Clinical Study Report Synopsis	
Drug Substance	Adavosertib (AZD1775)
Study Code	D601HC00002
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A Phase 2b, Open-label, Single-arm, Multi-centre Study Assessing the Efficacy and Safety of Adavosertib as Treatment for Recurrent or Persistent Uterine Serous Carcinoma (ADAGIO)

Study dates: First subject enrolled: 14 December 2020
Last subject enrolled: 23 November 2021
The analyses presented in this report are based on a clinical data lock date of 16 August 2022

Phase of development: Therapeutic exploratory (II)

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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

A total of 28 sites participated in the study: 15 sites in the United States, 1 site in Canada, 5 sites in France, 3 sites in Italy, and 4 sites in Spain.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of adavosertib by the assessment of objective response rate (ORR)	• ORR is defined as the proportion of participants with measurable disease at baseline who have a confirmed complete response (CR) or partial response (PR), as determined by Blinded Independent Central Review (BICR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
Secondary	
• To evaluate efficacy of adavosertib by assessment of duration of response (DoR)	• DoR is defined as the time from the date of first documented response until date of documented progression per RECIST v1.1 as assessed by BICR, or death in the absence of disease progression
• To evaluate efficacy of adavosertib by assessment of depth of response	• Depth of response is defined as the best percentage change from baseline in Target Lesions
• To evaluate the efficacy of adavosertib by assessment of progression-free survival (PFS)	• PFS is defined as time from date of first dose until progression per RECIST v1.1 as assessed by BICR, or death due to any cause
• To evaluate the efficacy of adavosertib by assessment of PFS6	• PFS6 is defined as the proportion of participants alive and progression free at 6 months, and will be reported as the Kaplan-Meier estimate of PFS per RECIST v1.1 as assessed by BICR at 6 months
• To evaluate the efficacy of adavosertib by assessment of overall survival (OS)	• OS is defined as time from date of first dose until the date of death due to any cause
• To evaluate the efficacy of adavosertib by assessment of disease control rate (DCR)	• DCR is defined as the percentage of participants who have a best overall response of CR or PR or who have stable disease for at least 5 weeks after start of treatment (to allow for an early assessment within the assessment window)

Table S1 Objectives and Endpoints

Objectives	Endpoints
• To evaluate the pharmacokinetics of adavosertib	• Plasma concentration of adavosertib: lowest concentration (C_{trough}, pre dose) and maximum concentration (C_{max})
• To assess the safety and tolerability of adavosertib in participants with uterine serous carcinoma	• Safety and tolerability will be evaluated in terms of adverse event (AEs), vital signs, clinical laboratory assessments, electrocardiograms, and AEs leading to dose interruptions, dose reductions, and dose discontinuations • Vital signs parameters include systolic and diastolic blood pressure, and pulse as well as heart rate, body temperature, body weight, height, and body mass index (BMI) • Laboratory parameters include clinical chemistry and haematology parameters as well as urinalysis

Note: For exploratory objectives see Study protocol (version 6.0). None of the exploratory objectives are reported in this report.

Study design

This was a Phase 2b, single-arm, open-label, multi-centre study to assess the efficacy and safety of adavosertib in participants with recurrent or persistent uterine serous carcinoma (USC) who had received at least 1 prior platinum-based chemotherapy regimen for the management of USC. The primary objective was to estimate ORR by BICR.

Target population and sample size

The study included participants aged ≥ 18 years of age with histologically confirmed recurrent or persistent USC. For the purposes of this study, participants with endometrial carcinoma of mixed histology where the serous component comprised at least 10% of the tumour were also included. Participants with carcinosarcomas were not eligible. Only participants with evidence of measurable disease, as per RECIST v1.1, were included. There was no restriction on the number of prior lines of systemic therapy a participant may have previously received, and the platinum-based chemotherapy may have been given in the adjuvant setting.

Approximately 120 participants were planned to be enrolled and dosed, with an intent to include approximately 40 participants or more who had previously been exposed to inhibitors of either programmed cell death-1 receptor (PD-1) or programmed death-ligand 1 (PD-L1). With 120 participants, if the observed ORR was CCI the width of the 2-sided 90% CI would be CCI Following the final protocol amendment (version 6.0), recruitment was closed after 109 participants had been enrolled and dosed (91% of planned recruitment).

Investigational product: dosage, mode of administration and batch numbers

Participants were to receive oral adavosertib (AZD1775; MK-1775) 300 mg once daily (QD) for 5 days followed by 2 days off in Weeks 1 and 2 out of a 21-day cycle. Dose reductions or holds were allowed per protocol-defined guidelines.

As part of protocol amendments made in March 2022 (version 5.0), the starting dose was changed from 300 mg to [CCI] adavosertib (QD; 5 days on, 2 days off in Weeks 1 and 2 out of a 21-day schedule) for the remaining participants to be recruited to the study; however, following the final protocol amendment in May 2022 (version 6.0), recruitment was closed before any participants had been enrolled at the [CCI] starting dose.

Batch numbers used during the course of the study: [CCI]

Duration of treatment

Participants continued to receive adavosertib in 21-day treatment cycles until objective radiological disease progression by investigator assessment using RECIST v1.1, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met.

Statistical methods

This report describes the primary analysis, which was performed 6 months after the last participant first dose (as per protocol-defined guidelines). No further analyses will be performed beyond the primary analysis.

The primary analysis population used for the efficacy and safety endpoints was the full-analysis set (FAS), which included all participants who received at least one (non-zero) dose of study treatment.

The pharmacokinetic analysis set included all dosed participants who had at least one measurable plasma concentration collected post-dose which was obtained without any deviation or event thought to significantly affect the pharmacokinetic analysis.

No formal statistical comparisons have been performed. Descriptive statistics were used for all variables. Continuous variables have been summarised by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables have been summarised by frequency counts and percentages for each category. Unless otherwise stated, percentages were calculated out of the population total.

All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 and are described using the MedDRA Preferred Term unless otherwise stated. Adverse events were considered treatment emergent (TEAEs) if the onset date was, or if they worsened, on or after the first dose of adavosertib and within 30 days after the last dose of

adavosertib. Severity of AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.

Study population

A total of 144 participants were screened, from which 109 participants were enrolled in the study, treated, and included in the FAS; 31 enrolled participants (28.4%) had previously been exposed to PD-1/PD-L1 inhibitors.

Of the 109 participants in the FAS, 104 participants had measurable disease at baseline per BICR.

Participants in the FAS had a mean age of 68.8 years (range: PPD Most participants were white (84.4%) and most had their ethnicity described as not Hispanic or Latino (89.9%). Mean (standard deviation) body mass index was 29.6 (± 7.70) kg/m^2. All participants had received prior therapy for USC: 35.8% had 1 prior line of therapy; 22% had 2 prior lines of therapy; 42.2% had 3 or more prior lines of therapy.

At the time of data cut off (23 May 2022), 7 participants (6.4%) were still ongoing study treatment and 102 (93.6%) had discontinued study treatment. The most common reason for discontinuation was objective disease progression (58.7%), followed by TEAEs (17.4%) and subject decision (9.2%).

Summary of efficacy results

- ORR, as determined by BICR, was 26.0% (27/104 evaluable participants; 95% CI: 17.9% – 35.5%), with 1.0% complete response (1 participant) and 25.0% partial response (26 participants)
- Median DoR in participants with confirmed objective response, by BICR, was 4.7 months (95% CI: 3.84 – 8.34 months)
- The median depth of response by BICR was -21.6%; the mean depth of response by BICR was -20.8% (standard deviation = 31.60%)
- Median PFS by BICR was 2.8 months (95% CI: 2.60 – 3.94 months)
- PFS6 by BICR was 18.1% (95% CI: 10.42% – 27.55%)
- Median OS was 9.6 months (95% CI: 8.28 – non calculable months)
- DCR by BICR was 51.4% (95% CI: 41.6% – 61.1%)

Summary of pharmacokinetic results

- The geometric mean C_{trough} (pre dose) at Day 5 of Cycle 1 was 307.2 nM (geometric coefficient of variation [gCV%] 105.6) and at Day 5 of Cycle 2 was 328.7 nM (gCV% 70.3)

- The geometric mean plasma concentration 2 hours post dose[1] at Day 5 of Cycle 1 was 1115.9 nM (gCV% 82.1) and at Day 5 of Cycle 2 was 1356.6 nM (gCV% 59.3)
- These data are consistent with other adavosertib clinical studies utilising the same dose and schedule, albeit with higher inter-subject variability

Summary of safety results

- Median total treatment duration by the data cut off was 2.46 months (range: 0.1 to 15.2 months). Median duration of therapy at starting dose was 0.49 months (range: 0.1 to 3.3 months). Median relative dose intensity was 66.67% (range: 10% to 100%).
- Overall, 100% of participants experienced at least 1 TEAE. The most commonly reported TEAEs (≥ 15% of participants) were diarrhoea (67.0%), anaemia (66.1%), nausea (65.1%), asthenia (41.3%), constipation and fatigue (40.4% each), vomiting (36.7%), neutropenia (27.5%), abdominal pain and thrombocytopenia (26.6% each), alanine aminotransferase increased and blood creatinine increased (24.8% each), decreased appetite (23.9%), platelet count decreased (21.1%), dyspnoea (20.2%), hypokalaemia (19.3%), aspartate aminotransferase increased and oedema peripheral (18.3% each), neutrophil count decreased (16.5%), and dysgeusia and hyperglycaemia (15.6% each).
- Overall, 68.8% of participants experienced a TEAE of CTCAE Grade 3 or higher
  - The most commonly reported TEAEs of CTCAE Grade 3 or higher (≥ 10% of participants) were neutropenia (21.1%), fatigue (13.8%), anaemia (12.8%), and neutrophil count decreased (10.1%)
  - Overall, 22% of participants experienced a TEAE of CTCAE Grade 4; the most common (≥ 2% of participants) were neutropenia (11.9%), neutrophil count decreased (8.3%), thrombocytopenia (7.3%) and sepsis (2.8%)
- Deaths were reported in 47 participants (43.1%)
  - Deaths due to disease progression were reported in 37 participants (33.9%)
  - TEAEs with outcome of death were reported in 4 participants (3.7%)
    - One death was considered possibly related to adavosertib per investigator: a Grade 5 sepsis (urosepsis per investigator) that occurred in a participant with preceding Grade 4 neutropenia (neutropenia was reported 5 days prior to sepsis and was assessed as possibly related to adavosertib). The participant also experienced Grade 3 anaemia and Grade 4 thrombocytopenia at this time (both assessed as possibly related to adavosertib).
    - A second fatal case of sepsis was reported: a Grade 5 biliary sepsis that was not considered related to adavosertib per investigator and occurred in a participant with preceding Grade 4 neutropenia (neutropenia was reported 1 day prior to sepsis and was assessed as possibly related to adavosertib). The participant also experienced Grade 3 acute kidney injury, Grade 3 anaemia and Grade 4 thrombocytopenia at this time (all assessed as possibly related to adavosertib).

[1] The plasma concentration 2 hours post dose is the estimated C_{max}

- Overall, 45.9% of participants experienced serious TEAEs
  - Serious TEAEs experienced by ≥ 1.0% of participants were sepsis and pulmonary embolism (4.6% each); neutropenia, dyspnoea, vomiting, and neutrophil count decreased (3.7% each), anaemia and diarrhoea (2.8% each), and thrombocytopenia, syncope, embolism, hypotension, pleural effusion, abdominal pain, acute kidney injury, and fatigue (1.8% each)
  - 26.6% of participants experienced serious TEAEs considered possibly related to adavosertib per investigator; the most common (≥ 1.0% of participants) were neutropenia, neutrophil count decreased, sepsis and vomiting (3.7% each), diarrhoea (2.8%), and anaemia, syncope, pulmonary embolism, acute kidney injury and fatigue (1.8% each)
- Overall, 7 cases of sepsis were reported (5 reported as sepsis, 1 as biliary sepsis and 1 as Escherichia sepsis); 5 events recovered, 2 events were fatal, and 5 events were considered possibly related to adavosertib per investigator
- Five of the sepsis cases (including the 2 fatal cases) were associated with Grade 4 neutropenia or Grade 4 neutrophil count decreased: in 3 cases, neutropenia was reported preceding sepsis; in 1 case, neutrophil count decreased was reported on the same day as sepsis; and in 1 case, neutropenia was reported one day after sepsis. Five of the sepsis cases occurred during the first 2 cycles of treatment.
- Overall, 17.4% of participants had a TEAE leading to discontinuation of adavosertib; those TEAEs experienced by > 1.0% of participants were sepsis (3.7%), anaemia (2.8%), and abdominal pain and alanine aminotransferase increased (1.8% each)
- Overall, 56.9% of participants had a TEAE leading to dose reduction; those TEAEs experienced by ≥ 5% of participants were anaemia and nausea (11.0% each), fatigue (10.1%), diarrhoea and asthenia (8.3% each), and neutropenia and neutrophil count decreased (6.4% each)
- Overall, 66.1% of participants had TEAEs leading to dose interruption; those TEAEs experienced by ≥ 5% of participants were fatigue (13.8%), asthenia (11.9%), anaemia and diarrhoea (8.3% each), thrombocytopenia and nausea (7.3%), and vomiting (5.5%)
- Clinically relevant shifts in certain haematology parameters were observed: ≥ Grade 3 decreases in neutrophils were reported in 26.2% of participants; ≥ Grade 3 decreases in lymphocytes were reported in 25.7% of participants; and ≥ Grade 3 decreases in leukocytes were reported in 21.1% of participants. Excluding these haematology parameters, no clinically relevant shifts in laboratory values were observed.
- No Hy's law cases were reported

Conclusions

- Adavosertib showed evidence of antitumor activity based on the primary and secondary efficacy endpoints in participants with recurrent or persistent USC previously treated with platinum-based chemotherapy

- The main adverse events in the study were haematological or gastrointestinal in nature; this is consistent with the established safety profile of adavosertib
- Dose reductions and dose interruptions due to TEAEs were frequent in the study
- Adavosertib dosed at 300 mg was not well tolerated, despite toxicity management, in this USC population
- In the study, adavosertib dosed at 300 mg was associated with a risk of severe neutropenia/neutrophil count decreased and sepsis, including fatal outcomes