Adavosertib with Chemotherapy in Patients with Primary Platinum-Resistant Ovarian, Fallopian Tube, or Peritoneal Cancer: an Open-Label, Four-Arm, Phase II Study

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Data sharing statement

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Anonymized datasets may be available on request. Requests for access to data may be submitted at https://astrazenecagroup-dt.pharmacm.com//DT/Home/Index/. The request will undergo an internal review process, and if approved, data will be prepared and shared with specified accessors named on the request form for 12 months via SAS Multi-Sponsor Environment.

Translational Relevance

This Phase II study investigated the safety and efficacy of adavosertib in combination with chemotherapy agents commonly used in patients with primary platinum-resistant ovarian cancer. Adavosertib showed preliminary efficacy when combined with chemotherapy in primary platinum-resistant patients. The most promising treatment combination was adavosertib 225 mg twice daily on days 1–3, 8–10, and 15–17 plus carboplatin every 21 days; however, hematologic toxicity was higher in this cohort than in the others and was more than what would be expected for carboplatin monotherapy. The combination of adavosertib plus carboplatin should be further studied to optimize the dose schedule and supportive medications.

ABSTRACT (250/250 words)

Purpose: This study assessed the efficacy, safety, and pharmacokinetics of adavosertib in combination with four chemotherapy agents commonly used in patients with primary platinum-resistant ovarian cancer.

Patients and Methods: Women with histologically or cytologically confirmed epithelial ovarian, fallopian tube, or peritoneal cancer with measurable disease were enrolled between January 2015 and January 2018 in this open-label, four-arm, multicenter, Phase II study. Patients received adavosertib (oral capsules, 2 days on/5 days off or 3 days on/4 days off) in six cohorts from 175 mg once daily to 225 mg twice daily combined with gemcitabine, paclitaxel, carboplatin, or pegylated liposomal doxorubicin. The primary outcome measurement was overall response rate.

Results: Three percent of patients (3/94) had confirmed complete response and 29% (27/94) had confirmed partial response. The response rate was highest with carboplatin plus weekly adavosertib, at 66.7%, with 100% disease control rate, and median progression-free survival of 12.0 months. The longest median duration of response was in the paclitaxel cohort (12.0 months). The most common grade ≥3 adverse events across all cohorts were neutropenia (45/94 [47.9%] patients), anemia (31/94 [33.0%]), thrombocytopenia (30/94 [31.9%]), and diarrhea and vomiting (10/94 [10.6%] each).

Conclusions: Adavosertib showed preliminary efficacy when combined with chemotherapy. The most promising treatment combination was adavosertib 225 mg twice daily on days 1–3, 8–10, and 15–17 plus carboplatin every 21 days. However, hematologic toxicity was more frequent than would be expected for carboplatin monotherapy, and the combination requires further study to optimize the dose, schedule, and supportive medications.

Trial Registration: ClinicalTrials.gov (NCT02272790) and European Clinical Trials Database (EudraCT2015-000886-30).

Introduction

Standard-of-care treatment for newly diagnosed cases of epithelial ovarian, fallopian tube, or peritoneal cancer (EOC) involves a combination of cytoreductive surgery and adjuvant platinum- and taxane-based chemotherapy (1, 2). While recurrent disease is treatable and most patients initially achieve remission with front-line therapy, tumors become resistant to currently available chemotherapies over time, and patients succumb to their disease (3).

Outcomes for patients with primary platinum-resistant (recurrence <6 months following frontline platinum chemotherapy), recurrent EOC remain particularly poor, with low response rates to further chemotherapy (10–20%), median progression-free survival (mPFS) of 3–4 months, and a median overall survival (mOS) of less than 14 months (3–5). Even these estimates may be optimistic given the results from JAVELIN 200 (NCT02580058) (6). In this randomized Phase III trial of avelumab + pegylated liposomal doxorubicin (PLD) versus avelumab or PLD monotherapy in platinum-resistant disease, the overall response rate (ORR) for PLD was 4.2%. This study was heavily populated with patients who had primary platinum-resistant disease (7). Development of novel drugs for use in the recurrent resistant setting is critical.

Progress has been made in the clinical application of molecularly targeted agents designed to shift EOC treatment away from broad-based cytotoxic use towards more tailored therapeutic interventions (8–10). Although the ORR is quite low, for patients who have platinum resistance (11, 12), targeting the DNA repair process is still an attractive possibility for improving response rates and survival. The ubiquitous loss of *TP53* (13) and dependence on DNA cell cycle checkpoint 2 (G2/M) makes checkpoint 2 inhibition of interest. Cell cycle and DNA replication control involves cyclin-dependent kinases (CDKs),

specifically CDK1 and CDK2, which are regulated by the tyrosine kinase WEE1. CDK1 regulates the G2/M checkpoint; inhibition of WEE1, combined with DNA-damaging agents, causes mitotic entry without completion of DNA repair and replication, leading to mitotic catastrophe (14). CDK2 deregulation through WEE1 inhibition also causes DNA replication stress, due to increased replication-origin firing and nucleotide depletion (15).

Adavosertib (AZD1775) is a potent, selective, small-molecule WEE1 inhibitor. In preclinical studies, adavosertib enhanced antitumor effects of chemotherapy and radiation (15–20), especially for *TP53*-mutated cells (15, 19, 20). Evidence from Phase I and II clinical trials indicates that adavosertib plus chemotherapy appears to be an active combination for consideration in the treatment of platinum-resistant ovarian cancer (PROC) (16, 21–23).

In a Phase I dose-escalation study in patients with solid tumors, the maximum tolerated dose (MTD) of adavosertib was 175 mg when given 2 days per week for 3 consecutive weeks, in combination with gemcitabine (1000 mg/m^2 weekly for 3 consecutive weeks) in a 4-week cycle (16). In the same study, adavosertib 225 mg twice daily (bid) orally for 2.5 days per 21-day cycle (five doses across days 1, 2, and morning of day 3) was the MTD, in combination with intravenous infusion of carboplatin (area under the concentration–time curve, concentration of 5 mg/mL·min [AUC5]) on day 1 (16). This dose achieved the target exposure of 240 nmol/L for 8 hours, which was associated with maximum efficacy in preclinical xenograft studies (16). The schedule of 2.5 days per 21-day cycle was designed to provide continued inhibition of WEE1 by adavosertib at the G2/M checkpoint for up to 60 hours (approximate doubling time of a tumor cell), thus maximizing the number of tumor cells that experience premature checkpoint escape. In a Phase II trial in women with platinum-sensitive *TP53*-mutant ovarian cancer, adavosertib (225 mg bid for 2.5 days per 21-day cycle) in combination with paclitaxel (175 mg/m^2) and carboplatin (AUC5) was

considered tolerable and showed signs of efficacy (21). Additionally, paclitaxel at 80 mg/m^2 every week for 4 weeks for the first three cycles (12 weekly doses) followed by three consecutive weekly doses during each 4-week cycle appeared to be efficacious in chemotherapy-resistant ovarian cancer (24). Pegylated liposomal doxorubicin (PLD) is one of the standard treatments in platinum-resistant ovarian cancer, with an approved dose ranging from 20 to 50 mg/m^2, depending on the cancer type. A stealth liposomal (pegylated) construct increases the circulation half-life of doxorubicin while minimizing the off-target toxicity (25). Potentiation of doxorubicin activity was observed when co-administered with other DNA damage response agents (26). Hence, combination of adavosertib with PLD may have increased efficacy compared with monotherapy.

Adavosertib is primarily metabolized by CYP3A4 and FMO3 and is a weak inhibitor of CYP3A, CYP1A2 and CYP2C19 (27); therefore, the likelihood of drug interactions between adavosertib and chemotherapies such as carboplatin, paclitaxel, gemcitabine, and PLD is unlikely. Gemcitabine is metabolized by cytidine deaminase, carboplatin is cleared mostly unchanged, and paclitaxel is metabolized by CYP2C8 and CYP3A4. In a Phase I study, the pharmacokinetics of adavosertib were approximately linear, increased in a dose-proportional manner, and were not significantly changed in combination with chemotherapy (16).

We therefore conducted a multisite trial exploring the efficacy, safety, and pharmacokinetics of several adavosertib and chemotherapy combinations in patients with primary PROC: adavosertib 175 mg 2 days per week for 3 consecutive weeks + gemcitabine (1000 mg/m^2 weekly for 3 consecutive weeks, reduced to 800 mg/m^2 weekly following a protocol amendment) in a 4-week cycle; adavosertib 225 mg bid for 2.5 days on weeks 1, 2, and 3 of a 28-day cycle + paclitaxel 80 mg/m^2 every week for 4 weeks; adavosertib 225 mg bid (five

doses on days 1–3 or on days 1–3, 8–10, and 15–17 per 21-day cycle) + carboplatin (AUC5) on day 1; and adavosertib (175 mg or 225 mg bid for 2.5 days) + 40 mg/m^2 PLD.

Methods

This study was conducted by Sarah Cannon Research Institute (SCRI) at 20 global investigational sites in the USA, Canada, and the Netherlands according to ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation (ICH)/Good Clinical Practice (GCP) guidance, and the AstraZeneca policy of bioethics. The institutional review boards of all participating sites approved the study, and patients were enrolled following written informed consent. This trial was registered with ClinicalTrials.gov (NCT02272790) and the European Clinical Trials Database (EudraCT2015-000886-30).

Study design

This open-label, four-arm, Phase II study with safety lead-in was designed to evaluate the ORR, safety, pharmacokinetics (PK), and tolerability of adavosertib combined with chemotherapy agents in women with primary PROC. Treatment arms are described in **Table 1**.

Eligibility criteria

Women with histologically or cytologically confirmed EOC with measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (28) were eligible.

All patients had disease progression within 6 months of completing (but without progression during) ≥4 cycles of first-line platinum-based chemotherapy for stage III/IV disease and had ≤4 prior treatment regimens. For treatment arms D and D2, only patients without any prior anthracycline exposure were eligible.

Additional entry criteria included age >18 years, Eastern Cooperative Oncology Group (ECOG) performance status 0–1, and adequate hematologic, liver, and renal function. *TP53* mutation status was not required for study entry.

Safety lead-in and dose-limiting toxicity

A six-patient safety lead-in for each drug combination was conducted during cycle 1 of treatment. Dose-limiting toxicities (DLTs) were defined as any of the following toxicities not attributable to the disease that occurred during cycle 1: grade 4 hematologic toxicity lasting >7 days; grade 3 thrombocytopenia associated with hemorrhage; grade ≥3 non-hematologic toxicity; and other toxicity that was clinically significant and/or unacceptable, was unresponsive to supportive care, resulted in a disruption of dosing schedule of >7 days, or was judged to be a DLT by the investigators.

Dose modifications

Dose modifications for each drug were specified in the protocol and management was detailed for anticipated adavosertib- and chemotherapy-related toxicities. Patients received a serotonin 5-HT_3 antagonist and dexamethasone prior to each dose of adavosertib to prevent nausea and vomiting. If one drug was held as a result of toxicity, treatment with the other drug was allowed to continue as appropriate. If treatment was delayed for >4 weeks because of toxicity, the patient was discontinued from the study. Patients who benefited from treatment were allowed to continue the non-offending medication.

Grade 3 or 4 toxicity required stopping treatment with the offending agent until the toxicity improved to grade ≤1. All patients were followed up for toxicity in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03

(29) from informed consent until 30 days after the end of the last investigational product administration.

Any patient who developed a grade 3 or 4 non-hematologic toxicity that did not resolve to grade ≤1 within 21 days was removed from the study treatment unless approved by the medical monitor. Patients requiring >2 dose reductions of adavosertib and the chemotherapy were discontinued from study treatment. Dose re-escalation was not permitted.

Determination of response

Patients in arms A, B, D, and D2 were evaluated for response every 8 weeks, and patients in arm C were evaluated every 6 weeks. All patients were assessed according to RECIST version 1.1 (23). Patients with elevated cancer antigen 125 (CA-125) serum levels that could be monitored for response were also assessed according to the Gynecological Cancer Intergroup (GCIG) CA-125 response criteria (30).

Pharmacokinetics and exploratory analysis

PK sample collection was based on treatment schedules of adavosertib and the four chemotherapeutic agents. PK analysis was designed to characterize the exposure of analytes in the safety lead-in group, help determine the cause of any adverse events (AEs), and assess the drug interaction between adavosertib and each chemotherapeutic agent.

Exploratory, unblinded analysis of efficacy was also conducted according to the presence of potential genomic biomarkers determined from archival formalin-fixed and paraffin-embedded tissue samples (collected prior to adavosertib treatment) using the FoundationOne® assay and analyzed using Foundation Medicine, Inc's F1 classification

rules (31). Targeted genomic profiling was presented using an in-house bioinformatics platform and correlated with clinical outcomes. All tissue samples were shipped at ambient temperature to a central laboratory for processing. Patients provided additional informed consent for the optional collection of genetic material from archival tumor tissue. Germline and somatic variants were reported if they were known pathogenic, likely pathogenic, or variants of unknown significance (VUS; defined as a variant that cannot be determined to be either pathogenic or benign); only pathogenic or likely pathogenic aberrations were correlated with clinical response, regardless of whether they were somatic or germline.

Statistical analysis

Statistical analyses were performed using SAS® statistical analysis software (SAS Institute, Cary, NC) by Sarah Cannon Development Innovations under the direction of the Biometrics Group, AstraZeneca. All patients who received ≥1 dose of study treatment were included in the safety analyses, and all patients who received ≥1 dose of investigational drug and had measurable disease at baseline were included in the efficacy analysis.

The primary efficacy endpoint was ORR, defined as the proportion of patients with measurable disease with ≥1 confirmed complete response (CR; disappearance of all target lesions since baseline) or partial response (PR; ≥30% decrease in the sum of the diameters of target lesions). An exact two-sided 80%/95% confidence interval (CI) for the ORR was computed using the Clopper and Pearson method. Secondary endpoints included duration of response (DoR), disease control rate (DCR; defined as CR + PR + stable disease [neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease for ≥7 weeks for arms A, B, D, and D2, and for ≥5 weeks for arms C and C2]), PFS, overall survival (OS), PK parameters, and toxicity.

Arm B was designed to enroll 30 patients based on a 20–30% ORR historical reference for paclitaxel alone. Arm C enrollment was based on a primary endpoint of ORR (null hypothesis of 10% vs. an alternative hypothesis of 30% ORR). Arm C2 enrolled an additional 12 patients to assess weekly adavosertib in combination with carboplatin on a 21-day cycle. As arms A, D, and D2 were exploratory, no formal sample-size calculations were conducted.

Results

Disposition and patient characteristics

Ninety-four patients were enrolled between January 28, 2015 and January 29, 2018. The majority of patients were Caucasian (77.7%), with a median (range) age of 60 (34–85) years. Demographics and tumor characteristics are listed in **Table 2**.

The median (range) number of initiated cycles for the overall population was 4 (1–23). Reasons for treatment discontinuation were progressive disease (57.4%), AEs (12.8%), patient decision (3.2%), physician decision (2.1%), death, clinical progression, and study closure at site (1.1% each).

Efficacy and safety

Efficacy for the overall study population, as well as each cohort of the study, is presented in **Table 3**, and a waterfall response plot is shown in **Figure 1**. A Kaplan–Meier plot of PFS by cohort is provided in **Supplementary Figure S1**.

Arm A: Adavosertib 175 mg once daily (qd) on days 1–2, 8–9, and 15–16 + gemcitabine 1000 mg/m^2 intravenous (IV) on days 1, 8, and 15 (every 28 days; *N* = 9). Two of the six safety lead-in patients experienced a DLT of grade 4 neutropenia. Gemcitabine was reduced from 1000 to 800 mg/m^2 after the first four patients experienced hematologic toxicity (5/9 patients were dosed at 800 mg/m^2). The most common non-hematologic AEs were nausea (55.6%), vomiting (44.4%), diarrhea, and fatigue (33.3% each). The most common hematologic AEs were neutropenia (88.9%), thrombocytopenia, and anemia (33.3% each; **Table 4**). Two patients (22.2%) experienced an AE leading to dose reduction

of adavosertib, and six patients (66.7%) experienced an AE leading to dose reduction of gemcitabine.

Arm B: Adavosertib 225 mg bid x 5 doses on days 1–3, 8–10, and 15–17 + paclitaxel 80 mg/m^2 IV on days 1, 8, and 15 (every 28 days; *N* = 38). One of the six safety lead-in patients experienced a DLT of grade 4 neutropenia. The most common non-hematologic AEs included nausea (60.5%), fatigue (60.5%), diarrhea (81.6%), and vomiting (50.0%). The most common hematologic AEs included neutropenia (65.8%), anemia (63.2%), and thrombocytopenia (39.5%; **Table 4**). Eighteen patients (47.4%) experienced an AE leading to dose reduction of adavosertib, and 19 patients (50.0%) experienced an AE leading to dose reduction of paclitaxel. One patient (1.1%) of three (7.9%) died of neutropenic sepsis causally related to chemotherapy (paclitaxel) and adavosertib.

Arm C: Adavosertib 225 mg bid x 5 doses on days 1–3 + carboplatin AUC5 IV on day 1 (every 21 days; N=23). Two of the six safety lead-in patients experienced a DLT of grade 2 diarrhea, and one of these patients experienced additional DLTs of grade 3 nausea and vomiting. The most common non-hematologic AEs were nausea (82.6%), fatigue (73.9%), diarrhea (69.6%), and vomiting (56.5%). Abdominal pain (34.8%) and headache (30.4%) were also reported (**Table 4**). Five patients (21.7%) experienced an AE leading to dose reduction of adavosertib, and eight patients (34.8%) experienced an AE leading to dose reduction of carboplatin.

Arm C2: Adavosertib 225 mg bid x 5 doses on days 1–3, 8–10, and 15–17 (weeks 1–3) + carboplatin AUC5 IV on day 1 (every 21 days; *N* = 12). No DLTs were reported for any of the six safety lead-in patients. The most common non-hematologic AEs were nausea (83.3%), fatigue (66.7%), diarrhea (50.0%), and vomiting (33.3%). Hematologic AEs were

notable and included neutropenia (91.7%), anemia (75.0%), and thrombocytopenia (91.7%; **Table 4**). Eleven patients (91.7%) experienced an AE leading to dose reduction of adavosertib, and 11 patients (91.7%) experienced an AE leading to dose reduction of carboplatin.

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 adavosertib (100%), and grade ≥3 AEs that were considered by the investigator to be causally related to chemotherapy (100%).

Arms D and D2: Adavosertib 175 or 225 mg bid x 5 doses on days 1–3 + PLD 40 mg/m^2 IV on day 1 (every 28 days; *N* = 6 for each dose). No DLTs were reported for any of the six safety lead-in patients at each dose. With the increase in dose of adavosertib, there was increased toxicity, including diarrhea (16.7% to 83.3%), fatigue (50.0% to 83.3%), neutropenia (16.7% to 33.3%), and thrombocytopenia (0% to 16.7%). Notably, the proportion of patients reporting anemia and vomiting decreased with increased dose (**Table 4**). No patients experienced an AE leading to dose reduction of adavosertib or PLD.

The most common (≥10%) AEs are listed in **Table 4**. The most common (≥10%) grade ≥3 treatment-related AEs are listed in **Supplementary Table S1**. A total of 46.8% of patients overall experienced serious AEs (SAEs), including 27.7% who experienced adavosertib-related SAEs (**Supplementary Table S2**).

Pharmacokinetics

Adavosertib was steadily absorbed following oral administration of the drug in combination with infusion of chemotherapy agents. Median time to maximum plasma concentration (t_{max})

values was 2.00–4.08 hours after a single dose on cycle 1 day 1 and 2.88–3.92 hours after multiple bid doses on cycle 1 day 3. After reaching maximum plasma concentration (C_{max}), adavosertib was slowly eliminated, with concentrations remaining relatively constant through 8 hours post-dose; geometric mean plasma concentrations at 8 hours post-dose were approximately 42–92% and 56% of the corresponding geometric mean C_{max} after single and multiple dosing, respectively.

Following a single dose of adavosertib 175 mg plus gemcitabine 1000 mg/m^2, adavosertib C_{max} and AUC from time zero to time t (AUC_{0-t}) values were slightly higher than with gemcitabine 800 mg/m^2. Mean systemic exposure (C_{max} and AUC_{0-t}) to adavosertib following a single dose of adavosertib 225 mg plus paclitaxel 80 mg/m^2 or carboplatin AUC5 was similar.

After multiple bid doses of adavosertib plus PLD, mean C_{max} was 42- to 44-fold higher and mean AUC_{0-t} was 36- to 46-fold higher than after single-dose adavosertib plus other chemotherapy agents. As the adavosertib dose increased from 175 to 225 mg (1.29-fold increase), adavosertib mean C_{max} increased 5.7-fold. This higher adavosertib plasma exposure associated with PLD had not been observed in any previous adavosertib studies, and PLD was not expected to result in a drug interaction with adavosertib. Additional investigations (bioanalytical interference, *in vitro* metabolism, and binding to liposomes) did not reveal a possible mechanism for higher exposure. The PLD-associated increased adavosertib concentration did not result in additional toxicity.

Genetic biomarkers

Exploratory analyses of response and next-generation sequencing (NGS) of pretreatment samples showed that the *TP53* mutation was the most common genetic aberration found

across all cohorts (range, 87.1–100%; **Supplementary Figure S2**). All functional *TP53* mutations were somatic. Only one *KRAS* hotspot mutation (G12V) was identified; all others were amplifications (**Supplementary Table S3)**. No statistically significant correlation was observed between genomic markers and clinical response.

Discussion

In this multisite, multi-arm, Phase II trial of adavosertib in combination with chemotherapy in the treatment of primary PROC, a notable efficacy signal was observed with the combination of adavosertib and carboplatin, particularly for patients in arm C2. The ORR in this arm was 66.7% and the efficacy signals were durable, with mPFS of 12.0 months and mOS of 19.2 months.

These findings are significant when one considers historical controls for ORR and time-to-event endpoints for primary platinum-resistant disease. In clinical trials of single-agent gemcitabine, paclitaxel, carboplatin, or PLD, overall tumor response rates ranged from 5% to 30% in platinum-resistant and platinum-refractory patients (32–37). At a median of 12.0 months, PFS was longer than usually observed in patients with PROC (3–4 months). The JAVELIN 200 ovarian cancer trial observed an ORR of 4.2%, mPFS of 3.5 months, and mOS of 13.1 months for patients treated with PLD (6). The results presented here are consistent with a Phase II study in which patients with *TP53*-mutated, recurrent EOC with relapse within 3 months following primary platinum-based chemotherapy were given adavosertib plus carboplatin (16). The ORR was 43% among all evaluable patients and 47% for patients with serous tumors, median PFS was 5.3 months, and mOS was 12.6 months (22). The time to relapse of ≤3 months following primary platinum treatment differed from the time to relapse of ≤6 months in this study. Furthermore, here, the efficacy signal in the carboplatin arms was not limited to the *TP53*-mutant cases. Two CRs were observed with the combination of adavosertib and carboplatin, both in patients without a *TP53* mutation: in arm C, a patient with clear-cell histology, a loss-of-function mutation in *ARID1A*, a hotspot mutation in *PIK3CA*, and amplification of *MET*, *ERBB2*, and *ZNF217*;

in arm C2, a patient with serous histology, a loss-of-function mutation in *ARID1A,* and a hotspot mutation in *PIK3CA*.

Owing to the known risk of gastrointestinal toxicity with adavosertib, premedication with a 5-HT3 antagonist and dexamethasone was mandatory prior to each adavosertib dose, regardless of study arm (aprepitant and fosaprepitant were not permitted because of the risk of drug–drug interactions). Vigorous antidiarrheal treatment with loperamide was also mandated at the first onset of diarrhea according to American Society of Clinical Oncology guidelines (38). Toxicity was considered generally manageable with dose delays, dose reductions, intermittent dosing, and/or the use of supportive care. Hematologic toxicity was more frequent in arm C2 than in the other arms and was also more frequent than would be expected for single-agent chemotherapy. This is an expected challenge, and additional studies with larger cohorts are required to further optimize the dose schedule and supportive medications for the combination of adavosertib and chemotherapy. The results here are in accordance with previous trials investigating the combination of adavosertib and chemotherapy. In patients with primary platinum-refractory or early platinum-resistant disease, hematologic toxicity was severe with adavosertib in combination with carboplatin, with 44% having grade 4 thrombocytopenia and 39% grade ≥3 neutropenia (22). Hematologic toxicity was also observed in a randomized Phase II trial of gemcitabine with or without adavosertib in patients with platinum-resistant, measurable disease, with grade ≥3 anemia in 31% versus 18%, thrombocytopenia in 31% versus 6%, and neutropenia in 62% versus 30% of patients (23).

Platinum-based chemotherapy remains an important treatment option for ovarian cancer. As recently outlined in ovarian cancer treatment recommendations, patients who are defined as ‘inappropriate for platinum’, based on true progression during receipt of platinum

or an allergy, may benefit from the addition of novel drugs such as adavosertib that disrupt the DNA damage response and potentiate the benefit of platinum treatment (40). It is noteworthy that the vast majority of patients in this study had grade 3 or 4 histology; therefore, further studies are required to explore adavosertib plus chemotherapy in other histologies.

In this study, the combination with gemcitabine did not appear to have preliminary activity, with an ORR of 11.1%. This differs from a recent study of gemcitabine with and without adavosertib in PROC presented by Lheureux and colleagues, which found that the addition of adavosertib improved mPFS from 3 to 4.6 months, mOS from 7.2 to 11.5 months, and ORR from 1% to 21% (23). However, the Lheureux et al. study allowed many prior lines of therapy, so it is likely that patients had acquired platinum resistance. Patients in this current study all had primary platinum resistance, which carries a poorer prognosis (41).

There were no apparent PK drug interactions between adavosertib and gemcitabine, paclitaxel, or carboplatin when co-administered. As previously reported by Leijen et al., plasma exposure in this work increased dose proportionally in the combination therapy arms, and the PK parameters were not different between the chemotherapy groups, with the exception of the PLD combination (16).

Several studies are investigating adavosertib combined with chemotherapy in ovarian cancer (NCT02272790, NCT02101775) and other tumor types. Different adavosertib monotherapy schedules are also being examined (NCT02482311, NCT02610075). Studies are selecting genetic aberrations that may affect response, including breast cancer gene 1/2 (BRCA1/2) mutations and *CCNE1* amplifications, which are usually mutually exclusive (NCT02482311, NCT02511795) (42). *CCNE1*-amplified tumors have a poor prognosis and

are generally refractory to therapies (43). In the present study, no clear correlation was observed between genomic markers and clinical response. However, the number of patients included in each arm was too small to reach meaningful conclusions.

In conclusion, adavosertib showed preliminary efficacy when combined with chemotherapy in primary platinum-resistant EOC. The most promising treatment combination was adavosertib 225 mg bid on days 1–3, 8–10, and 15–17 plus carboplatin every 21 days. The mPFS of 12 months was longer than usually observed in patients with PROC (3–4 months). However, hematologic toxicity was more frequent in this cohort than in the other cohorts, as well as higher than would be expected for carboplatin monotherapy.

Establishing an optimal strategy for managing safety and tolerability and identifying specific patient populations most likely to benefit from treatment may increase the clinical benefit of this regimen. Future studies could build on these and other findings to consider additional adavosertib doses within the chemotherapy treatment cycle and the potential for specific biomarker selection.

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Figure legend

Figure 1 Waterfall plot of best percentage change from baseline in target size, including details of the major driver mutations, in all cohorts

bid, twice daily; PLD, pegylated liposomal doxorubicin; qd, once daily; Trunc/FS, truncation/frameshift; VUS, variant of unknown significance.