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Citation for final published version:

Murphy, Alexander D, Porter, Catharine , White, Ann, Irving, Alys, Adams, Richard , Ray, Ruby, Casbard, Angela , Mahmood, Reem D., Karanth, Suman, Zhou, Cong, Pugh, Julia, Wheeler, Chelsey, Roberts, Victoria, Arnetoli, Giorgio, Salih, Zena, Hasan, Jurjees, Mitchell, Claire, Morgan, Robert D., Clamp, Andrew R. and Jayson, Gordon C. 2024. 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. *International Journal of Gynecological Cancer* 34 , pp. 1034-1040. 10.1136/ijgc-2024-005455

Publishers page: <https://doi.org/10.1136/ijgc-2024-005455>

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**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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27

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30

31 † The data in this manuscript was presented at the 2022 European Congress of  
32 Gynaecological Oncology Congress.

33

34 Word count:            Abstract        323/300

35                            Manuscript    2959/2900

36 Tables/Figures:        3/2

37 Supplements:            2 (1 supplementary material, 1 protocol)

38 References:             35

39 **ABSTRACT**

40

41 ***Objective***

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

47

48 ***Methods***

49 A phase II trial included eligible patients between March 2018 and February 2021 identified  
50 by clinical symptoms and radiographic risk factors for bowel obstruction. Cediranib (20  
51 mg/day) was added to paclitaxel (70 mg/m<sup>2</sup>/week) within 9 weeks of starting paclitaxel if  
52 pre-treatment bowel symptoms had improved. The primary endpoint was the number of  
53 patients treated for  $\geq 5$  days with cediranib that were free of grade 3-5 gastrointestinal  
54 perforation or fistula. Secondary endpoints were hospitalisation for bowel obstruction, grade  
55  $\geq 3$  adverse events, treatment compliance assessed by relative dose intensity, objective  
56 response, progression-free and overall survival.

57

58 ***Results***

59 Thirty patients were recruited. Of these, 12 received paclitaxel only and 17 went on to receive  
60 paclitaxel and cediranib in combination. One patient died before starting treatment. No  
61 patient developed a grade 3-5 gastrointestinal perforation or fistula (one-sided 95%  
62 confidence interval [CI] upper limit 0.16). One patient required hospitalisation for bowel  
63 obstruction but recovered with conservative management. The commonest cediranib-related  
64 grade  $\geq 3$  adverse events were fatigue (3/17), diarrhoea (2/17) and hypomagnesaemia (2/17).

65 Relative dose intensity for paclitaxel was 90% (interquartile range [IQR] 85-100; n=29) and  
66 cediranib was 88% (IQR 76-93; n=17). The objective response in patients who received  
67 paclitaxel plus cediranib was 65.0% (one complete and ten partial responses). Median  
68 progression-free survival was 6.9 months (95% CI 4.4-11.5; n=17) and overall survival was  
69 19.4 months (95% CI 10.1-20.4; n=17). Median follow-up was 12.4 months (8.9-not reached;  
70 n=17).

71

## 72 ***Conclusion***

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

76 **KEY MESSAGES**

77

78 *What is already known on this topic?*

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

83

84 *What this study adds?*

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

88

89 *How this study might affect research, practice or policy?*

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

92 **INTRODUCTION**

93 Ovarian cancer is the commonest cause of gynaecological cancer-related death in the  
94 developed world, accounting for approximately 180,000 deaths annually.<sup>(1)</sup> The most  
95 common mechanism of death is inoperable malignant bowel obstruction, where the tumour  
96 physically and neurologically arrests bowel function.<sup>(2)</sup> There is a critical need to develop  
97 treatment strategies to address malignant bowel obstruction, which typically occurs in  
98 patients whose disease has become resistant to platinum-based chemotherapy.

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

106         The above observations highlight that there is an unmet need for VEGF pathway  
107 inhibitors that can be safely combined with cytotoxic chemotherapy in patients at risk of  
108 bowel obstruction. Cediranib is an oral, small molecule inhibitor of multiple tyrosine kinases,  
109 including VEGF receptor-1, -2 and -3, platelet-derived growth factor receptor- $\alpha$  and - $\beta$  and c-  
110 Kit.<sup>(11)</sup> It has been safely used in a number of clinical trials as a monotherapy, and in  
111 combination therapy, to treat ovarian cancer.<sup>(7, 12-18)</sup> The main side effects of cediranib are  
112 fatigue, diarrhoea and hypertension.<sup>(19)</sup> We have shown in a phase I study that cediranib with  
113 chemo-radiation can be safely used to treat locally advanced rectal cancer despite bowel wall  
114 involvement<sup>(20)</sup>, contrasting previous reports of severe toxicity associated with bevacizumab  
115 in the same context.<sup>(21, 22)</sup> Together, these data led us to hypothesise that if we incorporated a  
116 VEGF pathway inhibitor into a treatment regimen for malignant bowel obstruction, it would  
117 be safer to use a receptor tyrosine kinase inhibitor, such as cediranib, rather than the

118 monoclonal anti-VEGF antibody, bevacizumab. Given the potential risks, and as a first step  
119 towards developing a regimen for bowel obstruction, we carried out this study, where the  
120 endpoints included the safety and feasibility of combining paclitaxel and cediranib.

121

## 122 **METHODS**

### 123 *Study design*

124 A single-arm, open-label, phase II trial of cediranib in combination with weekly paclitaxel to  
125 treat patients with recurrent platinum-resistant ovarian cancer at risk of developing malignant  
126 bowel obstruction, for whom bevacizumab was contraindicated.<sup>(23)</sup> For patients who  
127 developed progressive disease during maintenance cediranib, there was an option to add the  
128 poly(ADP-ribose) polymerase-1/2 inhibitor (PARPi), olaparib, to cediranib, based on data at  
129 the time highlighting the efficacy of this combination.<sup>(13)</sup>

130

### 131 *Participants*

132 Eligible patients were  $\geq 16$  years old with histologically confirmed, progressive, platinum-  
133 resistant/refractory, high-grade ovarian, fallopian tube or primary peritoneal cancer<sup>(24)</sup>, for  
134 whom weekly paclitaxel was a potential treatment option. Patients were required to be at risk  
135 of malignant bowel obstruction, defined by the presence of at least one of the following:  
136 abdominal pain and swelling, borborygmi, change in bowel habit, extensive serosal disease,  
137 or tethered bowel on radiological imaging; clinical correlates of bowel obstruction that we  
138 had previously reported.<sup>(25)</sup> Previous bowel obstruction was permitted so long as there was no  
139 concern about oral absorption of medications. Any number of previous anti-cancer treatments  
140 were permitted, including weekly paclitaxel in the first-line setting and prior bevacizumab,  
141 but prior treatment with a VEGF receptor tyrosine kinase inhibitor was not permitted.  
142 Patients who had received prior PARPi were eligible. An Eastern Cooperative Oncology  
143 Group performance status of 0-2, predicted life expectancy of greater than 12 weeks,



144 evaluable disease by Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1  
145 criteria, and adequate bone marrow, renal and liver function were also required.

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

151

### 152 ***Procedures***

153 The trial was separated into two components. In Component 1, patients were treated with  
154 intravenous paclitaxel 70 mg/m<sup>2</sup> on days 1, 8 and 15 of a 21-day cycle. Cediranib (tablets) 20  
155 mg once daily was started within the first 9 weeks of paclitaxel once all bowel symptoms had  
156 reduced to grade  $\leq 2$ . Patients whose bowel symptoms did not improve within 9 weeks, or had  
157 progressive disease prior to commencing cediranib, were withdrawn from the study.  
158 Paclitaxel was administered for a maximum of six cycles and cediranib was continued  
159 indefinitely as maintenance until the development of intolerable toxicities, clinical symptoms  
160 of progression or RECIST-defined radiological progression.

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

166 Dose interruptions and reductions of cediranib, olaparib and paclitaxel were  
167 permitted. Toxicities attributed to cediranib were managed through dose reduction to 15 mg  
168 daily (dose level -1) and/or 5 days-on/2 days-off dosing schedule. Toxicities attributed to  
169 olaparib independently of cediranib resulted in the dose of the olaparib being reduced to 250

170 mg twice daily (dose level -1), then 200 mg twice daily (dose level -2) if required. Treatment  
171 with paclitaxel or olaparib could be interrupted or discontinued independently of cediranib.

172 Computed tomography (CT) of the abdomen and pelvis was performed at baseline  
173 (i.e., pre-treatment) and repeated every third cycle. Progressive disease was defined  
174 radiologically according to RECIST<sup>(26)</sup> or clinically. Patients were asked a pre-defined series  
175 of bowel symptom-orientated questions every three weeks.<sup>(25)</sup> All adverse events were graded  
176 according to the NCI Common Terminology Criteria for Adverse Events version 4.03.

177

### 178 ***Endpoints***

179 The primary endpoint was the number of patients who were free of a grade 3-5  
180 gastrointestinal perforation or fistula that was causally related to cediranib or the combination  
181 of cediranib and olaparib, during treatment and up to 4 weeks after the cessation of cediranib.  
182 Secondary endpoints included hospitalisation for bowel obstruction, the number of grade  $\geq 3$   
183 adverse events related to cediranib, treatment compliance as assessed by the relative dose  
184 intensity, objective response, progression-free and overall survival.

185

### 186 ***Statistics***

187 The target recruitment was 30 patients over a 24-month period. A Simon's two-stage design  
188 was used to incorporate a planned check of the number of gastrointestinal perforation and  
189 fistula events. In a previous study the gastrointestinal perforation rate was 23.8% in pre-  
190 treated patients administered bevacizumab.<sup>(9)</sup> Taking this as the maximum acceptable rate to  
191 prompt early stopping of the trial, and assuming that 96% of participants would be free of  
192 gastrointestinal perforation or fistula in this trial, ten patients would be required to produce  
193 90% power and 5% significance for stage 1. After at least six weeks of follow-up on  
194 cediranib after the tenth patient was enrolled, an Independent Data Monitoring Committee  
195 would review the data and if at least nine patients were free of events, the trial would

196 continue with at least another 14 patients recruited. If at least 22 patients were free of events  
197 at the end of the trial period, then we would conclude that the treatment was safe. If  $\geq 3$   
198 patients in the entire trial experienced gastrointestinal perforation or fistula formation, then  
199 the trial would terminate early. Six additional patients were planned for recruitment to allow  
200 for replacement of patients who were not assessable for the primary endpoint because they  
201 did not receive cediranib. All patients who started cediranib and received  $\geq 5$  days of  
202 treatment were included in the primary endpoint analysis (per-protocol population). The final  
203 analysis occurred after all patients that started cediranib had received at least 18 weeks of  
204 treatment or had died or withdrawn from the study.

205 The primary endpoint was summarised with an exact 95% confidence interval (CI)  
206 using the Clopper-Pearson method. Secondary safety endpoints relating to bowel obstruction  
207 and serious adverse events causally related to cediranib were calculated for each treatment  
208 group: paclitaxel only, paclitaxel with cediranib (intention-to-treat and per-protocol  
209 populations), and cediranib with olaparib. The worst reported adverse events excluding pre-  
210 treatment symptoms were reported for patients receiving paclitaxel only, cediranib +/-  
211 paclitaxel and cediranib plus olaparib. Progression-free and overall survival were  
212 summarized descriptively using the Kaplan-Meier method. STATA software version 17.0 was  
213 used to perform statistical analysis. A description of the post hoc statistical analysis is  
214 provided in the Supplementary Material.

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

218

## 219 **RESULTS**

### 220 *Patient characteristics*

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

226 Twenty-nine patients in the intention-to-treat population completed the bowel  
227 symptom screening questionnaire at baseline and all reported  $\geq 1$  severe bowel symptoms  
228 (Table 2 and Supplementary Tables S1 and S2). Clinical symptoms correlated with  
229 radiological risk factors for bowel obstruction before treatment, where 26 patients had  $\geq 1$   
230 radiological risk factors (Supplementary Tables S3 and S4). Pre-treatment adverse events are  
231 provided in Supplementary Table S5.

232 Of the 30 patients in the intention-to-treat population, 29 received paclitaxel and one  
233 patient died from progressive disease prior to starting treatment. Twelve patients had disease  
234 progression before commencing cediranib and were excluded from the primary analysis.  
235 Seventeen patients received cediranib for  $\geq 5$  days and were included in the primary analysis  
236 (per-protocol population). Two patients started cediranib within the first cycle of paclitaxel  
237 and 15 started cediranib after their bowel symptoms had improved to grade  $\leq 2$ . The median  
238 time to starting cediranib in these patients was 50 days (interquartile range [IQR] 32-55).  
239 Thirteen patients continued cediranib after completion or withdrawal of paclitaxel. Five  
240 patients continued to Component 2 (olaparib plus cediranib). One of these patients was later  
241 found to be ineligible for olaparib plus cediranib due to uncontrolled hypertension and was  
242 excluded from the Component 2 analysis.

243 Twenty-five patients withdrew from paclitaxel +/- cediranib treatment and four  
244 withdrew from follow-up. The main reason for withdrawal was clinician's decision (13/29);  
245 all of these patients had developed symptoms or radiological findings of progressive disease  
246 prior to withdrawal. All patients in Component 2 were withdrawn from treatment due to

247 progression and none had died at the time of database lock (5<sup>th</sup> May 2022). One patient in  
248 Component 1 was still receiving cediranib at the time of database lock.

249 The median duration of follow-up in the intention-to-treat population was 18.2  
250 months (95% CI 9.1-not reached) and 12.4 months (8.9-not reached) in the per-protocol  
251 population.

252

### 253 *Primary outcome*

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

259

### 260 *Secondary outcomes*

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

269 The commonest grade  $\geq 3$  adverse events in the 17 patients who received paclitaxel  
270 plus cediranib were fatigue, diarrhoea, hypomagnesaemia, urinary tract infection and  
271 dehydration (Figure 2 and Supplementary Table S6 and S7).

272 In the intention-to-treat population the median and relative dose intensity of paclitaxel  
273 was 63.0 mg/m<sup>2</sup>/week (IQR 59.1-70.0) and 90.3% (IQR 85.0-100.0), respectively  
274 (Supplementary Table S8). In the per-protocol population in Component 1, the median and  
275 relative dose intensity for cediranib was 17.7 mg/day (IQR 15.1-18.5) and 88.4% (IQR 75.7-  
276 92.7), respectively (Supplementary Table S8).

277 The objective response was 37.0% (95% CI 19.9-56.1) in the intention-to-treat  
278 population and 65.0% (95% CI 38.3-85.8) in the per-protocol population (Supplementary  
279 Table S9). The median progression-free survival was 4.4 months (95% CI 3.3-6.9) in the  
280 intention-to-treat population and 6.9 months (95% CI 4.4-11.5) in the per-protocol population  
281 (Supplementary Figure S1 and Table S9). The median overall survival was 11.2 months (95%  
282 CI 8.5-20.4) in the intention-to-treat population and 19.4 months (95% CI 10.1-20.4) in the  
283 per-protocol population (Supplementary Figure S1 and Table S9). Pre-defined subgroup  
284 analysis of patients with prior bevacizumab exposure or a *BRCA1/2* mutation demonstrated  
285 shorter median progression-free and overall survival; however, subgroup numbers were too  
286 small to draw any meaningful conclusions (Supplementary Table S10).

287

### 288 ***Bowel symptom screening questionnaire***

289 Significant improvements in patient-reported borborygmi (p=0.001), abdominal swelling  
290 (p=0.015), abdominal pain (p=0.021) and constipation (p=0.027) were noted prior to  
291 initiation of cediranib, when compared with baseline, in the cohort of patients who received  
292 cediranib (Supplementary Figure S2). Other symptoms improved but did not reach  
293 significance.

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

298 frequency of diarrhoea after initiation of cediranib, a known adverse drug reaction<sup>(27)</sup>, also  
299 confirmed the validity of the patient-reported bowel symptom screening questionnaire.

300

## 301 **DISCUSSION**

### 302 *Summary of Main Results*

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

307

### 308 *Results in the Context of Published Literature*

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

318 It is notable that Cannistra *et al.* may have reported an unusually high percentage of  
319 gastrointestinal perforation.<sup>(28)</sup> The absence of gastrointestinal perforation reported in our  
320 study is likely due to the use of cytotoxic chemotherapy prior to starting a VEGF pathway  
321 inhibitor, where the clinical benefit was evident with improvements in patient-reported  
322 symptoms.

323

## 324 *Strengths and Weaknesses*

325 To our knowledge, this is the first clinical trial to investigate a VEGF pathway inhibitor in  
326 patients with ovarian cancer at risk of bowel obstruction. We also report the first anti-cancer  
327 regimen tested specifically in patients with platinum-resistant ovarian cancer at risk of  
328 malignant bowel obstruction. This study was a prospective clinical trial that achieved target  
329 recruitment. This was a particular achievement given the target patient population. All  
330 patients were symptomatic with  $\geq 1$  symptom of bowel obstruction, meaning there was a  
331 narrow window-of-opportunity to commence treatment.<sup>(29, 30)</sup> Despite achieving target  
332 recruitment, the unexpectedly high withdrawal rate during paclitaxel alone prevented the  
333 primary endpoint being analysed. This finding demonstrates the challenge of successfully  
334 treating patients with platinum-resistant ovarian cancer and impending bowel obstruction,  
335 even using standard therapy such as weekly paclitaxel.<sup>(31)</sup>

336 This trial was a single-arm, non-randomised, phase II trial, which recruited a  
337 relatively small cohort of patients from a single centre. Thus, the data must be interpreted  
338 within the context of biases associated with this type of study. In addition, the dose of  
339 paclitaxel (70 mg/m<sup>2</sup>/week) used was lower than that used in other trials (80 mg/m<sup>2</sup>/week)  
340 treating patients with platinum-resistant ovarian cancer<sup>(6, 32)</sup>. We recognise that this may have  
341 affected the response rate and/or the withdrawal rate for patients treated with paclitaxel alone.

342

## 343 *Implications for Practice and Future Research*

344 Malignant bowel obstruction in ovarian cancer is a clinical unmet need. The prognosis for  
345 patients with recurrent ovarian cancer and inoperable bowel involvement is poor<sup>(29, 30, 33)</sup>, with  
346 many often considered ineligible for further therapy. Our study has shown that a treatment  
347 strategy involving cytotoxic chemotherapy and a targeted therapy could be a potential option,  
348 although statistically powered trials are needed to confirm this. What remains unclear  
349 however, is how to select patients who will benefit from this strategy. Biomarkers of



350 response, such as changes in plasma Tie2 concentration, may offer an opportunity to select  
351 patients for anti-angiogenic agents, and should be included in future trials.<sup>(34)</sup> The use of  
352 screening instruments to detect early signs of malignant bowel obstruction should also be  
353 developed to allow more timely interventions.<sup>(25, 35)</sup> Results from our bowel symptom  
354 screening questionnaire imply that the three most severe symptoms experienced by patients  
355 with impending bowel obstruction are abdominal pain, swelling and borborygmi. These  
356 findings differ from those observed in our discovery cohort, in which abdominal pain, nausea,  
357 vomiting and constipation were more severely reported.<sup>(25)</sup> These contrasting observations  
358 demonstrate the difficulty of developing early warning scores for bowel obstruction, where  
359 gastrointestinal symptoms can be variable and non-specific.

360

## 361 **CONCLUSIONS**

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

365 **FUNDING**

366 The trial was funded by Astrazeneca, who also provided the investigational medicinal  
367 products (cediranib and olaparib). Astrazeneca had no role in designing the study, data  
368 collection, data analysis, interpretation of the results, writing of the statistical analysis final  
369 report or the final decision to submit the manuscript.

370

371 **ACKNOWLEDGEMENTS**

372 The trial was sponsored by the University of Manchester and co-ordinated by Cardiff  
373 University Centre for Trials Research. The study protocol was approved by the Medicine and  
374 Healthcare products Regulatory Agency and the North West Liverpool Central Research  
375 Ethics Committee (reference: 17/NW/0623). This trial is registered with the European Union  
376 Clinical Trial Register (EudraCT number: 2016-004618-93).

377

378 **COMPETING INTEREST STATEMENT**

379 ADM, CP, AW, AI, RA, RR, AC, ReDM, SSK, CZ, JP, CW, VR, GA, ZS, JH and CLM  
380 declare no conflicts of interest. ARC and GCJ have received research funding for this and  
381 other investigator-initiated studies from Astrazeneca. RDM is supported by a National  
382 Institute for Health Research Clinical Lectureship (CL-2022-06-002).

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**Table 1. Baseline characteristics.** Data are presented as number of patients (percentage) unless otherwise specified. Key: ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; PARPi, poly(ADP-ribose) polymerase-1/2 inhibitor.

	<b>Intention-to-treat population</b> <i>30 patients</i>	<b>Per-protocol population</b> <i>17 patients</i>
<b>Age / years – median (range)</b>	61 (31-83)	62 (51-83)
<b>ECOG performance status</b>		
0	12 (40%)	8 (47%)
1	15 (50%)	8 (47%)
2	3 (10%)	1 (6%)
<b>Histology</b>		
High-grade serous	28 (93%)	16 (94%)
High-grade endometrioid	0	0
Clear cell	0	0
Carcinosarcoma	2 (7%)	1 (6%)
<b>FIGO stage</b>		
I	2 (7%)	0
II	2 (7%)	0
III	20 (67%)	14 (82%)
IV	6 (20%)	3 (18%)
<b>Germline <i>BRCA1/2</i> status</b>		
Mutation	4 (13%)	1 (6%)
Wild-type	26 (87%)	16 (94%)
<b>Prior first-line platinum-based chemotherapy</b>	30 (100%)	17 (100%)
<b>Number of prior lines of chemotherapy</b>		
Median	3	3
Interquartile range	2-4	2-4
Range	1-6	1-6
<b>Prior primary cytoreductive surgery</b>	28 (93%)	16 (94%)
<b>Extent of residual disease after surgery</b>		
<10 mm	18 (64%)	10 (63%)
≥10 mm	10 (36%)	6 (38%)
Inoperable	2	1
<b>Prior therapy</b>		
Paclitaxel	29 (97%)	16 (94%)
Bevacizumab	7 (23%)	3 (18%)
PARPi	5 (17%)	2 (12%)
Radiotherapy	1 (3%)	1 (6%)
<b>High-risk symptoms/signs of bowel obstruction</b>		
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%)
Recto-sigmoid 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%)

**Table 2. Pre-treatment responses to bowel symptom screening questionnaire in the intention-to-treat population.** Data are presented as number of patients (percentage). Key: 29/30 patients completed the bowel symptom screening questionnaire at baseline (the severity of each symptom has been separated into severe = “a lot” or “quite a lot” or not severe = “sometimes” or “very little” or “not at all”); \* borborygmi; † nausea; ‡ vomiting.

<b>Question</b>	<b>Bowel symptoms experienced in the last 3 weeks</b>	<b>Severe</b>	<b>Not severe</b>
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	Diarrhoea	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	<b>Yes</b> <b>No</b>	25 (86%) 4 (14%)



## LEGENDS

**Figure 1.** CONSORT diagram.

**Figure 2.** Adverse events experienced in  $\geq 10\%$  of patients receiving paclitaxel plus cediranib (17 patients, Component 1, per-protocol population). Key: AP, alkaline phosphatase; AST, aspartate aminotransferase; ced, cediranib; disor, disorder; GI, gastro-intestinal; musculoskel, musculoskeletal; neut, neutrophil; periph, peripheral.