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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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ABSTRACT

Objective

Cytotoxic chemotherapy for ovarian cancer can be augmented by co-administration of vascular endothelial growth factor inhibitors but these are contra-indicated 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 high-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 bowel obstruction. Cediranib (20 mg/day) was added to paclitaxel (70 mg/m^2/week) within 9 weeks of starting paclitaxel if pre-treatment 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 hospitalisation for bowel obstruction, grade ≥3 adverse events, treatment compliance assessed by relative dose intensity, objective response, progression-free and overall survival.

Results

Thirty patients were recruited. Of these, 12 received paclitaxel only and 17 went on to receive 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 hospitalisation for bowel obstruction but recovered with conservative management. The commonest cediranib-related grade ≥3 adverse events were fatigue (3/17), diarrhorea (2/17) and hypomagnesaemia (2/17).

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

Conclusion

The unexpectedly high withdrawal rate during paclitaxel alone, prior to 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.

KEY MESSAGES

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 plus 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 investigate systemic treatments for patients with ovarian cancer at risk of bowel obstruction, thereby addressing a clinical unmet need.

INTRODUCTION

Ovarian cancer is the commonest cause of gynaecological 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 tumour 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]

The above 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 receptor-1, -2 and -3, platelet-derived growth factor receptor-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, diarrhorea and hypertension.[19] We have shown in a phase I study that cediranib with chemo-radiation 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 hypothesise 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

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]

Participants

Eligible patients were ≥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; clinical correlates of bowel obstruction that we had previously reported.[25] Previous bowel obstruction was permitted so long as there was no concern about oral absorption of medications. Any number of previous anti-cancer treatments were permitted, including weekly paclitaxel in the first-line setting and prior bevacizumab, but prior treatment with a VEGF receptor tyrosine kinase inhibitor was not permitted. Patients who had received prior PARPi were eligible. An Eastern Cooperative Oncology Group performance status of 0-2, predicted life expectancy of greater than 12 weeks,

evaluable disease by Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 criteria, and adequate bone marrow, 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 co-morbidities that precluded safe administration of the investigational medicinal products. All patients provided written informed consent before enrolment.

Procedures

The trial was separated into two components. In Component 1, patients were treated with intravenous paclitaxel 70 mg/m^2 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 once all bowel symptoms had reduced to grade ≤2. Patients whose bowel symptoms did not improve within 9 weeks, or had progressive disease prior to 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 outlined above, 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 (CT) of the abdomen and pelvis was performed at baseline (i.e., pre-treatment) and repeated every third cycle. Progressive disease was defined radiologically according to RECIST[26] or clinically. Patients were asked a pre-defined series of bowel symptom-orientated questions every three 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 hospitalisation for bowel obstruction, the number of grade ≥3 adverse events related to cediranib, treatment compliance as assessed by the relative dose intensity, objective response, progression-free and overall survival.

Statistics

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 pre-treated 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, ten patients would be required to produce 90% power and 5% significance for stage 1. After at least six weeks of follow-up on cediranib after the tenth 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 summarised 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 pre-treatment symptoms were reported for patients receiving paclitaxel only, cediranib +/- 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 Supplementary 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 centres 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 prior 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 Supplementary Tables S1 and S2). Clinical symptoms correlated with radiological risk factors for bowel obstruction before treatment, where 26 patients had ≥1 radiological risk factors (Supplementary Tables S3 and S4). Pre-treatment adverse events are provided in Supplementary Table S5.

Of the 30 patients in the intention-to-treat population, 29 received paclitaxel and one patient died from progressive disease prior to 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). Two patients started cediranib within the first cycle of paclitaxel and 15 started cediranib after their bowel symptoms had improved to grade ≤2. The 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 +/- 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 prior to withdrawal. All patients in Component 2 were withdrawn from treatment due to

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

The median duration of follow-up in the intention-to-treat population was 18.2 months (95% CI 9.1-not reached) and 12.4 months (8.9-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 hospitalisation 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 patients was discharged and subsequently commenced paclitaxel plus cediranib from cycle 3 onwards, eventually developing progressive disease 35 weeks after initiating treatment.

The commonest grade ≥3 adverse events in the 17 patients who received paclitaxel plus cediranib were fatigue, diarrhorea, hypomagnesaemia, urinary tract infection and dehydration (Figure 2 and Supplementary Table S6 and S7).

In the intention-to-treat population the median and relative dose intensity of paclitaxel was 63.0 mg/m^2/week (IQR 59.1-70.0) and 90.3% (IQR 85.0-100.0), respectively (Supplementary Table S8). In the per-protocol population in Component 1, the 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 (Supplementary Table S8).

The objective response was 37.0% (95% CI 19.9-56.1) in the intention-to-treat population and 65.0% (95% CI 38.3-85.8) in the per-protocol population (Supplementary Table S9). The median progression-free survival was 4.4 months (95% CI 3.3-6.9) in the intention-to-treat population and 6.9 months (95% CI 4.4-11.5) in the per-protocol population (Supplementary Figure S1 and Table S9). The median overall survival was 11.2 months (95% CI 8.5-20.4) in the intention-to-treat population and 19.4 months (95% CI 10.1-20.4) in the per-protocol population (Supplementary Figure S1 and Table S9). Pre-defined subgroup analysis of patients with prior 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 (Supplementary 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 prior to initiation of cediranib, when compared with baseline, in the cohort of patients who received cediranib (Supplementary 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 diarrhoea 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 shows 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 prior lines of chemotherapy and had risk factors for gastrointestinal perforation. We recruited patients with platinum-resistant ovarian cancer who had a median of three prior 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 to 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 prior to 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 also report the first anti-cancer 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 symptom of bowel obstruction, meaning there was a narrow window-of-opportunity to commence treatment.[29, 30] Despite achieving target recruitment, the unexpectedly high withdrawal rate during paclitaxel alone prevented the primary endpoint being analysed. 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-randomised, phase II trial, which recruited a relatively small cohort of patients from a single centre. 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/m^2/week) used was lower than that used in other trials (80 mg/m^2/week) treating patients with platinum-resistant ovarian cancer[6, 32]. We recognise 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 anti-angiogenic 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, prior to introducing cediranib, meant we were unable to definitely conclude that paclitaxel plus cediranib did not cause gastrointestinal perforation or fistula. However, the regimen was tolerated.

FUNDING

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.

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COMPETING INTEREST STATEMENT

ADM, CP, AW, AI, RA, RR, AC, ReDM, SSK, CZ, JP, CW, VR, GA, ZS, JH and CLM declare no conflicts of interest. 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).

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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 *30 patients*	**Per-protocol population** *17 patients*
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 *BRCA1/2* 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***	25 (86%)
		No	4 (14%)

LEGENDS

Figure 1. CONSORT diagram.

Figure 2. Adverse events experienced in ≥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.