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

Kathleen N. Moore[1,2], Setsuko K. Chambers[3], Erika P. Hamilton[1,4], Lee-may Chen[5], Amit M. Oza[6], Sharad A. Ghamande[7], Gottfried E. Konecny[8], Steven C. Plaxe[9], Daniel L. Spitz[1,10], Jill J.J. Geenen[11], Tiffany A. Troso-Sandoval[12], Janiel M. Cragun[3], Esteban Rodrigo Imedio[13], Sanjeev Kumar[13], Ganesh M. Mugundu[14], Zhongwu Lai[15], Juliann Chmielecki[15], Suzanne F. Jones[1], David R. Spigel[1,4], and Karen A. Cadoo[12,16]

ABSTRACT

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.

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). Although 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 to 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; ref. 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

[1]Sarah Cannon Research Institute, Nashville, Tennessee. [2]Stephenson Cancer Center at the University of Oklahoma HSC, Oklahoma City, Oklahoma. [3]The University of Arizona Cancer Center, Tucson, Arizona. [4]Tennessee Oncology, PLLC, Nashville, Tennessee. [5]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, California. [6]Bras Drug Development Program, Princess Margaret Cancer Centre, Toronto, Canada. [7]Augusta University, Augusta, Georgia. [8]UCLA, Los Angeles, California. [9]UC San Diego Health, La Jolla, California. [10]Florida Cancer Specialists & Research Institute, Wellington, Florida. [11]Netherlands Cancer Institute, Amsterdam, the Netherlands. [12]Memorial Sloan Kettering Cancer Center, New York, New York. [13]Oncology Global Medicines Development (GMD), AstraZeneca, Cambridge, United Kingdom. [14]Quantitative Clinical Pharmacology, Early Clinical Development, IMED Biotech Unit, AstraZeneca, Boston, Massachusetts. [15]Translational Medicine, Oncology Research and Development, AstraZeneca, Boston, Massachusetts. [16]Weill Cornell Medical College, New York, New York.

Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Clinical Trial registration ID: NCT02272790

European Clinical Trials Database: EudraCT2015-000886-30.

Corresponding Author: Kathleen N. Moore, Stephenson Cancer Center at the University of Oklahoma Health Sciences Center, 800 N.E. 10th St., Oklahoma City, OK 73104. E-mail: Kathleen-Moore@ouhsc.edu

Clin Cancer Res 2022;28:36–44

doi: 10.1158/1078-0432.CCR-21-0158

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.

an attractive possibility for improving response rates and survival. The ubiquitous loss of *TP53* (13) and dependence on DNA cell-cycle checkpoint 2 (G_2–M) makes checkpoint 2 inhibition of interest. Cell-cycle and DNA replication control involves cyclin-dependent kinases (CDK), specifically CDK1 and CDK2, which are regulated by the tyrosine kinase Wee1. CDK1 regulates the G_2–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; refs. 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 (1,000 mg/m^2 weekly for 3 consecutive weeks) in a 4-week cycle (16). In the same study, adavosertib 225 mg twice daily 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 G_2–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 twice daily 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). In addition, 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). 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 low. 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 (1,000 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 twice daily 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 twice daily (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 twice daily for 2.5 days) + 40 mg/m^2 PLD.

Patients and Methods

This study was conducted by Sarah Cannon Research Institute 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 RECIST v1.1 (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 6-patient safety lead-in for each drug combination was conducted during cycle 1 of treatment. Dose-limiting toxicities (DLT) were

Table 1. Treatment arms ($N = 94$).

Treatment arm	Adavosertib dosing	Chemotherapy agent	Chemotherapy dosing	Cycle length
Arm A ($N = 9$)	175 mg orally daily days 1–2, 8–9, 15–16	Gemcitabine	1,000 or 800 mg/m^2 i.v. days 1, 8, 15[a]	28 days
Arm B ($N = 38$)	225 mg orally twice daily × 5 doses days 1–3, 8–10, 15–17	Paclitaxel	80 mg/m^2 i.v. days 1, 8, 15	28 days
Arm C ($N = 23$)	225 mg orally twice daily × 5 doses days 1–3	Carboplatin	AUC5 i.v. day 1	21 days
Arm C2 ($N = 12$)	225 mg orally twice daily × 5 doses days 1–3, 8–10, 15–17	Carboplatin	AUC5 i.v. day 1	21 days
Arm D ($N = 6$)	175 mg orally twice daily × 5 doses days 1–3	PLD	40 mg/m^2 i.v. day 1	28 days
Arm D2 ($N = 6$)	225 mg orally twice daily × 5 doses days 1–3	PLD	40 mg/m^2 i.v. day 1	28 days

[a]A protocol amendment was implemented to reduce the gemcitabine dose to 800 mg/m^2 after the first 4 patients experienced toxicity (4 patients were dosed at 1,000 mg/m^2 and 5 patients were dosed at 800 mg/m^2).

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 nonhematologic 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 nonoffending 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 nonhematologic 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 v1.1 (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 (AE), 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) 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 (SD; 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% to 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.

Table 2. Demographics and prior systemic therapy ($N = 94$).

Demographic characteristics	Arm A ($N = 9$)	Arm B ($N = 38$)	Arm C ($N = 23$)	Arm C2 ($N = 12$)	Arm D ($N = 6$)	Arm D2 ($N = 6$)	Overall ($N = 94$)
Median age, years (range)	63 (46–72)	60 (45–76)	62 (34–85)	58.5 (52–76)	58.5 (40–72)	60.5 (54–70)	60 (34–85)
Age <65 years, *n* (%)	5 (55.6)	26 (68.4)	14 (60.9)	8 (66.7)	3 (50.0)	3 (50.0)	59 (62.8)
Age ≥65 years, *n* (%)	4 (44.4)	12 (31.6)	9 (39.1)	4 (33.3)	3 (50.0)	3 (50.0)	35 (37.2)
ECOG performance status, *n* (%)							
0	5 (55.6)	19 (50.0)	13 (56.5)	4 (33.3)	1 (16.7)	3 (50.0)	45 (47.9)
1	4 (44.4)	19 (50.0)	10 (43.5)	8 (66.7)	5 (83.3)	3 (50.0)	49 (52.1)
Histology, *n* (%)							
Serous	9 (100.0)	33 (86.8)	21 (91.3)	12 (100.0)	4 (66.7)	6 (100.0)	85 (90.4)
Endometrioid	0	1 (2.6)	0	0	0	0	1 (1.1)
Clear cell	0	2 (5.3)	1 (4.3)	0	1 (16.7)	0	4 (4.3)
Mucinous	0	0	0	0	1 (16.7)	0	1 (1.1)
Mixed	0	1 (2.6)	0	0	0	0	1 (1.1)
Missing	0	1 (2.6)	1 (4.3)	0	0	0	2 (2.1)
Histological grade, *n* (%)							
G1: well differentiated	1 (11.1)	1 (2.6)	0	2 (16.7)	0	0	4 (4.3)
G2: moderately differentiated	0	1 (2.6)	1 (4.3)	0	0	0	2 (2.1)
G3: poorly differentiated	5 (55.6)	28 (73.7)	15 (65.2)	9 (75.0)	5 (83.3)	3 (50.0)	65 (69.1)
G4: undifferentiated	0	3 (7.9)	2 (8.7)	0	1 (16.7)	1 (16.7)	7 (7.4)
GX: could not be assessed/not applicable	2 (22.2)	3 (7.9)	3 (13.0)	1 (8.3)	0	2 (33.3)	11 (11.7)
Missing	1 (11.1)	2 (5.3)	2 (8.7)	0	0	0	5 (5.3)
Number of prior regimens, *n* (%)							
1	3 (33.3)	12 (31.6)	8 (34.8)	4 (33.3)	3 (50.0)	2 (33.3)	33 (35.1)
2	6 (66.7)	16 (42.1)	9 (39.1)	5 (41.7)	3 (50.0)	4 (66.7)	42 (44.7)
3	0	10 (26.3)	6 (26.1)	2 (16.7)	0	0	18 (19.1)
4	0	0	0	1 (8.3)	0	0	1 (1.1)
Prior bevacizumab, *n* (%)							
Yes	2 (22.2)	12 (31.6)	7 (30.4)	5 (41.7)	3 (50.0)	3 (50.0)	32 (34.0)
No	7 (77.8)	26 (68.4)	16 (69.6)	7 (58.3)	3 (50.0)	3 (50.0)	62 (66.0)
Prior surgery, *n* (%)							
Yes	8 (88.9)	35 (92.1)	22 (95.7)	11 (91.7)	6 (100.0)	6 (100.0)	88 (93.6)
No	1 (11.1)	3 (7.9)	1 (4.3)	1 (8.3)	0	0	6 (6.4)
tBRCA1, *n/N* (%)[a]							
Yes	1/9 (11.1)	3/31 (9.7)	1/16 (6.3)	0/11 (0)	0/5 (0)	0/4 (0)	5/76 (6.6)
No	8/9 (88.9)	28/31 (90.3)	15/16 (93.8)	11/11 (100)	5/5 (100)	4/4 (100)	71/76 (93.4)
tBRCA2, *n/N* (%)[a]							
Yes	1/9 (11.1)	0/31 (0)	1/16 (6.3)	1/11 (9.1)	0/5 (0)	0/4 (0)	3/76 (3.9)
No	8/9 (88.9)	31/31 (100)	15/16 (93.8)	10/11 (90.9)	5/5 (100)	4/4 (100)	73/76 (96.1)

Note: Arm A: adavosertib 175 mg daily on days 1–2, 8–9, and 15–16 + gemcitabine 1,000 or 800 mg/m^2 i.v. on days 1, 8, and 15 (every 28 days); arm B: adavosertib 225 mg twice daily × 5 doses on days 1–3, 8–10, and 15–17 + paclitaxel 80 mg/m^2 i.v. on days 1, 8, and 15 (every 28 days); arm C: adavosertib 225 mg twice daily × 5 doses on days 1–3 + carboplatin AUC5 i.v. on day 1 (every 21 days); arm C2: adavosertib 225 mg twice daily x 5 doses on days 1–3, 8–10, and 15–17 (weeks 1–3) + carboplatin AUC5 i.v. on day 1 (every 21 days); arms D and D2: adavosertib 175 or 225 mg twice daily × 5 doses on days 1–3 + PLD 40 mg/m^2 i.v. on day 1 (every 28 days).
Abbreviation: tBRCA1/2, tumor breast cancer gene 1/2.
[a]Determined from optional tumor biopsy samples, which were not provided by all patients.

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%); and 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 **Fig. 1**. A Kaplan–Meier plot of PFS by cohort is provided in Supplementary Fig. S1.

Arm A: Adavosertib 175 mg daily on days 1–2, 8–9, and 15–16 + gemcitabine 1,000 mg/m^2 i.v. on days 1, 8, and 15 (every 28 days; $N = 9$). Two of the 6 safety lead-in patients experienced a DLT of grade 4 neutropenia. Gemcitabine was reduced from 1,000 to 800 mg/m^2 after the first 4 patients experienced hematologic toxicity (5 of 9 patients were dosed at 800 mg/m^2). The most common nonhematologic 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 6 patients (66.7%) experienced an AE leading to dose reduction of gemcitabine.

Arm B: Adavosertib 225 mg twice daily × 5 doses on days 1–3, 8–10, and 15–17 + paclitaxel 80 mg/m^2 i.v. on days 1, 8, and 15 (every

Table 3. Response and survival rates ($N = 94$).

Arm	CR, *n* (%)	PR, *n* (%)	SD, *n* (%)	ORR, *n/N* (%)	DCR, *n/N* (%)	CA-125 response rate, *n/N* (%)	Median PFS, months (95% CI)	Median OS, months (90% CI)
Arm A	0	1 (11.1)	2 (22.2)	1/9 (11.1)	3/9 (33.3)	2/8 (25.0)	1.7 (0.3–5.5)	16.0 (2.2–NC)
Arm B	1 (2.6)	10 (26.3)	16 (42.1)	11/38 (28.9)	27/38 (71.1)	15/28 (53.6)	5.5 (3.7–7.4)	NC (11.6–NC)
Arm C	1 (4.3)	6 (26.1)	12 (52.2)	7/23 (30.4)	19/23 (82.6)	4/15 (26.7)	4.2 (2.8–8.9)	8.9 (6.5–NC)
Arm C2	1 (8.3)	7 (58.3)	4 (33.3)	8/12 (66.7)	12/12 (100.0)	7/11 (63.6)	12.0 (2.7–NC)	19.2 (12.4–19.2)
Arm D	0	2 (33.3)	1 (16.7)	2/6 (33.3)	3/6 (50.0)	1/4 (25.0)	2.7 (0.5–NC)	6.2 (2.0–NC)
Arm D2	0	1 (16.7)	4 (66.7)	1/6 (16.7)	5/6 (83.3)	1/4 (25.0)	NC (NC–NC)	NC (NC–NC)
Overall[a]	3/94 (3.2)	27/94 (28.7)	39/94 (41.5)	30/94 (31.9)	69/94 (73.4)	30/70 (42.9)	5.5 (3.9–7.2)	19.2 (12.4–19.2)

Note: Arm A: adavosertib 175 mg daily on days 1–2, 8–9, and 15–16 + gemcitabine 1,000 or 800 mg/m^2 i.v. on days 1, 8, and 15 (every 28 days); arm B: adavosertib 225 mg twice daily × 5 doses on days 1–3, 8–10, and 15–17 + paclitaxel 80 mg/m^2 i.v. on days 1, 8, and 15 (every 28 days); arm C: adavosertib 225 mg twice daily × 5 doses on days 1–3 + carboplatin AUC5 i.v. on day 1 (every 21 days); arm C2: adavosertib 225 mg twice daily × 5 doses on days 1–3, 8–10, and 15–17 (weeks 1–3) + carboplatin AUC5 i.v. on day 1 (every 21 days); arms D and D2: adavosertib 175 or 225 mg twice daily × 5 doses on days 1–3 + PLD 40 mg/m^2 i.v. on day 1 (every 28 days).
Abbreviations: CA-125, cancer antigen 125; NC, not calculable.
[a]Overall values are presented as *n/N* (%) for CR, PR, SD, ORR, DCR, and CA-125 response.

28 days; $N = 38$). One of the 6 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 3 (7.9%) died of neutropenic sepsis causally related to chemotherapy (paclitaxel) and adavosertib.

Arm C: Adavosertib 225 mg twice daily × 5 doses on days 1–3 + carboplatin AUC5 i.v. on day 1 (every 21 days; $N = 23$). Two of the

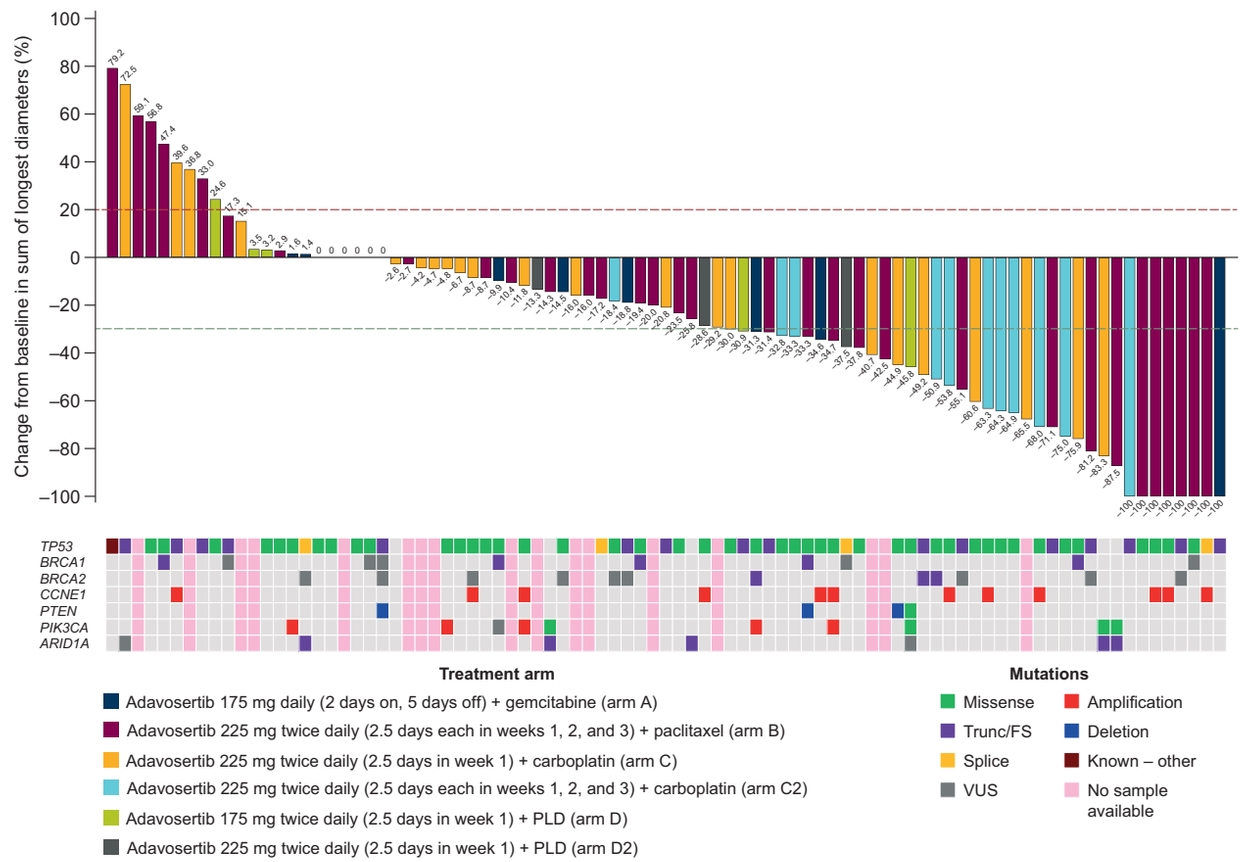

Figure 1.
Waterfall plot of best percentage change from baseline in target size, including details of the major driver mutations, in all cohorts. Trunc/FS, truncation/frameshift; VUS, variant of unknown significance.

Table 4. Most frequent adverse events ($N = 94$).

MedDRA preferred term, *n* (%)	Arm A ($N = 9$)	Arm B ($N = 38$)	Arm C ($N = 23$)	Arm C2 ($N = 12$)	Arm D ($N = 6$)	Arm D2 ($N = 6$)	Overall ($N = 94$)
Patients with at least one adverse event	9 (100.0)	38 (100.0)	23 (100.0)	12 (100.0)	6 (100.0)	6 (100.0)	94 (100.0)
Nausea	5 (55.6)	23 (60.5)	19 (82.6)	10 (83.3)	4 (66.7)	4 (66.7)	65 (69.1)
Diarrhea	3 (33.3)	31 (81.6)	16 (69.6)	6 (50.0)	1 (16.7)	5 (83.3)	62 (66.0)
Fatigue	3 (33.3)	23 (60.5)	17 (73.9)	8 (66.7)	3 (50.0)	5 (83.3)	59 (62.8)
Anemia/hemoglobin decreased	3 (33.3)	24 (63.2)	14 (60.9)	9 (75.0)	3 (50.0)	2 (33.3)	55 (58.5)
Neutropenia/neutrophil count decreased	8 (88.9)	25 (65.8)	8 (34.8)	11 (91.7)	1 (16.7)	2 (33.3)	55 (58.5)
Thrombocytopenia/platelet count decreased	3 (33.3)	15 (39.5)	16 (69.6)	11 (91.7)	0	1 (16.7)	46 (48.9)
Vomiting	4 (44.4)	19 (50.0)	13 (56.5)	4 (33.3)	3 (50.0)	2 (33.3)	45 (47.9)
Abdominal pain	2 (22.2)	8 (21.1)	8 (34.8)	1 (8.3)	1 (16.7)	2 (33.3)	22 (23.4)
Leukopenia/white blood cell count decreased	2 (22.2)	13 (34.2)	5 (21.7)	0	1 (16.7)	1 (16.7)	22 (23.4)
Dyspnea	1 (11.1)	10 (26.3)	4 (17.4)	4 (33.3)	0	1 (16.7)	20 (21.3)
Hypomagnesemia/blood magnesium decreased	1 (11.1)	8 (21.1)	7 (30.4)	2 (16.7)	0	0	18 (19.1)
Headache	1 (11.1)	8 (21.1)	7 (30.4)	1 (8.3)	0	0	17 (18.1)
Decreased appetite	2 (22.2)	7 (18.4)	5 (21.7)	1 (8.3)	1 (16.7)	0	16 (17.0)
Back pain	1 (11.1)	6 (15.8)	4 (17.4)	3 (25.0)	1 (16.7)	0	15 (16.0)
Constipation	1 (11.1)	4 (10.5)	5 (21.7)	3 (25.0)	2 (33.3)	0	15 (16.0)
Hypokalemia/blood potassium decreased	1 (11.1)	4 (10.5)	3 (13.0)	2 (16.7)	1 (16.7)	0	11 (11.7)
Edema peripheral	0	10 (26.3)	0	4 (33.3)	0	0	14 (14.9)
Pyrexia	4 (44.4)	8 (21.1)	1 (4.3)	0	1 (16.7)	0	14 (14.9)
Dysgeusia	1 (11.1)	4 (10.5)	3 (13.0)	4 (33.3)	1 (16.7)	0	13 (13.8)
Hyperglycemia	1 (11.1)	6 (15.8)	3 (13.0)	0	1 (16.7)	0	11 (11.7)
Insomnia	1 (11.1)	6 (15.8)	2 (8.7)	1 (8.3)	1 (16.7)	0	11 (11.7)
Urinary tract infection	0	6 (15.8)	2 (8.7)	1 (8.3)	1 (16.7)	1 (16.7)	11 (11.7)

Note: Arm A: adavosertib 175 mg daily on days 1–2, 8–9, and 15–16 + gemcitabine 1,000 or 800 mg/m^2 i.v. on days 1, 8, and 15 (every 28 days); arm B: adavosertib 225 mg twice daily × 5 doses on days 1–3, 8–10, and 15–17 + paclitaxel 80 mg/m^2 i.v. on days 1, 8, and 15 (every 28 days); arm C: adavosertib 225 mg twice daily x 5 doses on days 1–3 + carboplatin AUC5 i.v. on day 1 (every 21 days); arm C2: adavosertib 225 mg twice daily × 5 doses on days 1–3, 8–10, and 15–17 (weeks 1–3) + carboplatin AUC5 i.v. on day 1 (every 21 days); arms D and D2: adavosertib 175 or 225 mg twice daily × 5 doses on days 1–3 + PLD 40 mg/m^2 i.v. on day 1 (every 28 days).
Abbreviation: MedDRA, Medical Dictionary for Regulatory Activities.

6 safety lead-in patients experienced a DLT of grade 2 diarrhea, and 1 of these patients experienced additional DLTs of grade 3 nausea and vomiting. The most common nonhematologic 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 8 patients (34.8%) experienced an AE leading to dose reduction of carboplatin.

Arm C2: Adavosertib 225 mg twice daily × 5 doses on days 1–3, 8–10, and 15–17 (weeks 1–3) + carboplatin AUC5 i.v. on day 1 (every 21 days; $N = 12$). No DLTs were reported for any of the 6 safety lead-in patients. The most common nonhematologic 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 twice daily × 5 doses on days 1–3 + PLD 40 mg/m^2 i.v. on day 1 (every 28 days; $N = 6$ for each dose). No DLTs were reported for any of the 6 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 (SAE), 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 to 4.08 hours after a single dose on cycle 1 day 1 and 2.88 to 3.92 hours after multiple twice-daily 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 postdose; geometric mean plasma concentrations at 8 hours postdose were approximately 42% to 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 1,000 mg/m^2, adavosertib C_{max} and AUC from time zero to time t ($AUC_{0\text{-}t}$) values were slightly higher than with gemcitabine 800 mg/m^2. Mean systemic exposure (C_{max} and $AUC_{0\text{-}t}$) to adavosertib following a single dose of adavosertib 225 mg plus paclitaxel 80 mg/m^2 or carboplatin AUC5 was similar.

After multiple twice-daily doses of adavosertib plus PLD, mean C_{max} was 42- to 44-fold higher and mean $AUC_{0\text{-}t}$ 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% to 100%; Supplementary Fig. 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, multiarm, 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 (24, 32–36). 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 (22). 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 (37). 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 48% 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 (38). 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 11.4 months, and ORR from 6% to 23% (23). However, the study by Lheureux and colleagues allowed many prior lines of therapy, so it is likely that patients had acquired platinum resistance. Patients in this study all had primary platinum resistance, which carries a poorer prognosis (39).

There were no apparent PK drug interactions between adavosertib and gemcitabine, paclitaxel, or carboplatin when co-administered. As previously reported by Leijen and colleagues, 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; ref. 40). *CCNE1*-amplified tumors have a poor prognosis and are generally refractory to therapies (41). In this 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 twice daily 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.

This clinical trial adds to the mounting data regarding efficacy of adavosertib in combination with chemotherapy. However, its long-term tolerability profile and generalized use may not be feasible at the explored doses and regimens. As previously stated, future studies are planned to evaluate the efficacy of alternative dosing strategies, combination partners, and biomarker enrichment in an effort to individualize this therapy to those most likely to benefit, while also establishing the optimal safety and tolerability profile (21).

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.

Authors' Disclosures

K.N. Moore reports grants and personal fees from AstraZeneca during the conduct of the study. K.N. Moore also reports grants and personal fees from Genentech/Roche, Immunogen, Clovis, Tesaro, Pfizer, and OncoMed; grants from Lilly; personal fees from Janssen, Aravive, VBL Therapeutics, Samumed, Eisai, GSK, Vavotar, and Tarveda outside the submitted work. E.P. Hamilton reports grants from OncoMed, Genentech/Roche, Zymeworks, Rgenix, ArQule, Clovis, Silverback Therapeutics, Millenium, Acerta, Sermonix, Torque, Black Diamond, Karyopharm, Infinity Pharmaceuticals, Curis, Syndax, Novartis, Boehringer Ingelheim, Immunomedics, FujiFilm, Taiho, Deciphera, Fochon, Molecular Templates, Onconova Therapeutics, Dana-Farber Cancer Hospital, Hutchinson MediPharma, MedImmune, Seagen, Puma Biotechnology, Compugen, TapImmune, Lilly, Pfizer, H3 Biomedicine, Takeda, Merus, Regeneron, Arvinas, StemCentRx, Verastem, eFFECTOR Therapeutics, CytomX, InventisBio, Lycera, Mersana, Radius Health, AbbVie, Nucana, Leap Therapeutics, Zenith Epigenetics, Harpoon, Orinove, AstraZeneca, Tesaro, Macrogenics, EMD Serono, Daiichi Sankyo, Syros, Sutro, G1 Therapeutics, Merck, PharmaMar, Olema, Polyphor, Immunogen, Plexxicon, Amgen, Akesobio Australia, and Shattuck Labs, as well as other support from Genentech/Roche, Boehringer Ingelheim, Novartis, Dantari, Lilly, Merck, Puma Biotechnology, Silverback Therapeutics, CytomX, Pfizer, Mersana, Black Diamond, H3 Biomedicine, Daiichi Sankyo, AstraZeneca, Arvinas, Deciphera Pharmaceuticals, Eisai, and Seagen during the conduct of the study. A.M. Oza reports grants, non-financial support, and other support from AstraZeneca outside the submitted work. S.A. Ghamande reports grants from AstraZeneca during the conduct of the study, as well as personal fees from GSK and Eisai outside the submitted work. G.E. Konecny reports being a speaker for AstraZeneca, Clovis, and GSK, as well as research funding from Lilly and Merck. S.C. Plaxe reports grants from AstraZeneca during the conduct of the study, as well as other support from AstraZeneca outside the submitted work. D.L. Spitz reports personal fees from Sarah Cannon Research during the conduct of the study. E. Rodrigo Imedio reports other support from AstraZeneca during the conduct of the study, as well as other support from BioNTech SE outside the submitted work. Z. Lai reports employment and ownership of stock with AstraZeneca. J. Chmielecki reports personal fees and other support from AstraZeneca during the conduct of the study, as well as personal fees and other support from AstraZeneca outside the submitted work. S.F. Jones reports grants from AstraZeneca during the conduct of the study, as well as other support from HCA Healthcare/Sarah Cannon and Amgen outside the submitted work. D.R. Spigel reports grants from Aeglea Biotherapeutics, Astellas, BIND Therapeutics, Calithera, Celldex, Clovis, Daiichi Sankyo, Eisai, Elevation Oncology, G1 Therapeutics, GRAIL, InClone Systems, Ipsen, MedImmune, Molecular Partners, Neon, Takeda, Tesaro, Transgene, UT Southwestern, Agios, Cyteir Therapeutics, and Apollomics; grants and other support from AstraZenca, Bristol Myers Squibb, Celgene, Lilly, EMD Serono, Roche/Genentech, GlaxoSmithKline, Janssen, Merck, Nektar Therapeutics, Novartis, and Novocure; and other support from Aptitude Health, Bayer, Curio Science, Dracen Pharmaceuticals, Evelo Biosciences, Exelixis, Iksuda Therapeutics, Intellisphere, Illumina, Ispen Biopharmaceuticals, Jazz Pharmaceuticals, Mirati, Molecular Therapeutics, Pfizer, Pharma Mar, Puma Biotechnology, Sanofi-Aventis, Seattle Genetics, Takeda, TRIPTYCH Health Partners, TRM Oncology, Williams and Connolly LP, and Regeneron Pharmaceutics outside the submitted work. K.A. Cadoo reports other support from AstraZeneca during the conduct of the study. K.A. Cadoo also reports personal fees from AstraZeneca, MJH Life Sciences, and MSD Ireland; other support from MSD Ireland, Immunogen, and Pfizer; and personal fees from GSK Ireland outside the submitted work. No disclosures were reported by the other authors.

Authors' Contributions

K.N. Moore: Formal analysis, investigation, methodology, writing–original draft, writing–review and editing. **S.K. Chambers:** Investigation, writing–original draft, writing–review and editing. **E.P. Hamilton:** Investigation, writing–original draft, writing–review and editing. **L-m. Chen:** Investigation, writing–original draft, writing–review and editing. **A.M. Oza:** Investigation, writing–original draft, writing–review and editing. **S.A. Ghamande:** Investigation, writing–original draft, writing–review and editing. **G.E. Konecny:** Investigation, writing–original draft, writing–review and editing. **S.C. Plaxe:** Investigation, writing–original draft, writing–review and editing. **D.L. Spitz:** Investigation, writing–original draft, writing–review and editing. **J.J.J. Geenen:** Investigation, writing–original draft, writing–review and editing. **T.A. Troso-Sandoval:** Investigation, writing–original draft, writing–review and editing. **J.M. Cragun:** Investigation, writing–original draft, writing–review and editing. **E. Rodrigo Imedio:** Formal analysis, methodology, writing–original draft, writing–review and editing. **S. Kumar:** Formal analysis, methodology, writing–original draft, writing–review and editing. **G.M. Mugundu:** Formal analysis, methodology, writing–original draft, writing–review and editing. **Z. Lai:** Formal analysis, methodology, writing–original draft, writing–review and editing. **J. Chmielecki:** Formal analysis, methodology, writing–original draft, writing–review and editing. **S.F. Jones:** Formal analysis, methodology, writing–original draft, writing–review and editing. **D.R. Spigel:** Formal analysis, investigation, methodology, writing–original draft, writing–review and editing. **K.A. Cadoo:** Formal analysis, investigation, methodology, writing–original draft, writing–review and editing.

Acknowledgments

The study was funded by AstraZeneca, which participated in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The authors would like to thank all participating patients and their families. Manuscript drafting was conducted by Sarah Cannon Development Innovations and Ben Drever, PhD, of AMICULUM, with funding from AstraZeneca.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received January 18, 2021; revised June 8, 2021; accepted October 6, 2021; published first October 13, 2021.

References

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: ovarian cancer version 2. 2018 [cited 2020 Dec 9]. https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf.
2. Ledermann JA, Raja FA, Fotopoulou C, Gonzalez-Martin A, Colombo N, Sessa C, et al. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24:vi24–32.
3. Davis A, Tinker AV, Friedlander M. "Platinum resistant" ovarian cancer: what is it, who to treat and how to measure benefit? Gynecol Oncol 2014;133:624–31.

4. Luvero D, Milani A, Ledermann JA. Treatment options in recurrent ovarian cancer: latest evidence and clinical potential. Ther Adv Med Oncol 2014;6:229–39.
5. Pujade-Lauraine E, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial. J Clin Oncol 2014;32:1302–8.
6. Javelin 200 press release. Merck KGaA, Darmstadt, Germany, and Pfizer provide update on avelumab in platinum-resistant/refractory ovarian cancer; 2018 [cited 2019 Mar 14]. https://www.emdgroup.com/en/news/avelumab-1x-11-2018.html.
7. Columbus G. Avelumab misses primary endpoints in phase III ovarian cancer trial; 2018 [cited 2020 Dec 9]. https://www.onclive.com/view/avelumab-misses-primary-endpoints-in-phase-iii-ovarian-cancer-trial.
8. Liu J, Matulonis UA. New strategies in ovarian cancer: translating the molecular complexity of ovarian cancer into treatment advances. Clin Cancer Res 2014;20:5150–6.
9. Colombo N, Conte PF, Pignata S, Raspagliesi F, Scambia G. Bevacizumab in ovarian cancer: focus on clinical data and future perspectives. Crit Rev Oncol Hematol 2016;97:335–48.
10. Konecny GE, Kristeleit RS. PARP inhibitors for BRCA1/2-mutated and sporadic ovarian cancer: current practice and future directions. Br J Cancer 2016;115:1157–73.
11. Sandhu SK, Schelman WR, Wilding G, Moreno V, Baird RD, Miranda S, et al. The poly(ADP-ribose) polymerase inhibitor niraparib (MK4827) in BRCA mutation carriers and patients with sporadic cancer: a phase 1 dose-escalation trial. Lancet Oncol 2013;14:882–92.
12. Moore K, Secord AA, Geller MA, Miller DS, Cloven NG, Fleming GF. QUADRA: a phase 2, open-label, single-arm study to evaluate niraparib in patients (pts) with relapsed ovarian cancer (ROC) who have received ≥3 prior chemotherapy regimens. J Clin Oncol 2018;36:15s (suppl. abstr. 5514).
13. Ahmed AA, Etemadmoghadam D, Temple J, Lynch AG, Riad M, Sharma R, et al. Driver mutations in TP53 are ubiquitous in high grade serous carcinoma of the ovary. J Pathol 2010;221:49–56.
14. Aarts M, Sharpe R, Garcia-Murillas I, Gevensleben H, Hurd MS, Shumway SD, et al. Forced mitotic entry of S-phase cells as a therapeutic strategy induced by inhibition of WEE1. Cancer Discov 2012;2:524–39.
15. Hirai H, Iwasawa Y, Okada M, Arai T, Nishibata T, Kobayashi M, et al. Small-molecule inhibition of WEE1 kinase by MK-1775 selectively sensitizes p53-deficient tumor cells to DNA-damaging agents. Mol Cancer Ther 2009;8:2992–3000.
16. Leijen S, van Geel RM, Pavlick AC, Tibes R, Rosen L., Abdul Razak AR, et al. Phase I study evaluating WEE1 inhibitor AZD1775 as monotherapy and in combination with gemcitabine, cisplatin, or carboplatin in patients with advanced solid tumors. J Clin Oncol 2016;34:4371–80.
17. Lewis CW, Jin Z, Macdonald D, Wei W, Qian XJ, Choi WS, et al. Prolonged mitotic arrest induced by WEE1 inhibition sensitizes breast cancer cells to paclitaxel. Oncotarget 2017;8:73705–22.
18. Hirai H, Arai T, Okada M, Nishibata T, Kobayashi M, Sakai N, et al. MK-1775, a small molecule WEE1 inhibitor, enhances anti-tumor efficacy of various DNA-damaging agents, including 5-fluorouracil. Cancer Biol Ther 2010;9:514–22.
19. Bridges KA, Hirai H, Buser CA, Brooks C, Liu H, Buchholz TA, et al. MK-1775, a novel WEE1 kinase inhibitor, radiosensitizes p53-defective human tumor cells. Clin Cancer Res 2011;17:5638–48.
20. Rajeshkumar NV, De Oliveira E, Ottenhof N, Watters J, Brooks D, Demuth T, et al. MK-1775, a potent WEE1 inhibitor, synergizes with gemcitabine to achieve tumor regressions, selectively in p53-deficient pancreatic cancer xenografts. Clin Cancer Res 2011;17:2799–806.
21. Oza AM, Estevez-Diz M, Grischke E-M, Hall M, Marmé F, Provencher D, et al. A biomarker-enriched, randomized phase II trial of adavosertib (AZD1775) plus paclitaxel and carboplatin for women with platinum-sensitive TP53-mutant ovarian cancer. Clin Cancer Res 2020;26:4767–76.
22. Leijen S, van Geel RM, Sonke GS, de Jong D, Rosenberg EH, Marchetti S, et al. Phase II study of WEE1 inhibitor AZD1775 plus carboplatin in patients with TP53-mutated ovarian cancer refractory or resistant to first-line therapy within 3 months. J Clin Oncol 2016;34:4354–61.
23. Lheureux S, Cristea MC, Bruce JP, Garg S, Cabanero M, Mantia-Smaldone G, et al. Adavosertib plus gemcitabine for platinum-resistant or platinum-refractory recurrent ovarian cancer: a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet 2021;397:281–92.
24. Markman M, Blessing J, Rubin SC, Connor J, Hanjani P, Waggoner S. Phase II trial of weekly paclitaxel (80 mg/m^2) in platinum and paclitaxel-resistant ovarian and primary peritoneal cancers: a Gynecologic Oncology Group study. Gynecol Oncol 2006;101:436–40.
25. Gabizon AA. Stealth liposomes and tumour targeting: one step further in the quest for the magic bullet. Clin Cancer Res 2001;7:223–5.
26. Park HJ, Bae JS, Kim KM, Moon YJ, Park S-H, Ha SH., et.al. The PARP inhibitor olaparib potentiates the effect of the DNA damaging agent doxorubicin in osteosarcoma. J Exp Clin Cancer Res 2018;37:107.
27. Någård M, Ah-See M-L, So K, Strauss J, Wise-Draper T, Safran H, et al. Phase I study to assess the effect of adavosertib (AZD1775) on the pharmacokinetics of substrates of CYP1A2, CYP2C19 and CYP3A4 in patients with advanced solid tumors. Cancer Res 80:16s, 2020 (suppl. abstr. 3035).
28. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.
29. Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Washington, DC: US Department of Health and Human Services; 2010.
30. Rustin GJ, Vergote I, Eisenhauer E, Pujade-Lauraine E, Quinn M, Thigpen T, et al. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). Int J Gynecol Cancer 2011;21:419–23.
31. Frampton GM, Fichtenholtz A, Otto GA, Wang K, Downing SR, He J, et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing. Nat Biotechnol 2013;31:1023–31.
32. Williams LL, Fudge M, Burnett LS, Jones HW. Salvage carboplatin therapy for advanced ovarian cancer after first-line treatment with cisplatin. Am J Clin Oncol 1992;15:331–6.
33. Kavanagh J, Tresukosol D, Edwards C, Freedman R, Gonzalez de Leon C, Fishman A, et al. Carboplatin reinduction after taxane in patients with platinum-refractory epithelial ovarian cancer. J Clin Oncol 1995;13:1584–8.
34. Naumann RW, Coleman RL. Management strategies for recurrent platinum-resistant ovarian cancer. Drugs 2011;71:1397–412.
35. Markman M, Webster K, Zanotti K, Kulp B, Peterson G, Belinson J. Phase 2 trial of single-agent gemcitabine in platinum-paclitaxel refractory ovarian cancer. Gynecol Oncol 2003;90:593–6.
36. D'Agostino G, Amant F, Berteloot P, Scambia G, Vergote I. Phase II study of gemcitabine in recurrent platinum-and paclitaxel-resistant ovarian cancer. Gynecol Oncol 2003;88:266–9.
37. Benson AB, Ajani JA, Catalano RB, Engelking C, Kornblau SM, Martenson JA Jr, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Oncol 2004;22:2918–26.
38. Colombo N, Sessa C, du Bois A, Ledermann J, McCluggage WG, McNeish I, et al. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. Ann Oncol 2019;30:672–705.
39. Trillsch F, Mahner S, Hilpert F, Davies L, García-Martínez E, Kristensen G, et al. Prognostic and predictive effects of primary versus secondary platinum resistance for bevacizumab treatment for platinum-resistant ovarian cancer in the AURELIA trial. Ann Oncol 2016;27:1733–9.
40. Bauer TM, Jones SF, Greenlees C, Cook C, Jewsbury PJ, Mugundu G, et al. A phase Ib, open-label, multi-center study to assess the safety, tolerability, pharmacokinetics, and anti-tumor activity of AZD1775 monotherapy in patients with advanced solid tumors: expansion cohorts. J Clin Oncol 34:15s, 2016(suppl. abstr. TPS2608).
41. Ayhan A, Kuhn E, Wu RC, Ogawa H, Bahadirli-Talbott A, Mao T-L, et al. CCNE1 copy-number gain and overexpression identify ovarian clear cell carcinoma with a poor prognosis. Modern Pathol 2017;30:297–303.