacokinetic drug interactions between AZD1775 and gemcitabine, paclitaxel, or carboplatin when co-administered.
- However, systemic exposure to AZD1775 was significantly increased by co-administered PEGylated doxorubicin, and doxorubicin exposure also increased as AZD1775 dose increased. Further investigation would be needed to understand the possible interactions between AZD1775 and doxorubicin.

Summary of safety results

- A total of 94 patients received the planned starting dose of AZD1775 and chemotherapy for their treatment arm. One patient was discontinued from the study prior to receiving the first dose of AZD1775 and chemotherapy.
- The median of total exposure to AZD1775 was 3.1 months, and total exposure to chemotherapy was 3.0 months. The median RDIs for AZD1775 and for chemotherapy were 90.8% and 87.4%, respectively.
- All study patients experienced at least one AE and 93 patients (98.9%) experienced an AE related to a study treatment. A total of 83.0% (78 out of 94 patients) experienced at least one Grade ≥3 AE, of which 73.4% (69 out of 94 patients) experienced a Grade ≥3 AE that was considered by the Investigator to be causally related to AZD1775 including 72.3% (68 out of 94 patients) who experienced a Grade ≥3 AE that was considered by the Investigator to be causally related to chemotherapy and AZD1775.
- Patients in Arm C2 experienced the highest rate of Grade ≥3 AEs (100%), Grade ≥3 AEs that were considered by the Investigator to be causally related to AZD1775 (100%), and Grade ≥3 AEs that were considered by the Investigator to be causally related to chemotherapy (100%).
- A total of 46.8% (44 out of 94) of patients experienced SAEs, including 27.7% (26 out of 94 patients) who experienced SAEs considered by the Investigator to be causally related to AZD1775 and 27.7% (26 out of 94 patients) who had SAEs considered by the Investigator to be causally related to chemotherapy.

- Patients in Arm C2 experienced the highest rate of SAEs (66.7%), including 58.3% (7 out of 12 patients) who experienced SAEs considered by the Investigator to be causally related to AZD1775 and 58.3% (7 out of 12 patients) who had SAEs considered by the Investigator to be causally related to chemotherapy.
- One patient (1.1%) had an SAE of [redacted] that resulted in death. The event was considered by the Investigator to be causally related to chemotherapy (paclitaxel) and AZD1775. This is described in more detail in a narrative (see Section 14.4.1).
- TEAEs experienced by >50% of all patients were nausea (65 patients [69.1%]), diarrhoea (62 patients [66.0%]), fatigue (59 patients [62.8%]), neutropenia/neutrophil count decreased (55 patients [58.5%]), and anaemia (55 patients [58.5%]).
- AZD1775-related AEs experienced by >10% of all patients were diarrhoea (58 patients [61.7%]), nausea (58 patients [61.7%]), fatigue (54 patients [57.4%]), neutropenia/neutrophil count decreased (53 patients [56.4%]), anaemia/haemoglobin decreased (51 patients [54.3%]), thrombocytopenia/platelet count decreased (43 patients [45.7%]), vomiting (39 patients [41.5%]), WBC count decreased (18 patients [19.1%]), decreased appetite (13 patients [13.8%]), and dysgeusia (10 patients [10.6%]).
- Chemotherapy-related AEs experienced by >10% of all patients were neutropenia/neutrophil count decreased (55 patients [58.5%]), nausea (53 patients [56.4%]), fatigue (51 patients [54.3%]), anaemia/haemoglobin decreased (50 patients [53.2%]), thrombocytopenia/platelet count decreased (44 patients [46.8%]), diarrhoea (40 patients [42.6%]), vomiting (35 patients [37.2%]), WBC count decreased (18 patients [19.1%]), and decreased appetite (12 patients [12.8%]).
- Thirty-seven patients (39.4%) experienced an AE leading to dose reduction of AZD1775 and 44 patients (46.8%) experienced an AE leading to dose reduction of chemotherapy. Patients in Arm C2 experienced the highest rate of AZD1775 dose reductions (91.7%) and chemotherapy dose reductions (91.7%).
- Sixty-four patients (68.1%) experienced an AE leading to dose interruption of AZD1775, and 62 patients (66.0%) experienced an AE leading to dose interruption of chemotherapy. Patients in Arm C2 experienced the highest rate of AZD1775 dose interruptions (91.7%) and patients in Arm A experienced the highest rate of chemotherapy dose interruptions (88.9%).
- Cohort C2 (carboplatin plus weekly AZD1775) was considered non-tolerable due primarily to haematological toxicity.

Conclusions

- This Phase II study provides preliminary evidence of anti-tumour activity of AZD1775 in combination with chemotherapy in this population of patients with primary platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer.
- Patients on Arm C2 exhibited highest anti-tumour activity, however the regimen was associated with increased toxicity and with increased AZD1775 and carboplatin dose reductions and interruptions; additional dose finding would be needed to find a better tolerated dose with similar efficacy.
- There were no apparent pharmacokinetic drug interactions between AZD1775 and gemcitabine, paclitaxel, or carboplatin when co-administered.

- However, systemic exposure to AZD1775 was significantly increased by co-administered PEGylated doxorubicin, and doxorubicin exposure also increased as AZD1775 dose increased. Further investigation would be needed to understand the possible interactions between AZD1775 and doxorubicin.
- The safety profile observed in the study was consistent with the known safety profile of AZD1775 and the chemotherapeutic agents used in this study. The toxicity was manageable with effective toxicity management, including dose delays, dose reductions, intermittent dosing and/or the use of supportive care approach in the patients with poor tolerance.