

Once daily cediranib and weekly paclitaxel to prevent malignant bowel obstruction in at-risk patients with platinum-resistant ovarian cancer (CEBOC): a single-arm, phase II safety trial

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► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/ijgc-2024-005455>).

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For 'Presented at statement' see end of article.

Received 29 February 2024
Accepted 25 April 2024



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To cite: Murphy AD, Porter C, White A, et al. *Int J Gynecol Cancer* Published Online First: [please include Day Month Year]. doi:10.1136/ijgc-2024-005455

ABSTRACT

Objective Cytotoxic chemotherapy for ovarian cancer can be augmented by co-administration of vascular endothelial growth factor inhibitors but these are contraindicated in patients with bowel obstruction due to the risk of gastrointestinal perforation. We evaluated the safety and feasibility of paclitaxel plus cediranib to treat patients with platinum-resistant ovarian cancer at risk of malignant bowel obstruction.

Methods A phase II trial included eligible patients between March 2018 and February 2021, identified by clinical symptoms and radiographic risk factors for malignant bowel obstruction. Cediranib (20 mg/day) was added to paclitaxel (70 mg/m²/week) within 9 weeks of starting paclitaxel if pretreatment bowel symptoms had improved. The primary endpoint was the number of patients treated for ≥5 days with cediranib that were free of grade 3–5 gastrointestinal perforation or fistula. Secondary endpoints were hospitalization for bowel obstruction, grade ≥3 adverse events, treatment compliance assessed by relative dose intensity, objective response, progression-free survival, and overall survival.

Results Thirty patients were recruited. Of these, 12 received paclitaxel alone and 17 received paclitaxel and cediranib in combination. One patient died before starting treatment. No patient developed a grade 3–5 gastrointestinal perforation or fistula (one sided 95% confidence interval (CI) upper limit 0.16). One patient required hospitalization for bowel obstruction but recovered with conservative management. The most common cediranib-related grade ≥3 adverse events were fatigue (3/17), diarrhoea (2/17), and hypomagnesaemia (2/17). Relative dose intensity for paclitaxel was 90% (interquartile range (IQR) 85–100%; n=29) and for cediranib 88% (IQR 76–93%; n=17). The objective response in patients who received paclitaxel and cediranib was 65.0% (one complete and 10 partial responses). Median progression-free survival was 6.9 months (95% CI 4.4–11.5 months; n=17) and overall survival was 19.4 months (95% CI 10.1–20.4 months; n=17). Median follow-up was 12.4 months (8.9–not reached; n=17).

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Malignant bowel obstruction is a significant cause of morbidity and mortality in patient diagnosed with ovarian cancer.
- ⇒ Vascular endothelial growth factor (VEGF) inhibitors are contraindicated in patients with ovarian cancer and impending bowel obstruction due to the risk of gastrointestinal perforation.

WHAT THIS STUDY ADDS

- ⇒ Cytotoxic chemotherapy with weekly paclitaxel and the VEGF receptor tyrosine kinase inhibitor, cediranib, was tolerated in patients with platinum-resistant ovarian cancer and impending bowel obstruction.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ This study should lead to new trials that will investigate systemic treatments for patients with ovarian cancer at risk of bowel obstruction, thereby addressing a clinical unmet need.

Conclusions The unexpectedly high withdrawal rate during paclitaxel alone, before introducing cediranib, meant we were unable to definitely conclude that paclitaxel plus cediranib did not cause gastrointestinal perforation or fistula. The regimen was however tolerated.

Trial registration number EudraCT 2016-004618-93

INTRODUCTION

Ovarian cancer is the the most common cause of gynecological cancer related death in the developed world, accounting for approximately 180,000 deaths annually.¹ The most common mechanism of death is inoperable malignant bowel obstruction, where the tumor physically and neurologically arrests bowel function.² There is a critical need to develop treatment strategies to address malignant bowel obstruction,

which typically occurs in patients whose disease has become resistant to platinum-based chemotherapy.

Combinations of vascular endothelial growth factor (VEGF) pathway inhibitors with cytotoxic chemotherapy have improved response rate and progression free survival in newly diagnosed^{3,4} and recurrent ovarian cancer.^{5–8} However, patients at risk of malignant bowel obstruction were excluded from these trials because an earlier study had reported an increased risk of gastrointestinal perforation with the monoclonal anti-VEGF antibody, bevacizumab.⁹ Thus, to date, VEGF pathway inhibitors have been contraindicated in patients at risk of bowel obstruction, depriving this group of potentially effective drugs.¹⁰

These observations highlight that there is an unmet need for VEGF pathway inhibitors that can be safely combined with cytotoxic chemotherapy in patients at risk of bowel obstruction. Cediranib is an oral, small molecule inhibitor of multiple tyrosine kinases, including VEGF receptors 1, 2, and 3, platelet derived growth factor receptors α and β , and c-Kit.¹¹ It has been safely used in a number of clinical trials as a monotherapy, and in combination therapy, to treat ovarian cancer.^{7,12–18} The main side effects of cediranib are fatigue, diarrhea, and hypertension.¹⁹ We have shown in a phase I study that cediranib and chemoradiation can be safely used to treat locally advanced rectal cancer despite bowel wall involvement,²⁰ contrasting previous reports of severe toxicity associated with bevacizumab in the same context.^{21,22} Together, these data led us to hypothesize that if we incorporated a VEGF pathway inhibitor into a treatment regimen for malignant bowel obstruction, it would be safer to use a receptor tyrosine kinase inhibitor, such as cediranib, rather than the monoclonal anti-VEGF antibody, bevacizumab. Given the potential risks, and as a first step towards developing a regimen for bowel obstruction, we carried out this study, where the endpoints included the safety and feasibility of combining paclitaxel and cediranib.

METHODS

Study Design

We conducted a single arm, open label, phase II trial of cediranib in combination with weekly paclitaxel to treat patients with recurrent platinum-resistant ovarian cancer at risk of developing malignant bowel obstruction, for whom bevacizumab was contraindicated.²³ For patients who developed progressive disease during maintenance cediranib, there was an option to add the poly(ADP-ribose) polymerase-1/2 inhibitor (PARPi), olaparib, to cediranib, based on data at the time highlighting the efficacy of this combination.¹³ This trial was registered with the European Union Clinical Trial Register (EudraCT 2016-004618-93).

Participants

Eligible patients were aged ≥ 16 years old with histologically confirmed, progressive, platinum resistant/refractory, high-grade ovarian, fallopian tube, or primary peritoneal cancer,²⁴ for whom weekly paclitaxel was a potential treatment option. Patients were required to be at risk of malignant bowel obstruction, defined by the presence of at least one of the following: abdominal pain and swelling, borborygmi, change in bowel habit, extensive serosal disease, or tethered bowel on radiological imaging; or clinical correlates of bowel obstruction that we had previously reported.²⁵

Previous bowel obstruction was permitted if there was no concern about oral absorption of medications. Any number of previous anticancer treatments were permitted, including weekly paclitaxel in the first-line setting and previous bevacizumab, but previous treatment with a VEGF receptor tyrosine kinase inhibitor was not permitted. Patients who had received a previous PARPi were eligible. An Eastern Cooperative Oncology Group performance status of 0–2, predicted life expectancy >12 weeks, evaluable disease by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria, adequate bone marrow, and renal and liver function were also required.

Patients were excluded if treatment with maintenance bevacizumab was planned, or if patients had experienced previous or concurrent gastrointestinal perforation, concurrent intra-abdominal abscess, or medical comorbidities that precluded safe administration of the investigational medicinal products. All patients provided written informed consent before enrollment.

Procedures

The trial was separated into two components. In component 1, patients were treated with intravenous paclitaxel 70 mg/m² on days 1, 8, and 15 of a 21 day cycle. Cediranib (tablets) 20 mg once daily was started within the first 9 weeks of paclitaxel when all bowel symptoms had reduced to grade ≤ 2 . Patients whose bowel symptoms did not improve within 9 weeks, or had progressive disease before commencing cediranib, were withdrawn from the study. Paclitaxel was administered for a maximum of six cycles and cediranib was continued indefinitely as maintenance until the development of intolerable toxicities, clinical symptoms of progression, or RECIST defined radiological progression.

At the point of radiological progression, if the patient still met the inclusion and exclusion criteria, they were optionally permitted to enter component 2 of the trial where they received olaparib (tablets) 300 mg twice daily, administered in combination with cediranib, until further radiological progression or unacceptable toxicity. Treatment with olaparib was available for patients regardless of their *BRCA1/2* status.

Dose interruptions and reductions of cediranib, olaparib, and paclitaxel were permitted. Toxicities attributed to cediranib were managed through dose reduction to 15 mg daily (dose level -1) and/or 5 days on/2 days off dosing schedule. Toxicities attributed to olaparib independently of cediranib resulted in the dose of the olaparib being reduced to 250 mg twice daily (dose level -1), then 200 mg twice daily (dose level -2), if required. Treatment with paclitaxel or olaparib could be interrupted or discontinued independently of cediranib.

Computed tomography of the abdomen and pelvis was performed at baseline (ie, pretreatment) and repeated every third cycle. Progressive disease was defined radiologically according to RECIST²⁶ or clinically. Patients were asked a predefined series of bowel symptom orientated questions every 3 weeks.²⁵ All adverse events were graded according to the NCI Common Terminology Criteria for Adverse Events version 4.03.

Endpoints

The primary endpoint was the number of patients who were free of a grade 3–5 gastrointestinal perforation or fistula that was causally related to cediranib or the combination of cediranib and olaparib,

during treatment and up to 4 weeks after the cessation of cediranib. Secondary endpoints included hospitalization for bowel obstruction, number of grade ≥ 3 adverse events related to cediranib, treatment compliance assessed by the relative dose intensity, objective response, progression-free survival, and overall survival.

Statistical Analysis

The target recruitment was 30 patients over a 24 month period. A Simon's two stage design was used to incorporate a planned check of the number of gastrointestinal perforation and fistula events. In a previous study, the gastrointestinal perforation rate was 23.8% in pretreated patients administered bevacizumab.⁹ Taking this as the maximum acceptable rate to prompt early stopping of the trial, and assuming that 96% of participants would be free of gastrointestinal perforation or fistula in this trial, 10 patients would be required to produce 90% power and 5% significance for stage 1. After at least 6 weeks of follow-up on cediranib after the 10th patient was enrolled, an independent data monitoring committee would review the data and if at least nine patients were free of events, the trial would continue with at least another 14 patients recruited. If at least 22 patients were free of events at the end of the trial period, then we would conclude that the treatment was safe. If ≥ 3 patients in the entire trial experienced gastrointestinal perforation or fistula formation, then the trial would terminate early. Six additional patients were planned for recruitment to allow for replacement of patients who were not assessable for the primary endpoint because they did not receive cediranib. All patients who started cediranib and received ≥ 5 days of treatment were included in the primary endpoint analysis (per protocol population). The final analysis occurred after all patients that started cediranib had received at least 18 weeks of treatment or had died or withdrawn from the study.

The primary endpoint was summarized with an exact 95% confidence interval (CI) using the Clopper–Pearson method. Secondary safety endpoints relating to bowel obstruction and serious adverse events causally related to cediranib were calculated for each treatment group: paclitaxel only, paclitaxel with cediranib (intention-to-treat and per protocol populations), and cediranib with olaparib. The worst reported adverse events excluding pretreatment symptoms were reported for patients receiving paclitaxel only, cediranib \pm paclitaxel, and cediranib plus olaparib. Progression-free and overall survival were summarized descriptively using the Kaplan–Meier method. STATA software version 17.0 was used to perform statistical analysis. A description of the post hoc statistical analysis is provided in the online supplemental material.

In accordance with the journal's guidelines, we will provide our data for independent analysis by a selected team by the editorial team for the purposes of additional data analysis or for the reproducibility of this study in other centers if such is requested.

RESULTS

Patient Characteristics

Fifty-four patients were assessed for eligibility and 30 patients were enrolled (intention-to-treat population) (Figure 1). Patient characteristics are provided in Table 1. In the intention-to-treat population, seven patients had received previous bevacizumab, and four patients had a germline *BRCA1/2* mutation (Table 1). Four patients had also been previously diagnosed with malignant bowel obstruction.

Twenty-nine patients in the intention-to-treat population completed the bowel symptom screening questionnaire at baseline and all reported ≥ 1 severe bowel symptoms (Table 2 and online

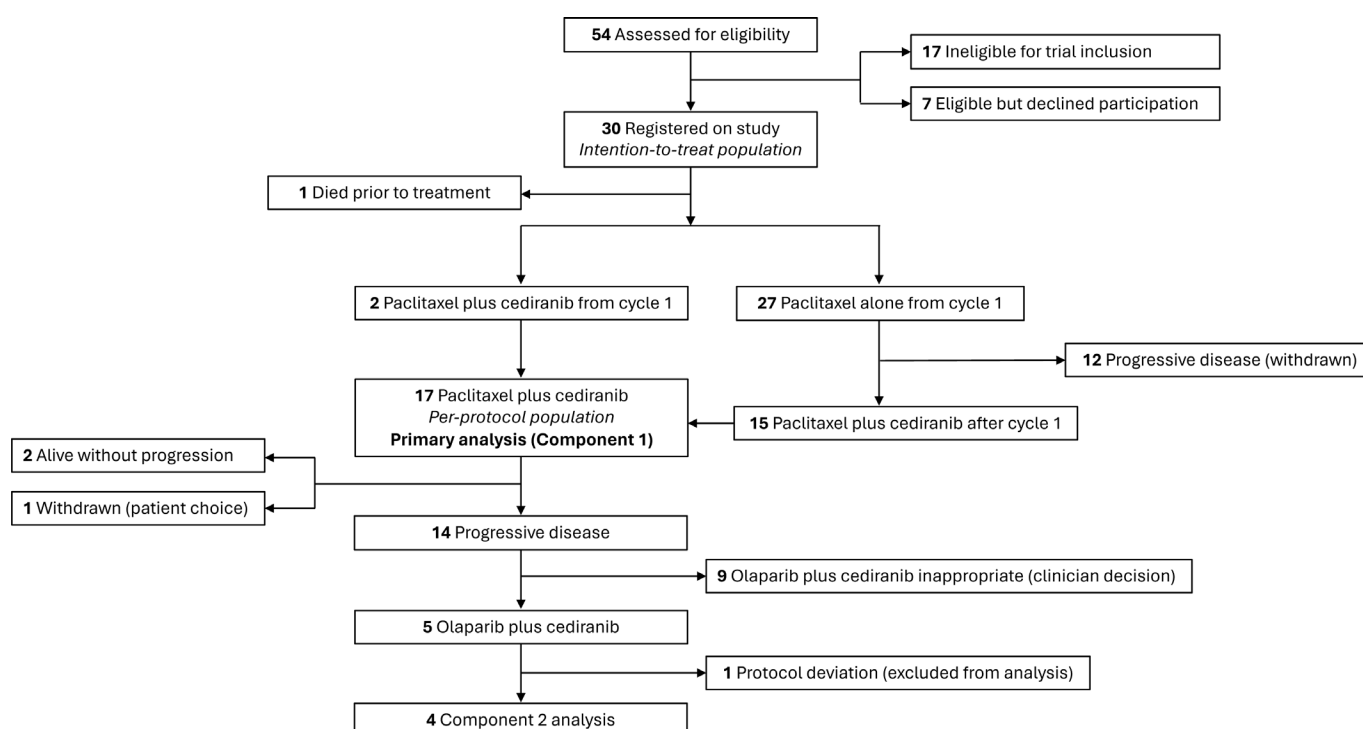


Figure 1 Consolidated Standards of Reporting Trials (CONSORT) diagram.

Table 1 Baseline characteristics

	Intention-to-treat population (n=30)	Per protocol population (n=17)
Age (years) (median (range))	61 (31–83)	62 (51–83)
ECOG performance status		
0	12 (40)	8 (47)
1	15 (50)	8 (47)
2	3 (10)	1 (6)
Histology		
High-grade serous	28 (93)	16 (94)
High-grade endometrioid	0	0
Clear cell	0	0
Carcinosarcoma	2 (7)	1 (6)
FIGO stage		
I	2 (7)	0
II	2 (7)	0
III	20 (67)	14 (82)
IV	6 (20)	3 (18)
Germline <i>BRCA1/2</i> status		
Mutation	4 (13)	1 (6)
Wild-type	26 (87)	16 (94)
Previous first line platinum based chemotherapy	30 (100)	17 (100)
No of previous lines of chemotherapy		
Median	3	3
Interquartile range	2–4	2–4
Range	1–6	1–6
Previous primary cytoreductive surgery	28 (93)	16 (94)
Extent of residual disease after surgery		
<10 mm	18 (64)	10 (63)
≥10 mm	10 (36)	6 (38)
Inoperable	2	1
Previous therapy		
Paclitaxel	29 (97)	16 (94)
Bevacizumab	7 (23)]	3 (18)
PARPi	5 (17)	2 (12)
Radiotherapy	1 (3)	1 (6)
High-risk symptoms/signs of bowel obstruction		
Abdominal pain	26 (87)	13 (76)
Serosal disease	22 (73)	12 (71)
Change in bowel habit	19 (63)	9 (53)
Borborygmi	13 (43)	8 (47)

Continued

Table 1 Continued

	Intention-to-treat population (n=30)	Per protocol population (n=17)
Rectosigmoid involvement	8 (27)	5 (29)
Dilated or tethered bowel	5 (17)	3 (18)
Early satiety	1 (3)	1 (6)
Rectal bleeding	1 (3)	1 (6)

Data are number of patients (%) unless otherwise specified. ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; PARPi, poly(ADP-ribose) polymerase-1/2 inhibitor.

supplemental Tables S1 and S2). Clinical symptoms correlated with radiological risk factors for bowel obstruction before treatment, where 26 patients had ≥1 radiological risk factors (online supplemental Tables S3 and S4). Pretreatment adverse events are provided in online supplemental Table S5.

Of the 30 patients in the intention-to-treat population, 29 received paclitaxel and one patient died from progressive disease before starting treatment. Twelve patients had disease progression before commencing cediranib and were excluded from the primary analysis. Seventeen patients received cediranib for ≥5 days and were included in the primary analysis (per protocol population).

Table 2 Pretreatment responses to bowel symptom screening questionnaire in the intention-to-treat population

Question	Bowel symptoms in past 3 weeks	Severe	Not severe
1	Tummy pain	13 (45)	16 (55)
2	Tummy swelling/ bloating	14 (48)	15 (52)
3	Rumbling noises in your tummy*	15 (52)	14 (48)
4	Feeling sick†	5 (18)	23 (82)
5	Being sick‡	3 (10)	26 (90)
6	Constipation	6 (21)	23 (79)
7	Diarrhea	4 (14)	25 (86)
8	Loss of appetite	8 (28)	21 (72)
9	Weight loss	6 (21)	23 (79)
10	Worsening symptoms in the last 2 months	Yes No	25 (86) 4 (14)

Data are number of patients (%). 29/30 patients completed the bowel symptom screening questionnaire at baseline. The severity of each symptom was categorized as severe (=a lot or quite a lot) or not severe (=sometimes or very little or not at all).

*Borborygmi.

†Nausea.

‡Vomiting.

Two patients started cediranib within the first cycle of paclitaxel and 15 started cediranib after their bowel symptoms had improved to grade ≤ 2 . Median time to starting cediranib in these patients was 50 days (interquartile range (IQR) 32–55). Thirteen patients continued cediranib after completion or withdrawal of paclitaxel. Five patients continued to component 2 (olaparib plus cediranib). One of these patients was later found to be ineligible for olaparib plus cediranib due to uncontrolled hypertension and was excluded from the component 2 analysis.

Twenty-five patients withdrew from paclitaxel \pm cediranib treatment and four withdrew from follow-up. The main reason for withdrawal was clinician's decision (13/29); all of these patients had developed symptoms or radiological findings of progressive disease before withdrawal. All patients in component 2 were withdrawn from treatment due to progression and none had died at the time of database lock (5 May 2022). One patient in component 1 was still receiving cediranib at the time of database lock. Median duration of follow-up in the intention-to-treat population was 18.2 months (95% CI 9.1 to not reached) and 12.4 months (8.9 to not reached) in the per protocol population.

Primary Outcome

None of the 17 patients in the per protocol population that received ≥ 5 days of cediranib developed a grade 3–5 gastrointestinal perforation or fistula. The attrition rate on paclitaxel alone was unexpectedly high (12/29) and so there were insufficient numbers treated with cediranib to test the primary endpoint. The upper limit of the Clopper–Pearson exact 95% CI for the proportion of patients developing gastrointestinal perforation or fistula was 0.16.

Secondary Outcomes

One patient in the intention-to-treat population required hospitalization for symptomatic bowel obstruction experienced on cycle 1, day 1 of weekly paclitaxel. The patient had radiologic evidence of multifocal, partial, small bowel obstruction. She was treated conservatively and received six doses of paclitaxel alone as an inpatient. Her symptoms improved and CT showed a significant radiographic improvement with transition of oral contrast to the distal small bowel. The patient was discharged and subsequently commenced paclitaxel plus cediranib from cycle 3 onward, eventually developing progressive disease 35 weeks after initiating treatment.

The most common grade ≥ 3 adverse events in the 17 patients who received paclitaxel plus cediranib were fatigue, diarrhea, hypomagnesemia, urinary tract infection, and dehydration (Figure 2 and online supplemental Table S6 and S7).

In the intention-to-treat population, median and relative dose intensity of paclitaxel was 63.0 mg/m²/week (IQR 59.1–70.0) and 90.3% (IQR 85.0–100.0), respectively (online supplemental Table S8). In the per protocol population, in component 1, median and relative dose intensity for cediranib was 17.7 mg/day (IQR 15.1–18.5) and 88.4% (IQR 75.7–92.7), respectively (online supplemental Table S8).

The objective response was 37.0% (95% CI 19.9 to 56.1) in the intention-to-treat population and 65.0% (95% CI 38.3 to 85.8) in the per protocol population (online supplemental Table S9). Median progression-free survival was 4.4 months (95% CI 3.3 to 6.9) in the intention-to-treat population and 6.9 months (95% CI 4.4 to

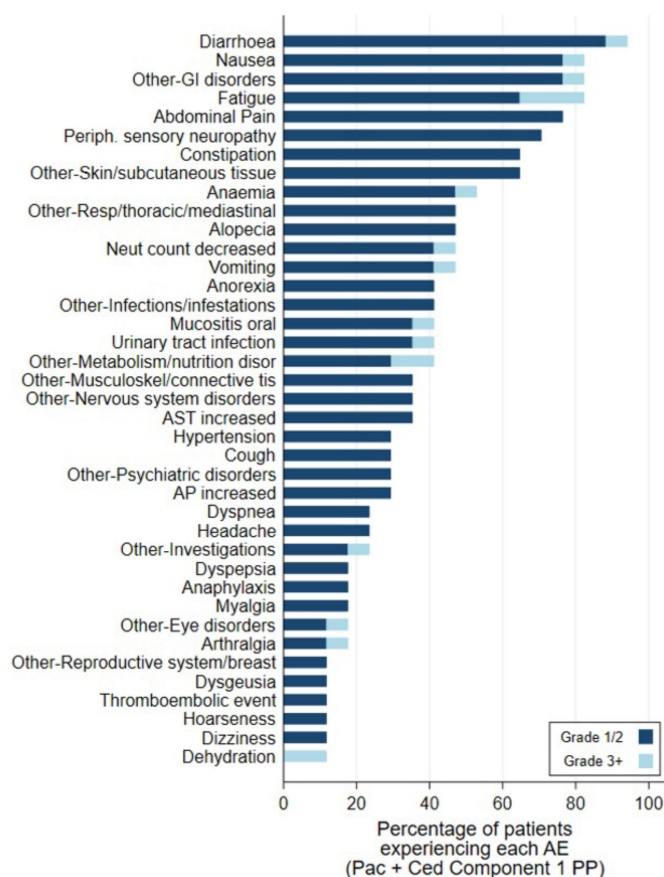


Figure 2 Adverse events in $\geq 10\%$ of patients receiving paclitaxel plus cediranib (17 patients, component 1, per protocol population). AP, alkaline phosphatase; AST, aspartate aminotransferase; ced, cediranib; disorder, disorder; GI, gastrointestinal; musculoskel, musculoskeletal; neut, neutrophil; periph, peripheral; tis, tissue.

11.5) in the per protocol population (online supplemental Figure S1 and Table S9). Median overall survival was 11.2 months (95% CI 8.5 to 20.4) in the intention-to-treat population and 19.4 months (95% CI 10.1 to 20.4) in the per protocol population (online supplemental Figure S1 and Table S9). Predefined subgroup analysis of patients with previous bevacizumab exposure or a *BRCA1/2* mutation demonstrated shorter median progression-free and overall survival; however, subgroup numbers were too small to draw any meaningful conclusions (online supplemental Table S10).

Bowel Symptom Screening Questionnaire

Significant improvements in patient reported borborygmi ($p=0.001$), abdominal swelling ($p=0.015$), abdominal pain ($p=0.021$), and constipation ($p=0.027$) were noted before initiation of cediranib, when compared with baseline, in the cohort of patients who received cediranib (online supplemental Figure S2). Other symptoms improved but did not reach significance.

There were significant differences in patient reported bowel symptoms when comparing those who did and did not receive cediranib. For example, borborygmi ($p=0.001$) and abdominal swelling ($p=0.043$) differed between the two groups of patients, providing additional evidence that bowel symptoms had improved with paclitaxel only. Increasing frequency of diarrhea after initiation

of cediranib, a known adverse drug reaction,²⁷ also confirmed the validity of the patient reported bowel symptom screening questionnaire.

DISCUSSION

Summary of Main Results

Although the primary endpoint of this phase II trial could not be tested, data from the trial showed that paclitaxel in combination with the VEGF receptor pathway inhibitor, cediranib, was tolerated in patients with platinum-resistant ovarian cancer who had clinical and radiological features of impending malignant bowel obstruction.

Results in the Context of Published Literature

In the original phase II trial investigating bevacizumab in platinum-resistant ovarian cancer, Cannistra et al reported five patients who developed gastrointestinal perforation.⁹ These five patients had been treated with three previous lines of chemotherapy and had risk factors for gastrointestinal perforation. We recruited patients with platinum-resistant ovarian cancer who had a median of three previous lines of chemotherapy along with clinical and radiological evidence of impending bowel obstruction. None of these patients developed gastrointestinal perforation. Although significance was not reached and the sample size was small, we were able to report a lower level of serious bowel toxicity compared with the original bevacizumab treated cohort, based on the upper limit of the exact 95% CI.

It is notable that Cannistra et al may have reported an unusually high percentage of gastrointestinal perforation.²⁸ The absence of gastrointestinal perforation reported in our study is likely due to the use of cytotoxic chemotherapy before starting a VEGF pathway inhibitor, where the clinical benefit was evident with improvements in patient reported symptoms.

Strengths and Weaknesses

To our knowledge, this is the first clinical trial to investigate a VEGF pathway inhibitor in patients with ovarian cancer at risk of bowel obstruction. We have also reported the first anticancer regimen tested specifically in patients with platinum-resistant ovarian cancer at risk of malignant bowel obstruction. This study was a prospective clinical trial that achieved target recruitment. This was a particular achievement given the target patient population. All patients were symptomatic with ≥ 1 symptoms of bowel obstruction, meaning that there was a narrow window of opportunity to commence treatment.^{29 30} Despite achieving target recruitment, the unexpectedly high withdrawal rate during treatment with paclitaxel alone prevented the primary endpoint being analyzed. This finding demonstrates the challenge of successfully treating patients with platinum-resistant ovarian cancer and impending bowel obstruction, even using standard therapy such as weekly paclitaxel.³¹

This trial was a single arm, non-randomized, phase II trial, which recruited a relatively small cohort of patients from a single center. Thus the data must be interpreted within the context of biases associated with this type of study. In addition, the dose of paclitaxel (70 mg/m²/week) used was lower than that used in other trials (80 mg/m²/week) treating patients with platinum-resistant ovarian cancer.^{6 32} We recognize that this may have affected the response

rate and/or the withdrawal rate for patients treated with paclitaxel alone.

Implications for Practice and Future Research

Malignant bowel obstruction in ovarian cancer is a clinical unmet need. The prognosis for patients with recurrent ovarian cancer and inoperable bowel involvement is poor,^{29 30 33} with many often considered ineligible for further therapy. Our study has shown that a treatment strategy involving cytotoxic chemotherapy and a targeted therapy could be a potential option, although statistically powered trials are needed to confirm this. What remains unclear, however, is how to select patients who will benefit from this strategy. Biomarkers of response, such as changes in plasma Tie2 concentration, may offer an opportunity to select patients for antiangiogenic agents, and should be included in future trials.³⁴ The use of screening instruments to detect early signs of malignant bowel obstruction should also be developed to allow more timely interventions.^{25 35} Results from our bowel symptom screening questionnaire imply that the three most severe symptoms experienced by patients with impending bowel obstruction are abdominal pain, swelling, and borborygmi. These findings differ from those observed in our discovery cohort, in which abdominal pain, nausea, vomiting, and constipation were more severely reported.²⁵ These contrasting observations demonstrate the difficulty of developing early warning scores for bowel obstruction, where gastrointestinal symptoms can be variable and non-specific.

CONCLUSIONS

The unexpectedly high withdrawal rate during weekly paclitaxel, before introducing cediranib, meant that we were unable to definitively conclude that paclitaxel plus cediranib did not cause gastrointestinal perforation or fistula. However, the regimen was tolerated.

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Presented at

The data in this manuscript were presented at the 2022 European Congress of Gynaecological Oncology.

Contributors GCJ, CZ, and ARC designed the study. AW, AI, and RR were responsible for project management. AI, AW, AM, RDM, SK, JP, CW, VR, GA, ZS, JH, CM, RDM, ARC, and GCJ collected data. CP and AC analyzed the data. CZ analyzed post hoc data. CP, AM, AC, CZ, RDM, ARC, and GCJ interpreted the data, and wrote the manuscript. CP and AC had access to the raw data.

Funding The trial was sponsored by the University of Manchester and coordinated by Cardiff University Centre for Trials Research. The trial was funded by AstraZeneca, who also provided the investigational medicinal products (cediranib and olaparib). AstraZeneca had no role in designing the study, data collection, data analysis, interpretation of the results, writing of the statistical analysis final report, or the final decision to submit the manuscript.

Competing interests ARC and GCJ have received research funding for this and other investigator initiated studies from AstraZeneca. RDM is supported by a National Institute for Health Research Clinical Lectureship (CL-2022-06-002).

Patient consent for publication Not applicable.

Ethics approval The study protocol was approved by the Medicine and Healthcare products Regulatory Agency and the North West Liverpool Central Research

Ethics Committee (reference 17/NW/0623). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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