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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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30

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33

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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/m²/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 ≥ 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 ≥ 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 ≥ 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.⁽¹⁾ The most
95 common mechanism of death is inoperable malignant bowel obstruction, where the tumour
96 physically and neurologically arrests bowel function.⁽²⁾ 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^(3, 4) and recurrent ovarian cancer⁽⁵⁻⁸⁾. 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.⁽⁹⁾ Thus, to date, VEGF pathway inhibitors have been contraindicated in
105 patients at risk of bowel obstruction, depriving this group of potentially effective drugs.⁽¹⁰⁾

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- α and - β and c-
110 Kit.⁽¹¹⁾ It has been safely used in a number of clinical trials as a monotherapy, and in
111 combination therapy, to treat ovarian cancer.^(7, 12-18) The main side effects of cediranib are
112 fatigue, diarrhoea and hypertension.⁽¹⁹⁾ 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⁽²⁰⁾, contrasting previous reports of severe toxicity associated with bevacizumab
115 in the same context.^(21, 22) 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.⁽²³⁾ 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.⁽¹³⁾

130

131 *Participants*

132 Eligible patients were ≥ 16 years old with histologically confirmed, progressive, platinum-
133 resistant/refractory, high-grade ovarian, fallopian tube or primary peritoneal cancer⁽²⁴⁾, 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.⁽²⁵⁾ 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/m² 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 ≤ 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⁽²⁶⁾ or clinically. Patients were asked a pre-defined series
175 of bowel symptom-orientated questions every three weeks.⁽²⁵⁾ 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 ≥ 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.⁽⁹⁾ 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 ≥ 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 ≥ 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 ≥ 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 ≥ 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 ≥ 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 ≤ 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 (5th 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 ≥ 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 ≥ 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/m²/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 *BRCAl/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⁽²⁷⁾, 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.⁽⁹⁾ 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.⁽²⁸⁾ 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 ≥ 1 symptom of bowel obstruction, meaning there was a
331 narrow window-of-opportunity to commence treatment.^(29, 30) 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.⁽³¹⁾

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/m²/week) used was lower than that used in other trials (80 mg/m²/week)
340 treating patients with platinum-resistant ovarian cancer^(6, 32). 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^(29, 30, 33), 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.⁽³⁴⁾ The use of
352 screening instruments to detect early signs of malignant bowel obstruction should also be
353 developed to allow more timely interventions.^(25, 35) 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.⁽²⁵⁾ 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

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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
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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.

	Intention-to-treat population <i>30 patients</i>	Per-protocol population <i>17 patients</i>
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%)
Prior first-line platinum-based chemotherapy	30 (100%)	17 (100%)
Number of prior lines of chemotherapy		
Median	3	3
Interquartile range	2-4	2-4
Range	1-6	1-6
Prior 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
Prior 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%)
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.

Question	Bowel symptoms experienced in the last 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	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	Yes No	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.